

**Identifying strategies to inform
interventions for the secondary prevention
of stroke in UK primary care**

James Jamison

Department of Public Health and Primary Care

School of Clinical Medicine

Darwin College

University of Cambridge

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James Jamison

Stroke is a significant contributor to the global burden of disease in adults. With the risk of recurrent stroke high, preventative medicines aimed at risk factor reduction are the method of choice for addressing the challenge of increased morbidity and mortality and improving patient outcomes. Research in stroke has shown that adherence to medication is problematic and survivors face considerable practical and physical barriers to taking prescribed medicines. Understanding these challenges can inform the development of strategies to improve medication taking behaviour through delivery of interventions in the primary care setting.

This thesis aims to identify potential strategies to inform interventions to improve medication taking in stroke. The research: identified key barriers and facilitators of medication adherence for the secondary prevention of stroke – firstly from within the primary care setting and then from the perspective of an online stroke forum; explored the appropriateness of the online forum as a method of data collection for conducting qualitative research compared with a traditional qualitative interview approach; investigated medication taking among community stroke survivors to characterise patients who receive help with medicines and estimate the proportion who have unmet needs and miss medicines; and examined attitudes from across the stroke spectrum towards a novel approach to medication taking for secondary prevention (i.e. fixed-dose combination polypill).

Findings showed that survivors face considerable barriers to medicine taking, but that facilitators, particularly the caregiver role, can encourage good medication taking practice. The online forum has potential as a source of data to understand stroke survivors' behaviour, and a novel strategy to taking stroke medicines has promise.

These findings enhance current thinking around medicine taking behaviour in stroke and can inform the development of effective interventions to improve medication taking practices and address nonadherence among stroke survivors. Implications for clinical practice are discussed, and recommendations are provided for future research.

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text

It does not exceed the prescribed word limit of 60,000 words excluding figures, photographs, tables, appendices and references as required by the Clinical Medicine and Clinical Veterinary Medicine Degree Committee.

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Copies of currently published studies completed in this thesis.

List of study publications produced from this thesis

1. Jamison J, Graffy J, Mullis R, Mant J, Sutton S. Barriers to medication adherence for the secondary prevention of stroke: a qualitative interview study in primary care. *Br J Gen Pract* 2016; 66 (649): e568-e576. DOI: 10.3399/bjgp16X685609
2. Jamison J, Sutton S, Mant J, et al. Barriers and facilitators to adherence to secondary stroke prevention medications after stroke: analysis of survivors and caregivers views from an online stroke forum. *BMJ Open* 2017;7:e016814. doi: 10.1136/bmjopen-2017-016814
3. Jamison J, Sutton S, Mant J, et al. Online stroke forum as source of data for qualitative research: insights from a comparison with patients' interviews *BMJ Open* 2018;8:e020133. doi: 10.1136/bmjopen-2017-020133.
4. Jamison J, Ayerbe L, Di Tanna GL, et al. Evaluating practical support stroke survivors get with medicines and unmet needs in primary care: a survey. *BMJ Open* 2018;8:e019874. doi:10.1136/bmjopen-2017-019874
5. Jamison, J. Mullis, R., Graffy, el al. Stroke survivors', caregivers' and GPs' attitudes towards a polypill for the secondary prevention of stroke: a qualitative interview study. *BMJ Open* 2016;6:e010458. doi: 10.1136/bmjopen-2015-010458

Glossary

Aetiology: The cause or set of causes, or manner of causation of a disease or condition.

Co-morbidities: The presence of one or more additional diseases co-occurring (concomitant or concurrent) with a primary disease or disorder;

Compliance: The degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, frequency or behaviour.

Concordance: An agreement between the individual and healthcare professional on taking medication, which accounts for both perspectives and has a broad focus on including prescribing communication and patient support.

Cardiovascular Risk: A general term for conditions affecting the heart or blood vessels, usually associated with a build-up of fatty deposits inside the arteries – known as atherosclerosis – and an increased *risk* of blood clots.

Carer/ caregiver: A paid or unpaid member of a person's social network who helps with activities of daily living.

Confidence interval (CI): A range of defined values that quantifies the level of confidence that a parameter lies within the interval.

Disability Adjusted Life Year (DALY): A measure of disease burden expressed as the number of years lost due to ill health, disability or early death.

Fixed-dose combination (FDC): A drug that includes two or more active pharmaceutical ingredients (APIs) combined in a single dosage

General Practitioner (GP): A medical doctor who treats acute and chronic illnesses and provides preventive care and health education to patients and refers those with serious conditions to a hospital.

Health literacy: The degree to which an individual has the capacity to obtain and understand basic health information.

Hospitalisation: Admission to hospital for treatment.

Incidence: a measure of the number of new cases of a disease (or another health outcome) that develop in a population of individuals at risk, during a specified time period.

Intentional nonadherence: Nonadherence that is deliberate and is associated with the patient's motivation to take medication (e.g. as a result of side effects)

Medication Adherence: The extent to which the person's behaviour (taking medication) corresponds with the agreed recommendations from a health care provider.

Multimorbidity: The presence of two or more chronic medical/health conditions.

Nonadherence: Deviation from a plan to follow the recommendations for prescribed medication.

Non-persistent: Not continuing treatment for the prescribed duration.

Odds ratio (OR): A measure of the association between an exposure and an outcome.

Paid caregiver: An individual who is paid (by the state, privately or insurer paid) to help another person with activities of daily living.

Persistence: The time from initiation to discontinuation of medication.

Pharmacotherapy: Medical treatment by the means of using drugs.

Pharmacy refill: A new instalment of medication prepared by the pharmacy.

Pharmacy refill data: Data on medication prescriptions prepared by the pharmacy.

Pill burden: The number of tablets, capsules, or other dosage forms that a person regularly takes.

Polyparmacy: The concurrent use of five or more medications by an individual.

Polypill: A medication in pill form (i.e. a tablet or capsule) that combines multiple active pharmaceutical ingredients.

Population Attributable Risk (PAR): The population attributable risk (PAR) estimates the excess rate of disease in the total study population that is attributable to the exposure.

Prevalence: A measure of the burden of disease in a population at a given point in time.

Relative risk (RR): The ratio of the probability of an event occurring in an exposed group to the probability of the event occurring in a comparison non-exposed group

Risk factor: A variable associated with an increased *risk* of *disease* or injury.

Secondary prevention: A comprehensive set of measures to reduce the recurrence of cardiovascular disease.

Self-management: The actions taken by a person to recognise, treat and manage their own health

Unintentional nonadherence: Nonadherence that it associated with a lack of capacity or resources to take medication (e.g. as a result of forgetting)

Abbreviations

AF	Atrial Fibrillation
ACE	Angiotensin Converting Enzyme
ADL	Activities of Daily Living
BI	Barthel Index
BMI	Body Mass Index
BMQ	Beliefs about Medicines Questionnaire
CCB	Calcium Channel Blockers
CRN	Clinical Research Network
CVD:	Cardiovascular disease
CT	Computer tomography
DBP	Diastolic Blood Pressure
DOH	Department Of Health
DALY	Disability Adjusted Life Year
F.A.S.T.	Face Arm Speech Time
FDC	Fixed-Dose Combination
GP	General Practitioner
HBM	Health Belief Model
HDL-C	High Density Lipoprotein-Cholesterol
ICH	Intracerebral Haemorrhage
IHD	Ischaemic Heart Disease
IPQ	Illness Perception Questionnaire
LDL-C	Low Density Lipoprotein-Cholesterol

LMIC	Low and Middle Income Country
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCD	Noncommunicable Disease
NCF	Necessity Concerns Framework
NHS	National Health Service
NOAC	Novel Oral anti-Coagulant
OR	Odds Ratio
PAPA	Perceptions and Practicalities Approach.
PAR	Population Attributable Risk
PPI	Patient and Public Involvement
RR	Relative Risk
SAH	Subarachnoid Haemorrhage
SBP	Systolic Blood Pressure
SPARCL	Stroke Prevention by Aggressive Reduction of Cholesterol Levels
SRM	Self-Regulation Model
TDF	Theoretical Domains Framework
TIA	Transient Ischaemic Attack
TPB	Theory of Planned Behaviour
TRA	Theory of Reasoned Action
TIA	Transient Ischaemic Attack
TTM	Transtheoretical Model
WHO	World Health Organisation

Chapter 1- Introduction

The aim of this piece of work was to identify strategies which could inform the development of interventions to assist medication taking behaviour and improve health outcomes among survivors of stroke or transient ischaemic attack. A number of key objectives were set out.

- To identify and evaluate potential barriers and facilitators of medication adherence for the secondary prevention of stroke in the primary care setting.
- To understand and explore the role of the informal caregiver in facilitating medication taking behaviour among survivors of stroke or transient ischaemic attack.
- To investigate the medication needs of stroke survivors living in the community, exploring practical areas in which stroke survivors receive help as well as their unmet needs with respect to taking medication.
- To understand the attitudes of stroke survivors and caregivers towards a novel medication for the prevention of secondary stroke.
- To identify strategies that can be used across the stroke care pathway to improve medication taking behaviour of stroke survivors.

To meet these objectives a series of studies were undertaken. Firstly, through a qualitative investigation, barriers to medication adherence for the secondary prevention of stroke were explored from the perspective of stroke survivors, caregivers and general practitioners (GP) using semi-structured interviews in the general practice setting. Next, the views of survivors and caregivers were examined qualitatively through contributions made to an online stroke forum. This permitted an understanding of attitudes from two unique perspectives and with two different stroke sub-groups. A methodological comparison of the two methodologies was then undertaken to assess the appropriateness of an online forum as a source of data for conducting qualitative research on barriers and facilitators of medication adherence in stroke. To understand stroke survivors' unmet medication needs and areas of practical medicine taking in which they received help, a community based survey study was completed. Finally, to explore the acceptability of a novel medication taking strategy, using a polypill approach, the attitudes and perspectives of stroke survivors, caregivers and general practitioners were investigated.

1.1 Background

1.1.1 Cardiovascular disease

Non-communicable diseases (NCDs) are a group of non-transferable diseases often characterised by long duration and slow progression to which cardiovascular disease (CVD) is a major contributor. NCDs are responsible for the deaths of more people each year than all other causes of death combined, contributing to almost 36 million or 63% of the 57 million deaths worldwide in 2008.¹ Often thought to be the consequence of lifestyle in high income countries, the burden of noncommunicable diseases worldwide is considerable with almost three quarters of all NCD deaths occurring in low to middle income countries (LMICs) worldwide.² The most widely known of these is cardiovascular disease (CVD), a collection of diseases of the heart and circulatory system including ischaemic heart disease or coronary artery disease (e.g. heart attack), cerebrovascular disease (e.g. stroke), and diseases of the arteries including hypertension and peripheral artery disease.

CVD is the single greatest contributor to premature death and adult disability worldwide.^{3,4} In 2013, CVD accounted for 17.3 million or 32% of deaths worldwide,⁵ with heart attacks and strokes responsible for 7.3 and 6.2 million deaths, respectively.⁴ In the UK, just over a quarter of all deaths, or 160,000 deaths per year, can be attributed to cardiovascular disease. It is further estimated that there are around 7 million people living with cardiovascular disease in the UK.⁶ Although worldwide rates of cardiovascular events are lower in high income countries⁷ and have steadily declined over the years⁸, the burden of CVD continues to increase in low to middle income countries where around 80% of all deaths from cardiovascular disease now occur.⁴ The WHO predicts that by 2030, ischaemic heart disease and stroke, both significant components of cardiovascular disease, will be the leading causes of death worldwide.⁹ As well as the significant morbidity and increased levels of mortality, the economic implications of CVD are considerable with an estimated cost to the European economy of around 196 billion euros a year in healthcare expenditure (54%) productivity losses (24%) and the informal care (22%) of people with CVD¹⁰ and £19 billion per annum in the UK due to treatment, lost productivity and premature mortality.¹¹

Traditionally, the prevention of CVD involves the identification of key risk factors, then a process of lifestyle modification, followed by a preventative programme involving immediate and prolonged intervention using appropriate pharmacotherapies to reduce the incidence or frequency of risk before it establishes as cardiovascular disease.

1.1.2 *Stroke*

A key component of the group of disorders known as cardiovascular diseases, a Stroke is a cerebrovascular accident, or the brain equivalent of a heart attack, which occurs in response to a disturbance in the blood supply to the brain. Stroke was first defined according to World Health Organisation (WHO) criteria as “a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than that of vascular origin”.^{12 13} Stroke was then characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause and including cerebral infarction, intracerebral haemorrhage (ICH), and subarachnoid haemorrhage (SAH).¹⁴ Both ICH and SAH are stroke sub-types, more commonly known as haemorrhagic strokes. ICH is defined as

“rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma”.

SAH on the other hand has been defined as

“rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma”.

There are two main types of stroke, the most common of which is caused by a blood clot or narrowing of blood vessels due to atherosclerosis, leading to a restriction in the blood flow reaching the brain. This event is known as an ischaemic stroke and accounts for around 80-85% of all strokes that occur.¹⁵ The second type of stroke is haemorrhagic, caused by blood vessels bursting and leading to bleeding on the brain which causes damage.¹⁶ In both cases, this disruption in blood supply resulting in a lack of oxygen leads to tissue damage and causes brain cells to die.¹⁶ Most strokes occur suddenly, develop quickly and can damage the brain within minutes. Stroke occurrence is characterised by the sudden onset of several key symptoms including weakness or numbness in the face, arm or leg, especially on one side of the body, and difficulty speaking or understanding or a loss of balance or coordination, resulting in difficulty walking.¹⁷ A stroke can also vary in severity and intensity, from the temporary disruption of brain functioning to severe brain damage or even death.

1.1.3 Transient ischaemic attack (TIA)

A Transient Ischemic Attack (TIA), often called a mini-stroke, is a temporary disruption in the blood supply to the brain. TIAs are considered to be transient events of neurological dysfunction caused by focal cerebral ischaemia and without signs of acute infarction on imaging.^{18 19} This event is characterised by symptoms usually resolving themselves within 24 hours. The original definition of TIA as “any focal cerebral ischaemic event with symptoms lasting less than 24 hours” has since been revised to reflect a tissue based definition rather than a time based definition and in light of the growing debate around the length of time of a TIA. A TIA is now considered as being “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction”.¹⁸

A TIA is considered a warning sign that unless preventative measures are quickly taken, a further event or major stroke incident is likely to occur soon. With the risk of a further stroke at its highest in the first 24 hours following a TIA,²⁰ the immediate and prompt identification of a TIA is essential followed by urgent preventative treatment. Following a TIA, early treatment has been shown to reduce the 90-day risk of ischemic stroke by as much as 80%.²¹ Nevertheless, stroke survivors often fail to recognise when a stroke event has occurred.²²

1.1.4 Burden of Stroke

Stroke and transient ischaemic attack are a global health concern. The burden of stroke is considerable and requires significant and systematic intervention to reduce the potential human and economic costs.²³ Worldwide, stroke is the second most common cause of death after ischaemic heart disease, responsible for 9-12% of all deaths annually.^{24 25} Globally, the burden of stroke is significant with an estimated 17 million first time stroke events, 33 million stroke survivors and around 5.9 million stroke deaths reported in 2010, an increase of 68%, 84% and 26% respectively, since 1990, with most occurring in low to middle income countries.²⁶ The incidence of stroke also varies worldwide from country to country. A systematic review of studies between 1970-2008 reported a statistically significant divergent trend in stroke incidence with a 42% reduction in stroke incidence reported in high income countries compared with a rise of more than 100% in stroke incidence for low to middle income countries.²⁷ Assessment of the findings of the global burden of disease study of 2010 also reported around 102 million lost Disability-Adjusted Life-Years (DALYs) as a result of stroke.²⁶ One DALY is considered the equivalent of one year of healthy life lost.

Despite a reduction in its occurrence over the last decade, stroke remains a significant cause of premature adult mortality in the UK, resulting in over 53,000 deaths per year²⁸ or 9% of all deaths, second only to coronary heart disease.²⁸ Around 152,000 strokes occur in the UK annually²⁹ and there are 1.1 million people thought to be currently living with stroke and its consequences.³⁰ It is estimated that between 174 and 216 people per 100,000 of the population in the UK are affected each year by a stroke.³¹

Stroke is also the single largest cause of long-term disability among adults.³² At least one third of survivors are disabled by a stroke event, making stroke a significant cause of disability adjusted life years (DALYs) worldwide.^{33 34} It is thought that there are around 300,000 people in the UK living with disabilities that are associated with stroke³⁵ and around one third of stroke survivors are left dependent on others for support and rehabilitation and of those one in five are cared for by family and/or friends.³⁶ The incidence of stroke is also known to increase with age,²⁸ doubling for every decade after the age of 45 with 70% of strokes occurring in those over the age of 65.³⁶ Stroke also represents a considerable financial burden. In 2010, the cost of stroke in the USA alone was estimated to be 73.7 billion dollars annually.³⁷ In the UK, the cost attributed to stroke is estimated to be around £8.9 billion a year in treatment and lost productivity.³⁸ Treatment costs attributed to stroke are thought to account for around 5% of total costs to the NHS in the UK with direct care accounting for around 50% of the costs, around 27% of costs attributed to informal care and approximately one quarter of total costs (24%) attributed to indirect costs.²³

1.1.5 Recurrent stroke

People who have had a stroke or transient ischaemic attack are at risk of a further cerebrovascular incident, with the risk of vascular events remaining high for some time.^{39 40} Early research reported that stroke survivors were up to 15 times more likely than the general population to have a second stroke in the year following the primary event.⁴¹ In a study investigating long term risk of recurrent stroke, over the 10 years of follow up the cumulative risk of a first recurrent stroke was 43% with the risk of recurrent stroke greatest in the first six months at 9%.⁴² Intervening early and providing immediate medical treatment is essential to prevent lasting damage and improve patient outcomes following a stroke event. Nevertheless, research has shown that stroke survivors can lack knowledge on stroke symptoms and risk factors for stroke and that inability to identify a stroke is not uncommon.⁴³

An assessment of the effects of treatment found that early initiation of treatment after stroke or transient ischaemic attack was associated with an 80% reduction in the risk of early recurrent stroke.²¹ Secondary prevention medicine has the potential to reduce the relative risk of recurrent stroke by about three quarters.⁴⁴

Even in the case of minor strokes or transient ischaemic attack, there is a significant risk of recurring stroke or TIA following an initial event.⁴⁵ A population-based cohort study of patients with TIA and minor stroke found a recurring rate of 8% at 7 days rising to 11.5% at 1 month and 17.3% at 3 months following a TIA.⁴⁶ Elsewhere in a systemic review and meta-analysis of 13 studies containing 9115 patients, the cumulative risk of stroke recurrence was 3% at 1 month, 11% at 1 year and 25% at 5 years rising to 39% at 10 years post stroke.⁴⁷ Research also shows that transient ischaemic attack is associated with a high early risk of stroke⁴⁸ and that the risk is significant in the days and weeks immediately following the primary event.⁴⁷ Rothwell and Marlow found that in patients who presented with an ischaemic stroke, TIAs most often occurred in the hours and days just preceding the stroke with 17% on the day of the stroke and 43% within the previous 7 days.⁴⁹ Given the potential for increased mortality and functional decline as a result of recurrent stroke, guidelines recommend that pharmacotherapies for secondary prevention should be initiated promptly and adhered to persistently in order to achieve effective risk reduction.⁵⁰⁻⁵²

1.1.6 Risk factors for stroke

Multiple factors are known to be associated with an increased risk of a stroke occurring.⁵³ The term risk factor, defined by the World Health Organisation as “an attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury”, was first coined in an early investigation of the Framingham Heart study.⁵⁴

Risk factors for stroke can be categorised as modifiable or non-modifiable. Key non-modifiable risk factors include age, ethnicity and family history, while potentially modifiable risk factors consist of clinical and lifestyle factors. Addressing key risk factors associated with cardiovascular disease has the potential to significantly reduce the incidence of future cardiovascular events.⁵⁵ Clinical factors known to increase the likelihood of a stroke include high blood pressure otherwise known as hypertension, high blood cholesterol and diabetes.⁵⁶ as well as atrial fibrillation (AF).⁵⁷

Guidelines on the management of high blood pressure have identified hypertension as a major risk factor for stroke.⁵⁸ Hypertension occurs when high pressure of blood pressing against artery walls places additional strain on blood vessels, including those leading to the brain, which can result in an increased risk of a blood clot occurring or a bleed within the blood vessel, both of which can lead to a stroke. Lowering blood pressure is known to reduce the risk of vascular disease including stroke.⁵⁹ The results of a significant meta-analysis consisting of 1 million patients across 61 studies concluded that high blood pressure was directly associated with stroke mortality.⁶⁰

High cholesterol has been identified as an important modifiable risk factor for cardiovascular disease, including stroke.⁶¹ Cholesterol is a fatty substance essential for the normal functioning of the body. However, too much cholesterol can have a detrimental effect on health. Lipoproteins carry cholesterol through the blood with the two most important lipoproteins known as high-density lipoprotein (HDL) and low-density lipoprotein (LDL). High-Density Lipoprotein- Cholesterol (HDL-C) or ‘good cholesterol’ is known for its cardio protective effect, carrying cholesterol away from the cells and back to the liver where it is flushed from the body.^{62 63} Low-Density Lipoprotein- Cholesterol (LDL-C) often referred to as ‘bad cholesterol’ carries cholesterol to the cells, however, too much can lead to a build-up of fat on the artery walls. Atherosclerosis is a condition in which plaque builds up on the artery walls and over time hardens, resulting in a narrowing of the arteries which can eventually lead to a blockage of the artery. Atherosclerosis is known to be associated with the increased risk of stroke or TIA.⁶⁴ A review of randomised controlled trials found that the lowering of cholesterol levels had clear benefits for the reduction of stroke and CVD mortality.⁶⁵

Atrial fibrillation (AF) , another well-known independent risk factor for stroke and TIA, is associated with a fivefold increase in the risk of a stroke occurring.⁶⁶ In a study of nationwide registries examining AF, researchers found an increased risk of stroke and TIA when prior stroke or TIA was present, while AF was associated with an increase in the risk of stroke or TIA in the absence of other risk factors.⁶⁷ In an investigation to determine the rates of stroke or TIA in patients with ‘resolved’ AF compared to ‘unresolved’ AF and no diagnosis of AF, researchers found that risk of stroke or TIA remained high in patients with resolved AF compared to patients without AF and the risk was increased in those patients in whom recurrent AF was not documented.⁶⁸

Poor lifestyle factors such as unhealthy diet, physical inactivity, obesity, increased alcohol consumption and smoking are known to be associated with increased stroke risk.⁶⁹ This INTERSTROKE study highlighted potentially important, modifiable risk factors for stroke and TIA.⁵⁶ In this large scale case-control study conducted across 22 different countries with the aim of establishing an understanding of the risk factors for stroke and assessing how these stroke factors contribute to the burden of stroke overall, 3000 participants with stroke (78% ischaemic stroke and 22% haemorrhagic stroke) were compared with 3000 controls. The study identified up to 10 risk factors for stroke. Hypertension, smoking, diet risk score, diabetes, regular physical activity, alcohol consumption, stress, cardiac causes, depression and ratio of apolipoproteins B to A1, together accounted for 88.1% (CI 82.3–92.2) of the population attributable risks (PAR) for all stroke including ischaemic and intracerebral haemorrhagic stroke. However when an alternative definition of hypertension was used (i.e. history of hypertension or a BP reading of >160/90 mmHg), the combined PAR was 90.3% (CI 85.3–93.7) for all stroke. The strongest risk factor for stroke was self-reported history of hypertension which was stronger for haemorrhagic stroke than for ischaemic stroke.⁵⁶

A meta-analysis of randomised trials to assess the efficacy of secondary prevention strategies for stroke reported that a combination of 5 preventative strategies including exercise, dietary modification, a statin, aspirin and an antihypertensive agent, when applied to survivors of initial stroke or transient ischaemic attack, could result in a cumulative relative risk reduction of around 80% for recurrent vascular events.⁷⁰ While there has been success in the management of important risk factors for stroke such as hypertension and lipid treatment, greater efforts are needed to improve the risk of a recurrent stroke.⁷¹ Aggressive risk factor management including blood pressure lowering with antihypertensives, cholesterol lowering with statins and initiating antiplatelet therapy (except in those where anticoagulant therapy is indicated), along with a concerted effort to improve lifestyle, are key to the effective treatment of stroke and transient ischaemic attack.^{51 72}

Guidelines for the prevention of secondary stroke also advise adopting positive lifestyle change such as following healthy dietary habits, taking regular exercise, quitting smoking and maintaining alcohol consumption within recommended levels.⁷³ Following a low risk lifestyle, consisting of modest alcohol consumption, not smoking, having a healthy body mass index (BMI) and moderate physical activity has a beneficial effect on the prevention of stroke.⁷⁴ Adherence to a combination of different lifestyle interventions

(including obesity, smoking, physical activity, consumption of alcohol and diet) has also been found to be associated with a reduction in all-cause mortality.⁷⁵

Smoking is a well-known and important independent risk factor for stroke⁷⁶ with the risk of first stroke in smokers four times that of non-smokers⁷⁷ and double that of non-smokers for secondary stroke.⁷⁸ In a Scottish study looking at risk factors for stroke incidence, smoking was found to be a strong predictor of stroke mortality and incidence.⁷⁹ Smoking cessation support is recommended as an effective strategy to reduce stroke risk, with face to face counselling known to successfully increase the success of smoking cessation by as much as 70%.⁸⁰ As an important risk factor for cardiovascular events and mortality even in older age groups, smoking can advance cardiovascular mortality by as much as 5 years.⁸¹

Excessive consumption of alcohol has also been found to increase the risk of stroke occurring⁸²⁻⁸⁴ and is also associated with increased mortality from stroke.⁸⁵ On the other hand, a protective effect against stroke has been reported for moderate alcohol consumption.^{86 87} In a meta-analysis investigating the relationship between alcohol consumption and different types of stroke, results showed that light alcohol intake was inversely associated with ischaemic stroke while excessive consumption of alcohol was associated with a greater risk of all types of stroke and a stronger association for haemorrhagic strokes.⁸⁸

Guidelines on stroke prevention also recommend following a healthy diet to protect against risk of stroke.⁶⁹ Obesity is known to be associated with an increased risk of cardiovascular disease and mortality⁸⁹ as well as ischaemic stroke.⁹⁰ In one study, being overweight with a BMI reading greater than 25 kg/m² or obese with reading of 30 kg/m², was associated with having a greater risk of ischaemic stroke.⁹¹ Individuals who are obese are also likely to have more prevalent risk factors associated with stroke including diabetes, hypertension and hyperlipidaemia. Guidelines for stroke prevention around weight reduction have recommended a target body mass index (BMI) range of 18.5 to 24.9 kg/m².⁶⁹

Undertaking physical activity at moderate or high levels is known to be associated with a reduction in the risk of stroke.⁹² In people who have had a stroke, physical activity can improve lipid profiles, hypertension, glucose metabolism and insulin sensitivity.^{93 94} An investigation of the association between lifestyle factors and cardiovascular mortality after stroke found that abstinence from smoking and regular physical activity were independently

associated with lower all-cause mortality following a stroke.⁹⁵ Engaging in physical activity can be challenging for survivors following a stroke⁹⁶, with one study examining adherence to home-based exercise following a stroke reporting that adherence was superior during group participation, but declined after program completion.⁹⁷ A meta-analysis investigating lifestyle interventions in people after a stroke or TIA found that interventions were effective in lowering systolic blood pressure and that those that included cardiovascular fitness programmes lasting more than four months were the most effective.⁹⁸

Important evidence exists for the role of pharmacotherapies in stroke prevention. However further research is needed on the role of lifestyle interventions following a stroke or TIA.⁹⁹ Nevertheless, the potential for lifestyle interventions which include an element of physical activity, affecting positive change following stroke, is promising.^{99 100}

Non-modifiable factors have also been identified as contributing to the risk of stroke. Ethnicity is known to be a risk factor for stroke with one UK study examining ethnic differences reporting that incidence rates, when adjusted for age and sex, were significantly higher in Blacks compared with Whites ($P < 0.0001$), with an incidence rate ratio of 2.21 (1.77 to 2.76).¹⁰¹ Another investigation over a 10 year period observed ethnic disparities with a higher risk of stroke found in Black people compared to White people.¹⁰² In the UK, Diabetes which is considered a risk factor for stroke is known to have a higher prevalence among South Asian and Afro-Caribbean ethnic groups.¹⁰³

Understanding and recognising risk factors early on is important in initiating treatment for the prevention of stroke. The UK based F.A.S.T. initiative- Face Arm Speech Time campaign¹⁰⁴ was launched with the aim of improving awareness of the signs of stroke.¹⁰⁵ In a study assessing the impact of F.A.S.T. on response to stroke, delay in seeking and implementing medical treatment fell significantly in line with the commencement of the campaign.¹⁰⁶

Although such campaigns are considered more beneficial to professionals than the public at large¹⁰⁷, knowledge of stroke risk and the symptoms and aetiology of stroke varies widely among patients. An interview study of older community dwelling adults in which participants were questioned about warning signs and risk factors for stroke found that less than half of the sample was able to identify established stroke risk factors such as smoking and hypercholesterolemia, while less than half of the sample could identify established stroke

warning signs.¹⁰⁸ However around 74% identified hypertension as an important risk factor while 54% were able to identify slurred speech as a significant warning sign for stroke.¹⁰⁸

In another study with stroke and TIA patients asked about risk factors, almost 90% identified hyperlipidemia and hypertension as risk factors for a new stroke event.¹⁰⁹ Diabetes and Atrial Fibrillation however were recognised as risk factors by less than 50% of the patient sample, while only 56% and 48% of patients taking anticoagulant and antiplatelet medication respectively recognised that these medicines were for prevention.¹⁰⁹ It is thought that poor knowledge about stroke symptoms and disabling consequences¹¹⁰ as a result of stroke may contribute to poor awareness around the importance of optimal risk factor control. A community-based interview survey study reported that almost a quarter of participants were unable to correctly list more than one established stroke risk factor while just over half correctly listed more than one warning sign with smoking identified as the most important risk factor by almost 40% of survey participants.¹¹¹ Public recognition of major stroke symptoms in a US population was also found to be low with a general survey study reporting that less than 20% of patients could correctly classify all the symptoms of stroke.¹¹²

1.1.7 Stroke outcome assessments

Stroke is a significant cause of adult disability with many survivors suffering permanent disability and requiring constant care.¹¹³ In an effort to better understand functional ability after a stroke or TIA, a number of outcome scales have been developed for use within clinical research. Two qualitative studies described in this thesis report the use of two of these scales, the modified Rankin Scale (mRS) and the Barthel Index (BI), both of which are commonly used scales designed to measure disability or dependence on activities of daily living (ADL) in people with stroke.¹¹⁴

First introduced in 1957, the modified Rankin scale is a functional outcome scale¹¹⁵ designed to assess the degree of disability in patients who had suffered a stroke. The mRS has become the most widely used clinical outcome measure for use in clinical stroke trials.¹¹⁶ Introduced to evaluate outcome in patients who had experienced a vascular accident or stroke¹¹⁷, the scale was then modified for use in the UK-TIA study of the late 1980s.¹¹⁸ The mRS scores levels of function from no symptoms or functional impairments (mRS score =0) through to complete dependence and requiring care (mRS score =5). Over the years, greater efforts have been made to improve the precision of mRS assessments.¹¹⁹ while the mRS-9Q, a nine question yes/no questionnaire, has been developed to determine the mRS across a

broader range of patients.¹²⁰ Studies have demonstrated the validity and reliability of the mRS as a valuable tool for assessing the impact of new stroke treatments.¹²¹

The Barthel Index (BI) is another scale used to measure performance in Activities of Daily Living (ADLs).¹²² This Index consists of 10 variables describing mobility and ADLs and includes activities such as feeding, grooming, walking, dressing, going up and down stairs, transfer to and from bed and toileting. A higher number on the scale is associated with a greater likelihood of functional independence and being able to live at home with a score from 0 (totally dependent) to 100 (totally independent). In 1988 a modified version of the BI was introduced, giving a maximum score of 20, with scores ranging from 0 to 2 or 3 for each activity.¹²³

1.1.8 Stroke management

With the risk of recurrent stroke known to be high following a stroke or TIA event, rapid diagnosis, medical assessment and implementation of preventative treatment is important within the first few hours following a stroke event.^{124 125} The risk of recurrent stroke is significant when compared with the risk of first ever stroke in the general population, ranging from 2.6%¹²⁶ to 4%¹²⁷ in the first 7 days. Therefore prompt recognition of stroke symptoms and initiation of immediate treatment is essential for improved patient outcomes.

In patients with an onset of neurological symptoms, an assessment tool such as F.A.S.T. is used for prompt diagnosis of stroke or transient ischaemic attack outside the hospital. For people with a suspected TIA with no neurological symptoms at the time of assessment, a validated scoring system such as ABCD² can be used for assessing patients in the acute stage.¹²⁸ The ABCD² score is a risk assessment tool that has been designed to enable a better prediction of the short term risk of stroke within as little as 2 days of a TIA, but also up to 90 days following a TIA. The ABCD² score is decided by accumulating the scores obtained across 5 independent risk factors: 1. Age- 60 yrs or more; 2. Blood pressure- SBP: 140mm Hg or more, DBP: 90mm Hg or more; 3. Clinical feature of TIA- Unilateral weakness with or without speech impairment OR Speech impairment without unilateral weakness. 4. Duration of TIA- TIA duration 10-50 minutes OR TIA duration 60 minutes or more, and 5. Diabetes diagnosis- Yes or No. The higher the score attained, the greater the risk of a stroke occurring with an ABCD² score of 4 or more signalling a high risk of stroke in people who have had a suspected TIA.¹²⁹

For people in whom a TIA is suspected and who are at high risk of stroke (ABCD² score of 4 or more), immediate brain imaging is recommended and in line with National Stroke Strategy Guidelines¹²⁴, preferably with Magnetic Resonance Imaging (MRI), or where MRI is contraindicated, CT (Computer Tomography) scanning is used.¹³⁰ In some people who have had a stroke or TIA and have experienced narrowing of the carotid artery, surgical intervention may be needed with carotid imaging required to determine the extent of narrowing of the carotid artery. Patients should be assessed within one week of onset of symptoms and be referred for carotid endarterectomy with two weeks of onset of symptoms.¹²⁹

For patients with acute stroke, urgent specialist attention is warranted. Following brain imaging, pharmacological intervention is urgently required to reverse the effect of the stroke. Undertaking thrombolysis with alteplase which is a recombinant tissue plasminogen activator (rtPA), intravenously, is recommended for treating acute ischaemic stroke in patients where haemorrhage has been discounted through appropriate imaging techniques, with guidelines recommending commencing this treatment within 4.5 hours of the onset of stroke symptoms.^{131 132}

1.1.9 Stroke prevention and treatment

Prevention of stroke is categorised as either primary or secondary with primary prevention defined as any treatment before the stroke with the intention of reducing risk factors.⁵³ Secondary prevention on the other hand refers to treatment provided after a stroke has taken place to prevent another event occurring, which is itself often more severe than an initial event.¹³³

It is widely accepted that cerebrovascular events including stroke or transient ischaemic attack require an urgent treatment response with the implementation of preventative therapy that is effective in modifying key risk factors and preventing recurrence.^{69 134 135} Since the 1990s the upward trend in mortality as a result of cardiovascular and circulatory diseases in many high and middle income countries, has been halted and in some cases reversed due to the successful implementation of non-pharmacological strategies and the availability of effective preventative medications.⁵

Identifying and modifying risk factors, initiating effective lifestyle change and implementing appropriate pharmacotherapies are important for the effective management of stroke and successful secondary prevention.¹³⁶ Pharmacological intervention consisting of antithrombotic drugs, blood pressure lowering medicines (Angiotensin-Converting-Enzyme (ACE) inhibitors, calcium channel blockers (CCBs), thiazide diuretics) and lipid lowering therapies have been widely recommended in the prevention of CVD and stroke.^{137-139 140 141}

1.2 Pharmacotherapies for secondary stroke prevention

Over the last decade, the incidence of stroke in the UK has fallen and survival rates have improved with better control of stroke risk factors such as hypertension and hypercholesterolemia using antihypertensives and cholesterol lowering therapies, respectively, likely to have contributed to this.¹⁴²

Evidence-based guidelines on the prevention of ischaemic stroke and TIA advocate the prompt initiation of medication including antithrombotic agents- primarily anti-platelet agents and anticoagulants, as well as anti-hypertensives- including ACE inhibitors, calcium channel blockers (CCBs), thiazide diuretics, and lipid modifiers such as statins, along with lifestyle guidance to reduce the incidence of risk factors and stroke.^{50 143 51 125 144 124} As a result, multiple pharmacotherapies are available with patients requiring at least one and possibly many, of a statin, aspirin, or antihypertensive therapy for the prevention of stroke.¹⁵

1.2.1 Evidence for lipid lowering drugs

Heightened lipid levels, resulting in hypercholesterolemia, is an important risk factor for CVD and medication used to lower lipid levels is effective for the secondary prevention of stroke. Statins are a widely prescribed and effective treatment used for the management of lipid levels in people who have had a stroke or TIA.¹⁴⁵ Guidelines suggest the use of statin therapy to reduce lipid levels and the subsequent risk of cardiovascular events including stroke.^{146 147}

Commencing treatment with a high intensity statin such as atorvastatin 80 mg daily is recommended, unless contraindicated.¹⁴⁸ An alternative is Simvastatin 80mg daily¹⁴⁹ with the aim of a reduction in non HDL-C of over 40%. Being offered lifestyle advice around smoking and alcohol intake as well as on diet and physical activity, is also recommended to help modify lipid levels.¹²⁴ Initiating statin therapy soon after a stroke or TIA incident is associated with improved stroke outcomes including better post stroke survival, with

temporary withdrawal of statin treatment associated with poorer survival.¹⁵⁰ Prompt initiation of statin treatment was also associated with higher rates of adherence to this medication for secondary stroke prevention at 3 month follow up.¹⁵¹

Statins work by blocking the action of a liver enzyme responsible for producing cholesterol, which can lead to the build-up of plaque on artery walls, and a hardening and narrowing of the arteries, leading to a heart attack or stroke. Too much LDL-C can lead to fatty build-ups known as ‘atherosclerosis’, contributing to an increased risk of stroke. High density lipoprotein cholesterol (HDL-C) otherwise known as ‘good cholesterol’ is thought to have a protective effect against heart attack and stroke and statins are known to lower LDL-C while at the same time raising HDL-C.^{152 153}

A review and meta-analysis on the use of statins in stroke prevention found that reduction of LDL-C using statins significantly reduced the risk of a recurrent stroke (RR 0.84, 0.71–0.99, $p=0.03$) as well as major cardiovascular events (RR 0.80, 0.69–0.92, $p=0.002$).¹⁴⁵ In another meta-analysis of 15 trials and over 63,000 participants, statin therapy significantly reduced the relative risk of non-fatal strokes (RR, 0.74, 95% CI, 0.67, 0.82, $p < 0.0001$) as well as the relative risk of total (fatal and non-fatal) stroke (RR, 0.77, 95% CI, 0.70, 0.84, $p < 0.001$) and CVD mortality (RR, 0.78, 95% CI, 0.73, 0.84, $*p < 0.0001$), particularly in secondary prevention.¹⁵⁴

Most people who use statin medication do so without any significant adverse effects. Side effects attributed to statin therapy include aching joints, headaches, difficulty sleeping, dizziness, sore throat, nausea or vomiting, drowsiness, digestive problems including abdominal discomfort and constipation, hyperglycaemia and increased blood sugar or risk of diabetes.¹⁵⁵ Although the proven benefits of statin treatment are widely acknowledged, important adverse effects associated with using statins include myopathy (defined as muscle pain or weakness) and diabetes.¹⁵⁶

Concerns reported in the media around statin use have the potential to negatively influence medication taking behaviour, with patients who are already taking statins more likely to stop them.¹⁵⁷ In qualitative interviews conducted with patients, general practitioners and cardiologists, researchers found that adverse coverage on statins was associated with an increased reluctance among healthcare providers to discuss and to prescribe statins and with lower adherence among patients due to increased awareness of the likelihood of side effects.¹⁵⁸ Failure to achieve cholesterol lowering goals through using statins may be

attributed to suboptimal medication taking behaviour as a result of interrupted medication intake or failure to persist with treatment.¹⁵⁹ In a survey study of side effects associated with taking statin, results showed that patients who were concerned about the adverse effects of statins were more likely to stop taking them.¹⁶⁰ A US survey investigating the role of side effects on statin use reported that 62% of former statin users cited side effects as the reason for stopping taking this medication.¹⁶¹

Nevertheless, evidence for the preventative effects of statins in stroke is strong. A meta-analysis of 42 trials demonstrated beneficial effects of statin therapy with a pooled relative risk (RR) of 0.84 for all-stroke prevention as well as a pooled relative risk (RR) for all-cause mortality of 0.88.¹⁶² Another meta-analysis of 18 trials in people at high risk for stroke found that compared with placebo, statins showed efficacy in reducing the overall incidence of stroke and had the potential to reduce the incidence of fatal and haemorrhagic stroke.¹⁶³

In a meta-analysis of 15 randomised trials to investigate the use of statins for primary and secondary prevention, results showed that statins significantly reduced the relative risk of non-fatal stroke (RR, 0.74, $p < 0.0001$), as well as total (fatal and non-fatal) stroke (RR, 0.77, $p < 0.001$).¹⁵⁴ Elsewhere, in a study quantifying the effects of statins on cholesterol for ischaemic heart disease and stroke, results showed that statins reduced LDL-C which reduces the risk of ischaemic heart disease (IHD) events by 60% and stroke by 17%.¹⁶⁴ An examination of the effect of statins on patients with high cardiovascular risk showed that adding simvastatin to current treatment resulted in substantial additional benefits including a significant reduction in all-cause mortality and first event rates for non-fatal myocardial infarction and for non-fatal or fatal stroke.¹³⁹

An investigation of 20,536 patients with cerebrovascular disease and other high risk conditions found a significant 25% reduction in the first event rate for ischaemic stroke in the treatment group compared to placebo, reflecting a definite 28% reduction in presumed ischaemic strokes ($p < 0.0001$), as well as a significant reduction in the number of patients reporting a transient ischaemic attack alone (2.0% vs 2.4%; $p = 0.02$).¹⁴⁹

The stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study a placebo controlled trial investigating cholesterol lowering with statins in 4731 patients for the prevention of stroke and TIA, found that an intensive cholesterol reduction in patients with

TIA or minor stroke reduced the risk of both fatal and non-fatal stroke in patients (n= 265 patients; 11.2%) receiving atorvastatin 80mg compared to placebo (n=311; 13.1%).¹⁴⁰

The benefits of cholesterol lowering therapies on reduction in stroke risk and mortality were demonstrated in a review reporting a significant reduction of 29% in the risk of stroke and 22% in total mortality which was attributable to a significant reduction of 28% in cardiovascular disease deaths.⁶⁵ A more intensive LDL-C lowering regimen with statins also produced a highly significant further reduction in major cardiovascular events (15%: 95% CI 11–18; p<0.0001) including a 16% reduction in ischaemic stroke.¹⁶⁵

1.2.2 Evidence for Anti-Hypertensives

High-blood pressure (hypertension) is the leading modifiable risk factor for both ischaemic and haemorrhagic stroke.^{166 167} It accounts for about 50% of all strokes that occur¹⁶⁸ and is associated with heightened risk of early stroke recurrence.¹⁶⁹ The burden of stroke associated with an elevated systolic blood pressure measurement of 110-115 mmHg and >140mmHg is considerable¹⁷⁰ with the risk of stroke in individuals aged 40-69 years doubling for an increase of 20 mmHg in systolic blood pressure.¹³⁷ Following diagnosis of a stroke or TIA, treatment for hypertension should be initiated promptly and may include thiazide diuretics, long acting calcium channel blockers (CBBs) angiotensin-converting enzyme inhibitor (ACE-inhibitor) or beta-blockers.⁷³

The role of blood pressure reducing medication on the prevention of cardiovascular disease is well known with regimens of different antihypertensive drug classes demonstrating risk reduction in total major cardiovascular events.¹⁷¹ In a Cochrane review of the literature on the use of blood pressure lowering tablets for preventing recurrent stroke in patients with a history of stroke or TIA, results showed that the pooled RR for the use of antihypertensives on recurrent stroke was 0.81 (95% confidence interval (CI) 0.70 to 0.93) and 0.90 for a major vascular event (95% CI 0.78 to 1.04), with the authors concluding that the use of blood pressure lowering drugs including ACE inhibitors and diuretics reduced the risk of recurrent stroke and TIA.¹⁷²

Treatment with anti-hypertensives is known to be associated with reduced risk of stroke, CVD events and all-cause mortality among patients with a clinical history of CVD.¹⁷³ With the introduction of antihypertensive therapy, treatment to lower BP should be monitored frequently and adjusted to achieve a target systolic blood pressure below 130 mmHg. ACE-

inhibitors have emerged as an important anti-hypertensive treatment for their role in vascular protection.^{174 175} In a study to investigate the protection from stroke with the use of ACE-inhibitors and CCBs, results showed that CCBs were superior to ACE-inhibitors as a preventative treatment for stroke.¹⁷⁶ In an investigation undertaken to determine the effect of ACE-inhibitor Ramipril for the secondary prevention of stroke, results of a randomised controlled trial conducted in 19 countries found that Ramipril reduced the relative risk of any stroke by 32% compared with placebo and the relative risk of fatal stroke by 61%, despite a modest reduction in blood pressure.¹⁷⁵

A study exploring routine care versus a standardised blood pressure lowering regimen reported a 44% reduction in fatal stroke as well as a 35% reduction in total stroke.¹⁷⁷ Elsewhere a population- based study assessing association between risk of stroke and poor adherence to blood pressure lowering medicines among hypertensives found that those who did not take antihypertension medication faced an almost four-fold increase in the risk of stroke occurring compared to patients who were adherent.¹⁷⁸ In a meta-analysis of 147 trials examining the use of blood pressure lowering drugs in the prevention of cardiovascular disease, results showed an approximate 35% reduction in the risk of stroke (RR 0.64) for a difference of 10 mm Hg for systolic blood pressure (SBP) , or 5 mm Hg for diastolic blood pressure (DBP).¹³⁸

Investigating blood pressure reduction on recurrent vascular events in stroke or TIA, results from a systematic review and meta regression showed that the use of anti-hypertensives led to a reduction in stroke, nonfatal stroke, myocardial infarction and total vascular events.¹⁴¹ In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial investigating a blood pressure lowering regimen among 6105 stroke individuals randomised to receive either placebo or antihypertensive therapy, the group receiving active antihypertensive Perindopril reduced blood pressure by 9/4 mmHg leading to a 28% lower risk of stroke over a 4 year period, independent of baseline blood pressure.¹⁷⁹ In this trial, the treatment of patients with two anti-hypertensives- an angiotensin-converting enzyme (ACE) inhibitor combined with a thiazide diuretic- was found to reduce stroke risk by 43%, with the authors concluding that the two agents should be considered for the routine treatment of patients with stroke or transient ischaemic attack, irrespective of whether they had high blood pressure.¹⁸⁰

Poor medication adherence is considered a main cause of uncontrolled hypertension with high adherence to antihypertensive medications known to be associated with long term reduction in acute cardiovascular events.¹⁸¹ Drug related side effects associated with taking anti-hypertensive medications include cough, dizziness, light-headedness, feeling tired or weak, headache, nausea or vomiting. Such adverse effects reduce adherence to anti-hypertensive medications. In one study of patients starting or restarting anti-hypertensives, and followed up at 3, 6, 9 and 12 months, 85% of participants were found to experience side effects and 34.5% of those became non adherent to the antihypertensive medication.¹⁸²

1.2.3 Evidence for antiplatelet and anticoagulant agents

Antiplatelet medication should be prescribed for the secondary prevention in people who have had a stroke or TIA. In people in whom brain imaging has discounted a diagnosis of primary intracerebral haemorrhage, the immediate introduction of 300 mg of aspirin has been recommended. The 300mg of aspirin should be continued for up to 2 weeks following symptom onset, after which long- term antithrombotic medication should be initiated.¹²⁹

The antiplatelet Clopidogrel is recommended for the prevention of ischaemic stroke or TIA, as an alternative to aspirin, with a guideline recommendation of 75mg daily.^{183 184} In cases where Clopidogrel is contraindicated or not tolerated, modified-release dipyridamole should be administered, 200 mg twice a day, and this should be combined with low dose aspirin.^{185 186} Aspirin 75 mg should be administered in cases where neither Clopidogrel nor Dipyridamole are tolerated.¹⁸³ Regarding antiplatelet treatment following a TIA, a combination of aspirin and modified-release (MR) dipyridamole are suggested as first line treatment when clopidogrel is contraindicated or not tolerated.^{183 187} In a meta-analysis of trials, Leonardi-Bee and colleagues reported that aspirin combined with dipyridamole was significantly more effective than aspirin alone in preventing major vascular events with the risk of recurrent stroke reduced when this combination was used (OR 0.78, CI 0.65-0.93).¹⁸⁸ The ESPRIT study examining the use of aspirin plus dipyridamole versus aspirin alone for the secondary prevention of stroke also reported support for the combined regimen in patients with a history of cerebrovascular disease.¹⁸⁹

In a meta-analysis of 24 studies and over 88,000 patients to evaluate anti-platelet agents for secondary prevention of stroke using a mixed treatment comparison, results showed that the combination of aspirin plus dipyridamole (DP) was more protective against recurrent stroke than aspirin alone (RR = 0.78; 95% CI, 0.64–0.93), that aspirin plus DP was

associated with more overall haemorrhagic events than DP alone (RR = 1.83;95% CI,1.17–2.81) while a combination of aspirin plus clopidogrel was associated with an excess of overall haemorrhagic events compared with only clopidogrel (RR ¼ 2.81;95%CI,1.96–4.10).¹⁹⁰ Another study found no evidence that aspirin plus extended-release dipyridamole was superior to clopidogrel in the prevention of recurrent stroke.¹⁹¹ A randomised controlled trial found that intensive antiplatelet therapy (combined aspirin 75 mg, clopidogrel 75 mg, and dipyridamole 200 mg twice daily) in adult patients with a stroke or TIA, did not reduce the incidence and severity of stroke compared with taking guideline therapy (either Clopidogrel alone or combined aspirin and dipyridamole) but was associated with an increased risk of major bleeding.¹⁹²

The benefits of antiplatelet therapy on stroke prevention have been widely documented in the literature. In a meta-analysis of 287 trials investigating anti-platelet therapy, aspirin was found to reduce non-fatal myocardial infarction by one third, non-fatal stroke by one quarter and vascular mortality by one sixth, demonstrating that low dose aspirin was an effective antiplatelet treatment in protecting most patients from increased risk of vascular events including stroke.¹⁹³ A Cochrane review assessed the efficacy and safety of immediate oral anti-platelet therapy in people with acute ischaemic stroke, reporting on eight trials of over 41,000 participants. Results showed that the daily administration of antiplatelet therapy with aspirin 160-300mg and started within 48 hours of the onset of ischaemic stroke led to a reduction in the risk of recurrence of ischaemic stroke, without any significant risk of haemorrhagic complications and improvement in long-term outcomes.¹⁹⁴ In another study conducted in UK primary care to evaluate the risk of stroke or a TIA in those patients prescribed low dose aspirin for the prevention of cardiovascular and cerebrovascular events, discontinuation of therapy was associated with a 40% increased risk in a stroke event occurring, compared with those who continued therapy.¹⁹⁵

For the prevention of strokes attributed to non-valvular Atrial Fibrillation (AF), anticoagulants such as warfarin have been the treatment of choice over the last 50 years.¹⁹⁶ An important risk factor for stroke^{66 197 198}, AF is characterised by a rapid and irregular heart rhythm that increases the risk of clots forming and blocking a blood vessel in the brain, which in turn increases the likelihood of a stroke occurring. The prescription of antiplatelet therapy as an alternative to anticoagulant therapy is not recommended in the treatment of cardioembolic stroke and a contraindication such as undiagnosed bleeding.⁷¹

In England and Wales more than one fifth of the 130,000 strokes that occur annually can be attributed to atrial fibrillation.¹⁹⁹ The risk of recurrent stroke in patients with AF is known to be considerable.²⁰⁰ In a retrospective cohort study of stroke survivors with atrial fibrillation, an investigation into rates of stroke recurrence and the effects of AF on stroke risk found AF was an independent risk factor for stroke recurrence across a wide age range.²⁰¹ Stroke prevention in patients with AF can often require different combinations of preventative treatment including antiplatelet agents in combination or singly, anticoagulants, and anticoagulants along with antiplatelet agents.²⁰²

Anticoagulant medications such as warfarin for the prevention of AF are designed to reduce the likelihood of blood clots forming, however, the use of warfarin, the most commonly prescribed anticoagulant, has limitations including the need for careful monitoring and adjustment, increased risk of bleeding, a narrow therapeutic window and heightened risk of drug-drug interactions.^{203 204} Taking warfarin for the prevention of atrial fibrillation (AF), itself a key risk factor for stroke, has been found to reduce the risk of stroke in elderly patients with AF²⁰⁵ and has demonstrated significant benefits in reducing the relative risk of recurrent stroke by about 70% in patients who have already had a stroke or a TIA.²⁰⁶

Although warfarin remains the most widely prescribed anticoagulant, a new class of anticoagulant drugs have emerged called novel oral anticoagulants or NOACs.²⁰³ NOACs require less monitoring, are associated with fewer drug-drug interactions, offer a wider therapeutic window and are considered more convenient to use.^{207 208} When compared with vitamin K antagonists, such as warfarin, NOACs have been shown to be as effective in preventing stroke and to present with fewer significant bleeding events.²⁰⁹ While NOACs offer the potential for improved compliance through easier administration, continued management of patients receiving anticoagulant therapy is needed, particularly in those patients where there is a risk of bleeding.²¹⁰

These newer alternative direct-acting oral anticoagulants include drugs such as rivaroxaban, dabigatran and apixaban,^{203 211} and the introduction of these new therapies for AF treatment have helped to overcome some of the limitations attributed to vitamin K antagonists.^{212 213} Such limitations include an increase in the risk of bleeding and the need for patients to be monitored continuously. In 2014 the National Institute for Health and Care Excellence (NICE) recommended that NOACs including dabigatran and rivaroxaban should be considered for the prevention of stroke and systemic embolism in patients with non-

valvular atrial fibrillation.²¹⁴ The use of NOACs has increased significantly since 2009 and in 2015 accounted for around 56% of oral anticoagulant prescriptions in UK primary care.²¹⁵ In a meta-analysis of randomised trials comparing the efficacy of NOACs with warfarin in patients with AF, NOACs had a favourable risk benefit profile when compared with warfarin with significant reduction in stroke and haemorrhage rate reported.²¹⁶

Elsewhere, results obtained from a systematic review and meta-analysis demonstrated that for NOACs, efficacy and safety are comparable with warfarin for the prevention of stroke in patients with nonvalvular atrial fibrillation.²¹⁷ In another meta-analysis NOACs were found to be superior to warfarin in the prevention of the composite of stroke and systemic embolism in patients with AF and an additional risk factor for stroke.²¹⁸ Although NOACs have some important advantages compared with traditional vitamin K antagonists such as warfarin, disadvantages including higher costs as well as the limited understanding of these emerging therapies as a preventative treatment for AF warrant further research to assess their efficacy in clinical trials. Studies to date have also demonstrated the potential for improved medication taking behaviour with NOACs with one investigation finding higher persistence among patients using NOACs compared with vitamin K antagonists such as warfarin, with the potential to lead to fewer cardioembolic strokes.²¹⁹

1.3 Under-treatment and suboptimal risk factor control

Despite the significant available evidence advocating the use of pharmacotherapies for the prevention of CVD and stroke, under-treatment remains a problem, with failure to administer treatment in line with guideline recommendations, inappropriate prescribing practices, poor adherence and failure to continue treatment resulting in poor medication taking practices. With medicines not being taken in a way that can provide optimum benefits to the user, treatment is not translating into improved patient outcomes. With around a quarter of all strokes representing a recurrent event, deficiencies in secondary prevention care are common.¹³³ Among patients with ischaemic stroke, successful risk factor control for the secondary prevention of vascular events was found to be suboptimal with one study reporting only 23.8% of patients successfully controlling hypertension and 13.6% having control over dyslipidaemia with the use of antithrombotic drugs for the treatment of AF the only objective that was achieved in 97.2% of ischaemic stroke patients.²²⁰ It has been suggested that as little as 10% of individuals who are known to have cardiovascular disease or are at risk of developing the disease, receive the treatment necessary to prevent future cardiovascular

events including strokes and myocardial infarction.²²¹ In an analysis of primary care records in the UK, researchers explored prescribing practices for primary prevention drugs for stroke and transient ischaemic attack. The investigation found that, 49% of patient were not prescribed lipid-lowering drugs, 52% were not prescribed anticoagulant drugs, and 25% were not prescribed antihypertensive drugs.²²² A UK study examining the use of antiplatelet drugs, blood pressure lowering drugs and statins for the prevention of cerebrovascular disease found that while their use had increased between 1999 and 2005, only 1/3 received all 3 medications and the use of combined blood pressure treatment was limited.²²³

An investigation of the EUROASPIRE III core survey identified greater need for improvement in secondary prevention and risk factor control, with 87%, 84% and 57% of stroke patients using antiplatelet, antihypertensive and statin medicines respectively, resulting in around half of the patients across four centres not receiving guideline therapy for stroke prevention.²²⁴

Despite the widespread availability of evidence based pharmacotherapies, a prospective investigation of patients with ischaemic stroke found remaining modifiable risk factors were widespread or highly prevalent at six months, suggesting that secondary prevention among stroke survivors is suboptimal and that strategies were needed to improve preventative measures following stroke.²²⁵

1.4 Medication adherence

Medication adherence is the cornerstone of disease prevention and is important for the prevention and treatment of chronic disease and illness and to achieve optimal health outcomes.²²⁶ Adherence to medication refers to the extent to which patients take their medication in line with the recommendation of their healthcare provider.²²⁷ The term medication compliance in health care was originally defined as being the extent to which a 'patient follows medical instructions or is 'compliant' with the recommendation of the provider for health and medical advice.²²⁸ Compliance is associated with acting in accordance with a request or direction, and is the extent to which the patient follows the recommendations of the provider. Although compliance has been used to describe medication taking behaviour, it suggests that that the patient complies with the recommendations provided by the health professional in respect of the timing, dosage and frequency of medication taking.²²⁹ Adherence and compliance are often thought of as being synonymous, however, use of the term 'compliance' to describe medication taking behaviour has been

increasingly questioned due to the patient's implied subservience to the health professional, with increased emphasis now being placed on understanding the patient's own perspectives associated with medication taking.^{230 231}

The term 'adherence' is now increasingly used as an alternative to compliance, with a greater focus placed on the patient and the healthcare professional as partners in the medication decision making process. With compliance not considered sufficiently inclusive to reflect the act of medication taking, a WHO meeting in 2003 produced a report called 'Adherence to Long Term Therapies- Evidence for action', which resulted in a new definition of 'adherence'.²²⁷ This was defined as:

'The extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'.

This shift towards a patient centred approach in respect of timing, dosage and the frequency of medication involved a focus on a collaborative effort and joint decision between the patient and healthcare provider.²²⁹ However, a lack of consistency in the terminology used in the research field has resulted in the term adherence being used interchangeably with compliance.²³² A third term, 'concordance', was introduced to address some of the concerns around compliance and implies that the patient and prescriber should come to an agreement regarding the regime the patient should take, taking into account the perspectives of both parties.²³¹ Originally conceived with a narrow focus on the consultation process between patient and practitioner, this term has developed into a wider concept, including prescribing communication and patient support.²³³

Medication persistence refers to the length of time between the first and last dose of medicine taken and reflects the act of continuing with medication for the prescribed duration of time, from the point of initiation until therapy is discontinued.²²⁹ Nonpersistence or discontinuing medication soon after initiating treatment is not uncommon but can have significant health consequences. In one study exploring medication taking in patients at high risk of cardiovascular disease, medication nonpersistence was associated with significant cardiovascular events including myocardial infarction, stroke, and cardiovascular death, with an increase in cardiovascular events reported when medications were stopped.²³⁴ The benefits of medication adherence are well known with one large scale study on the impact of medication adherence across a population based sample of 137,000 patients, showing that

higher medication adherence was associated with better health outcomes, leading to lower disease related costs and less risk of hospitalisation.²³⁵

1.4.1 Burden of nonadherence

It is widely accepted that patients who do not take their medication as intended do not achieve the intended therapeutic benefit of treatment. Across patient populations it has been estimated that 20-50% of individuals do not take medicines as prescribed.^{226 227} Failure to adhere to essential medication is associated with deteriorating health status, disease progression, increased morbidity and premature mortality.^{226 227 236 237} Suboptimal medication taking behaviour, including delays in initiating treatment, problematic adherence to medication recommendations and non-persistence with treatment over time, contributes to adverse patient outcomes.^{234 238} Poor adherence can result in worse health outcomes, suboptimal risk factor control and contributes to the increased cost of medical care.

Given the associated negative health consequences, inappropriate medication taking practices remain a formidable challenge for both patients and healthcare providers. The economic burden of medication nonadherence is also substantial, accounting for around \$100 billion annual spend in preventable costs in the USA alone, where around two thirds of medication hospitalisations are directly attributable to poor adherence.²²⁶ A 2010 report in the UK estimated £300 million to be the estimated figure of pharmaceutical waste including £90 million pounds of unused prescriptions retained in people's homes and £110 million returned to pharmacies over a period of a year.²³⁹

1.4.2 Adherence to medications for cardiovascular disease and stroke

Reduction in cardiovascular risk through the management of blood cholesterol and blood pressure levels can be achieved by following a relatively straightforward medication regimen. The success of treatment for the prevention of cardiovascular disease and stroke, however, is largely determined by the patient's adherence to medication. Improving adherence to medication therefore requires recognition of the scale of the problem that patients face, and implementation of deliverable interventions that are designed to improve daily medication taking behaviour.^{238 240} Even though secondary prevention strategies using lipid lowering therapies and antihypertensives are known to be effective in reducing the risk of cardiovascular events including stroke,^{145 241} these medications are not being taken as prescribed. Suboptimal adherence to medication for the prevention of cardiovascular disease

is common. A meta-analysis of 44 studies of 1.9 million people exploring adherence to cardiovascular medication found that around 60% of participants reported good adherence to medicines while around 9% of all CVD events were potentially attributable to poor adherence.²⁴² This investigation found that for cardiovascular patients, 41% taking antihypertensives, 46% on cholesterol lowering statins and 30% taking aspirin were not adherent to their medications.²⁴²

Although antihypertensive medicines have emerged as an important preventative treatment with clear benefits for blood pressure control and cardiovascular outcomes, nonadherence to this medication is problematic with one meta-analysis of 20 studies including 376,162 patients reporting an estimate of poor adherence of around 43% as measured by pharmacy refill data.²⁴³ In a retrospective cohort study of over 250,000 patients, almost 80% of incident users of antihypertensive monotherapy were found to be nonpersistent while approximately 56% were considered nonadherent with both nonadherence and nonpersistence lowest for beta-blockers at 77.6% and 55.2% respectively and highest for diuretics at 85.4% and 66.3% respectively, within a 2 year period.²⁴⁴ Patient adherence to medication in the long term is also known to be suboptimal with one study showing discontinuation highest among statin medication and ACE inhibitors (28%), but lowest for the use of aspirin (18%) within the first year of prescription.²⁴⁵

Suboptimal adherence to antihypertensive medication regardless of the type of drug was reported in another meta-analysis with mean adherence to medication ranging from 28% for anti-hypertensive beta blockers to 65% for angiotensin II receptor blockers.²⁴⁶

In a systematic review examining adherence and persistence to statin medication, the majority of adherence studies reported increased risk of CVD and mortality among non-adherent individuals and increased CVD (risk estimate 1.22 -1.67) and mortality (risk estimate 1.79-5.00) among non-persistent individuals.²⁴⁷ This evidence shows that medication adherence is problematic across patient populations as well as for different groups of cardiovascular medications.

A similar picture can be found for the use of secondary prevention medications after stroke or TIA. Despite the widely acknowledged benefits of pharmacotherapies for the prevention of stroke, the evidence for adherence to medication among stroke survivors is mixed with some studies reporting that secondary prevention therapies for stroke are stopped prematurely or are not being taken in a way that confers maximum effectiveness. While

evidence indicates that a reduction in SBP of 10-mm Hg is associated with a relative risk reduction in stroke of around one-third ²⁴⁸, adherence remains problematic with nonadherence to anti-hypertensives an important factor contributing to poor blood pressure control ²⁴⁹, itself an important risk factor for stroke.

In one study examining adherence to antihypertensive medications in patients with a recent ischaemic stroke, high adherence to antihypertensives reflected similarly high adherence among the use of statins as well as antiplatelet agents and was associated with a significant 23% decreased risk of nonvascular events compared with lower adherence.²⁵⁰ Nonadherence among other classes of secondary prevention medications for stroke has also been reported. An investigation of statin therapy among 631 stroke survivors found that, within 12 months of discharge from hospital, 38.9% had discontinued taking statins with multivariable analysis showing that discontinuation of statin therapy was also an independent risk factor of all cause 1 year mortality.²⁵¹ In an investigation of patients at high risk of stroke and taking antiplatelet therapy, median 1 year follow showed that among patients taking NOACs, adherence measured as proportion of days covered at $\geq 80\%$ was 47.5%, and 40.2% for patients on warfarin.²⁵² A study of stroke survivors in Sweden reported a progressive decline in the use of secondary prevention medications for stroke prescribed at discharge during the first 2 years, to around 74.2% for anti-hypertensives, 56.1% for statins, 63.7% for antiplatelet medicine and 45% for warfarin.²⁵³ There is further evidence that among large stroke populations the use of secondary prevention medicines among stroke patients is suboptimal.²⁵⁴

A study of secondary prevention medicines 1 year after stroke found that 86.6% were adherent while up to one third of patients discontinued secondary prevention with 12 months of being discharged from hospital.²⁵⁵ Another investigation of medication taking at three months hospital discharge found one quarter of stroke survivors reported discontinuing one or more of their prescribed secondary prevention medicines.²⁵⁶ An investigation into the use of and adherence to antihypertensive after a stroke event found adherence ranging from 62% to 76% at 1 year, while adherence was also low in those newly initiated antihypertensives, where high adherence was reported in only 58% of those taking diuretics and 66% on ACE-inhibitors.²⁵⁷ Good compliance was reported in a prospective evaluation of secondary prevention medication for stroke with 87.6% of patients still reported to be on anti-thrombotic medication at 1 year follow up.²⁵⁸ While there is significant evidence to suggest

that use of secondary prevention medication in stroke is suboptimal and that strategies are needed to address this.

Medication nonadherence among patients can occur at any time throughout the treatment process²⁵⁹ with individuals known to not collect their prescription on time, delay starting treatment or not commence treatment at all, while medicines may be used incorrectly, at the wrong time or irregularly, resulting in preventative treatment ceasing prematurely. In a study examining what secondary prevention medications were obtained by patients following a stroke or TIA, results showed that 87% of stroke and 83% of TIA patients purchased antiplatelet agents including warfarin, 74% of stroke and 70% of TIA patient purchased blood pressure lowering medicines while 41% of stroke patients and 39% of patients diagnosed with TIA purchased lipid lowering therapies.²⁵⁴

Multiple factors associated with adherence to medication have been identified and these may be broadly defined as intentional or unintentional.^{260 261} Intentional nonadherence, largely associated with motivation, refers to the deliberate action or decision not to take medication and describes a situation where the patient consciously chooses to not follow the recommendation of the healthcare professional through actively altering or ceasing medication taking.²⁶² Patients may become concerned about side effects and have concerns around the perceived benefits of taking medication, or concerns around medication dependency. Unintentional nonadherence on the other hand is associated with a lack of capacity or resources to take medicines and is characterised by a passive approach as a result of forgetting, not knowing how medicines should be taken, or failing to follow instructions on treatment due to a lack of understanding or physical inability.²⁶²

Intentional nonadherence is known to occur among older people taking medicines for chronic disease.²⁶³ Stroke survivors unable to take medication as prescribed as a result of stroke may require the support of family members or caregivers to take tablets. Addressing both intentional and unintentional adherence among dependent stroke survivors from the perspective of the patient as well as the caregiver may be important.²⁶⁴

1.4.3 Factors predicting adherence to medication

Multiple reasons why patients do not take prescribed medication have been reported including factors categorised as patient focused, related to the practitioner or associated with the treatment itself.^{265 266 227 266} Patient centred factors contributing to nonadherence include

poor understanding of treatment, changes to drug regimen, lack of support to take medications, forgetfulness, a reduction of symptoms and limited access to using medications.²⁶⁷ Other factors identified include complex treatment regimens and dosing frequency,²²⁶ adverse drug effects and the patient provider relationship²⁶⁸, polypharmacy (the concurrent use of multiple medications by a patient), the cost of medication and drug tolerability.²⁶⁹ Poor health literacy inadequate communication and forgetting²⁷⁰ have also been reported. Patient beliefs about medication such as perceived concern and benefits of medication have been identified as factors predicting adherence among stroke survivors,^{271 272} while therapeutic complexity involving multiple medications and a frequent daily dosing schedule had a negative impact on medication adherence.²⁷³ A review of published systematic reviews of the factors associated with adherence to medications for CVD, identified key modifiable and non-modifiable risk factors across five main domains (disease, therapy, healthcare, patient and social factors) that were related to nonadherence and which may contribute to poorer clinical outcomes.²⁷⁴ Important factors identified included medication side effects, differing levels of adherence across drug classes, dosing regimen and frequency and communication and the practitioner relationship.²⁷⁴

Studies have also identified factors predicting adherence and persistence to stroke medicines including age and stroke severity²⁵⁸, being prescribed fewer medicines, having an appointment with the health care provider, understanding the reason for medicines being prescribed and the role of side effects.²⁵⁵ On the other hand being younger increased concerns about medicine and low perceived benefit was associated with nonadherence to medication among stroke survivors.²⁷¹ A systematic review and meta-analysis exploring secondary prevention medicine taking following stroke or TIA reported medication nonadherence across included studies to be 30.9% (95% CI 26.8%–35.3%).^{275 276} In this meta-analysis of the literature examining factors predictive of nonadherence to secondary prevention medication following a stroke, concerns about treatment regimen, polypharmacy and complex medication regimens were frequently reported to affect medication adherence among stroke survivors.²⁷⁶ This systematic review investigated patient related factors, social and economic related factors, therapy related factors, health system related factors and condition related factors, previously classified by the WHO²²⁷ as being predictive of nonadherence. The findings highlighted important areas of medication taking behaviour which could be used to inform strategies to improve adherence to secondary prevention medication in stroke.²⁷⁶

Ethnicity has been identified as a factor contributing to medication nonadherence. In an early study of the Black Caribbean population in the UK, patients using treatment to control hypertension reported that ‘leaving off’ medication, and using traditional therapies were important factors in the management of hypertension.²⁷⁷ Within ethnic minority groups older people are known to experience poorer health outcomes²⁷⁸, while lack of information, problems with not taking medication as advised, lack of monitoring, risk of adverse drug reactions and difficulties accessing healthcare services have been identified as medication related problems experienced by ethnic minority groups in the UK.²⁷⁹ In a semi-structured interview study of matched White and African-Caribbean patients attending 15 GP practices in inner London examining beliefs around the use of drugs prescribed for hypertension, adherence was found to be high among Whites but that less than half of the sample of Afro-Caribbeans patients took their medications regularly, with nonadherence influenced by traditional beliefs and practices.²⁸⁰ Evidence of a lack of communication between ethnic minority groups and their health care practitioners was also reported.²⁸⁰ Another investigation of self-care and adherence to medication in a multi-ethnic hypertension outpatient clinic in the UK reported that White British patients were significantly more likely to be perfectly adherent to anti-hypertensive medications compared to all other ethnicities (67.1% v 32.9%, $p < 0.00$), while results from a logistic regression found that being in an ethnic minority group predicted lower adherence (OR 0.31, (95% CI 0.14, 0.72)).²⁸¹

Polypharmacy, often defined as the use of five or more therapeutic agents at the same time, presents an important challenge for cardiovascular patients.^{282 283} With people now living to an older age and increasingly likely to experience multimorbidity, greater numbers of medicines are needed to meet the challenges they face. For cardiovascular patients in particular, multimorbidity presents an important burden.²⁸⁴ In one study investigating the prevalence of chronic conditions, researchers found that although the incidence of ischaemic heart disease and stroke fell by 34% in the 14 years prior to 2014, the proportion of patients with cardiovascular disease who had a higher number of comorbidities, increased substantially.²⁸⁵

The need for multiple medicines as a result of comorbidities is not uncommon among stroke survivors.^{286 287} A study in Scottish primary care investigating the use of multiple medications found that almost 20% of adults assessed were taking four to nine medications, with 4.6% taking 10 or more medication.²⁸⁸ In another investigation in Italy, the number of admission medications and cardiovascular conditions in patients was independently

associated with polypharmacy at hospital discharge.²⁸⁹ Polypharmacy is known to be associated with an increased risk of adverse drug reactions,^{290 291} while the use of multiple therapeutic agents has also been linked with inappropriate use of medicines and reduced medication adherence.²⁸²

Factors associated with medication regimen can also impact adherence to preventative therapies. In a review of the literature on medication taking behaviour across chronic conditions including cardiovascular disease, dose frequency and complexity of medication regimen were associated with suboptimal medication adherence.²⁹² In a study investigating adherence to medication for cardiovascular disease, with most participants on a once daily or twice daily regimen, adherence was inversely correlated to the number of doses per day, in that increased dosing was associated with poorer adherence.²⁹³

In a study of adherence to anticoagulants among patients with stroke, those patients who were fully adherent were more likely to take more medication daily (median 7 vs 6, $p=0.039$), received caregiver assisted medication administration (54.2 vs. 19.1%, $p < 0.001$) had more functional dependence (32.8 vs. 15%, $p = 0.011$) and were more familiar with taking antithrombotic medication previously (70.8 vs. 53.2%, $p = 0.023$) than those patients who were not fully adherent.²⁹⁴

In a further examination of the literature, AlShaikh and colleagues (2016) investigated the efficacy of interventions to improve adherence to secondary prevention medications following a stroke.²⁷⁵ Results from this systematic review and meta-analysis showed that interventions targeting risk factor control and encouraging self-care among stroke survivors resulted in high continuation of secondary prevention medications, while interventions with an education element increased awareness of prescribed medications among stroke survivors.²⁷⁵ The authors of the review found that those interventions that involved modification or simplification of the medication regime of the patient, provided reminders, and used medication dosette boxes were effective in maintaining use of secondary prevention therapies. This review demonstrated that while many interventions existed and were able to maintain current therapies for secondary prevention, further research was needed to determine what type of interventions were needed to enhance adherence to secondary prevention medications after stroke.²⁷⁵

Information provision and patient knowledge are considered important intervention components designed to improve adherence to medication.²⁹⁵ However, effective

interventions to improve medication adherence are known to benefit most from an approach consisting of several different proven strategies.²⁹⁶ Knowledge and information of the condition and medication can contribute to the patients' understanding of medication taking including what their medications are and why they are taking them, strategies they should follow to take medicine and the importance of medication adherence on future health. An investigation on the provision of an education support package to stroke survivors found better self-efficacy for accessing stroke information in the intervention group with intervention participants reporting being informed and more satisfied with the information received.²⁹⁷ Healthcare professionals may have a role to play in facilitating effective medication taking practices among patient groups, through direct communication and providing information on medication taking behaviour. A multi-national investigation exploring the management of medication adherence among patients by their healthcare professionals reported a missed opportunity among surveyed doctors, nurses and pharmacists to identify medication nonadherence in routine clinical practice, with pharmacists persistently reporting that they intervened less than both doctors or nurses to support patients with their medication taking behaviour.²⁹⁸ The authors concluded that an assessment to identify the extent of medication adherence is needed to support medication taking in long-term conditions.²⁹⁸

Interventions that have been found to be effective in improving medication adherence in patients have consisted of combinations of strategies, including information provision and counselling,²⁹⁹ with a lack of knowledge or understanding around medication (with regard to new medication for example) known to be associated with poor adherence.²⁶⁶ and an inability to recall medication instructions provided by the healthcare professional known to contribute to suboptimal medication taking behaviour.²⁶⁵

To date, interventions to improve adherence to medications have met with some success however adherence to treatment is a complex behaviour in which multifactorial strategies are needed to improve medication taking behaviour.^{238 300} The pervasiveness of suboptimal adherence to preventative medication has resulted in a greater emphasis on the need to understand the reasons why patients do not take medications as prescribed and to develop strategies and effective interventions that can be used to address the challenges of medication taking that they face.^{301 238}

1.4.4 Theories of medication adherence

With interventions to increase medication adherence reporting limited success to date, efforts to improve adherence have become a key focus for both researchers and healthcare practitioners alike.²²⁷ While multiple modifiable patient, medication and system related factors are known to predict medication adherence,²²⁷ there is a growing emphasis on understanding the psychological determinants of behaviour and the techniques of behavioural change that are likely to influence each one.³⁰²⁻³⁰⁴ Having a better understanding of potentially modifiable psychological determinants can help to inform the development of interventions that may be used to predict and explain nonadherence to medication among patient groups.

Considerable progress has been made towards understanding the role of psychological theory and its influence on behaviour, including medication adherence, with the emergence of a number of health psychology theories and theoretical frameworks.³⁰⁵ Although psychological theories have been beneficial in helping researchers to explore and understand a range of health behaviours^{306 307} including medication adherence,³⁰⁸ challenges remain in addressing key theoretical, methodological and intervention issues related to understanding medication adherence.³⁰⁹

A systematic review of the evidence for health psychology theories on predicting adherence to medication found support for theory constructs including self-efficacy, perceived barriers, medication concerns and necessity beliefs, suggesting that psychological theories are useful for predicting adherence to medication and can provide a platform for the development of effective interventions designed to enhance medication adherence.³⁰⁸

Many theories have been developed to understand psychological influences on behaviour and to explain variations in medication adherence. The theoretical models most widely used to understand and predict adherence to medication include social cognition models such as the Theory of Planned Behaviour (TPB)³¹⁰, the Theory of Reasoned Action (TRA)³¹¹ Health Belief Model (HBM)^{312 313} as well as social cognitive theory³¹⁴ and Leventhal's self-regulatory model (SRM) of illness.^{315 316}

An investigation of the use of theory in medication adherence identified the HBM, SRM and the Transtheoretical Model (TTM) as the theories most often linked with

Medication adherence, with results from the meta-analysis showing that theory-based interventions had a modest yet significant effect on medication adherence outcomes.³¹⁷

The TPB posits that a person's behaviour can be predicted by their intention to perform that behaviour and that intention is influenced by key constructs, including attitudes, subjective norm and perceived behavioural control.³¹⁰ Support for the theory of planned behaviour in adherence has been reported for antihypertensive medication.³¹⁸ In a meta-analysis of studies examining the role of the theory of planned behaviour in the development of interventions to improve medication adherence in chronic illness, results showed that the theory explained 33% of the variance in intention and 9% of the variance in adherence behaviour while theory constructs of attitude, subjective norm and perceived behavioural controlled were significant predictors of adherence intention, and intention significantly predicted adherence behaviour.³¹⁹ Elsewhere, a systematic review of applications of the TPB to behaviour change interventions including medication taking, concluded that although the theory had potential to explain behaviour, further work was needed to compare the theory with other social cognition models.³²⁰

Through the use of social cognition models, patient beliefs around medication have been studied in an effort to better understand adherence behaviour. The HBM has been used to predict health behaviours including medication adherence. This social cognition model posits that individuals assess whether the benefits of behaviour change outweigh the practical or psychological costs associated with it, based on four aspects - perceived severity of ill-health, perceived susceptibility to ill-health (risk perception), perceived barriers to taking action and perceived benefits of behaviour change. Therefore, with regards to medication adherence, if a person believes they are at risk of a specific condition, that there could be serious consequences, that taking medication would reduce the probability of the condition and that the benefit of medication outweigh the costs of taking the medication, then the likelihood of taking the medication may be increased. In a systematic review of 18 studies evaluating the effectiveness of HBM interventions in improving adherence, results found that 78% showed an improvement in adherence and 39% showed moderate to large effects.³²¹

The self-regulatory model of illness perceptions developed by Leventhal and colleagues was proposed as a way of conceptualising the adherence process and assessing beliefs related to health and illness and how these influence medication taking behaviour.³²² This theory posits that if an individual perceives that advice on taking medication makes

‘sense’ with regards to their own experiences (i.e. current symptoms or previous illness) as well as the beliefs they hold about the illness, then the likelihood of being adherent to medication is increased.³²² The self-regulatory model has shown promise in assessing patients’ health beliefs and has been applied to medication adherence across different conditions including diabetes³²³ and hypertension³²⁴ as well as chronic illness.^{325 326} This theory emphasises that patients’ illness representations and perception of treatment influence medication adherence.³²⁷ Patient beliefs about their illness are known to influence subsequent health behaviour outcomes³²⁸ and understanding day to day management of illness or disease may be improved through a better understanding of patients’ perceptions of illness.³²⁹ The Illness perceptions Questionnaire (IPQ) was developed to better understand people’s perceptions about illness and to develop effective interventions to facilitate disease self-management.³³⁰

Examining and understanding patients’ beliefs about their illness as well as beliefs about their treatment, namely medicine taking, has been a particular focus of research to understand decisions around medication adherence.³²⁵ It is well known that the beliefs of patients and their attitudes towards taking medicines have an influence on treatment adherence.³²⁵ For example, people who have strong beliefs about the need to take medication to improve their health are more adherent to medication, whereas those who have greater concerns about medicines such as the role of side effects or long term dependency are more likely to be nonadherent.³²⁵

Research on patients with a variety of conditions suggests that beliefs that influence evaluations of medications can be characterised under two core themes- beliefs about the *necessity* of prescribed medicines and perceptions of the condition as well as symptom expectations and experience, and *concerns* around the potential adverse effects of taking medicines and their disruptive effect on daily life.^{325 331} This understanding has informed the Necessity-Concerns framework (NCF)²⁷² which has been used to address key beliefs underpinning patients’ attitudes about medication and decisions around the treatment they use. A meta-analytic review of the necessity-concerns framework in understanding adherence related beliefs about medicines for long-term conditions identified 94 studies which showed that higher adherence was associated with a stronger perception of necessity of treatment and fewer treatment concerns, across country, study size and type of adherence measure used.²⁷² The authors concluded that the framework was a useful model for understanding patients

perspectives around medications and that taking account of their concerns and beliefs could contribute to engagement in treatment decisions and support adherence to medicines.

Both the HBM and the SRM suggest that when deciding to take medicines, people undertake a cost-benefit assessment, and consider whether their beliefs about the need for medicines outweigh the concerns they have around taking medicines, such as the impact of side effects. Within the literature, necessity beliefs and concerns about medication have been quantified using the validated Beliefs about Medicines Questionnaire (BMQ), a new method for assessing and understanding cognitive representations of medication.³³²

In a study designed to assess the role of patient beliefs on adherence to medication for hypertension, patients who believed in the necessity of medication were more likely to be compliant to the treatment, while the emotional response to illness and beliefs about the ability to control illness were also important predictive factors of adherence.³³³ The study authors further concluded that beliefs about illness had an important role to play in adherence and had the potential to be a target for interventions to improve medication adherence.³³³

A systematic review of observational studies of stroke survivors set out to understand determinants of medication adherence by mapping determinants of interventions onto the theoretical domains framework (TDF) to provide a more enhanced understanding of medication adherence behaviour.³³⁴ The TDF was developed by behavioural scientists who sought to identify constructs from major psychological theories that could be used to develop domains which together would form a theoretical framework that could be used to better understand the influences that affect behaviour.^{335 336} The review identified key determinants which were mapped onto the framework to enable better understanding of how these determinants influence adherence to medication, which included 'Emotions', 'Knowledge' and 'Beliefs about consequences of Medications'. Understanding modifiable determinants of adherence to medication can help to facilitate the development of interventions designed to change important health behaviours such as medication taking.³³⁴

1.4.5 Interventions to improve adherence

At a meeting of the World Health Organisation²²⁷ researchers exploring adherence to medication highlighted the comment made by Haynes and colleagues in their research on adherence interventions in which they stated that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any

improvement in specific medical treatments”. It has been argued that the improvement of adherence to medications may be more effective in increasing health benefits and improving health outcomes among patients than any improvement in medical treatment itself.²²⁷ Efforts to understand the role of adherence have led to a greater focus on the development of interventions designed to address this complex healthcare concern.^{226 337}

Easily delivered interventions have demonstrated potential in improving adherence for short-term treatments, while innovative approaches have been suggested to help patients to take their medications for long-term conditions.³⁰⁰ In a Cochrane review on medication adherence, investigators concluded that improving adherence to long-term chronic illness required multifaceted interventions consisting of follow-up procedures and educational components.³³⁸ A systematic review of the literature on medication adherence consisting of 771 intervention studies with medication adherence as an outcome concluded that although interventions improved adherence more research was needed, that behavioural interventions were most effective and that delivering face to face interventions had the potential to improve adherence.³³⁹ A review of systematic reviews on adherence to medical treatment identified 38 systematic reviews, reporting effectiveness of adherence interventions across four approaches: technical, behavioural, educational and multi-faceted or complex interventions.³⁴⁰ This review of reviews found that there were effective interventions with theoretical explanations of the mechanisms which stemmed from behavioural theories, but that interventions were complex and further work was needed to assess the effective components of interventions to improve adherence.³⁴⁰

A systematic review on interventions to enhance medication adherence in chronic medical conditions found that reducing dosing demands and providing monitoring and feedback were closely associated with increased adherence in patients.²⁹⁶

In a UK- based randomised controlled trial to improve medication adherence among stroke survivors receiving a brief intervention consisting of a plan linking medicine taking to environmental cues as well as modifying mistaken patient beliefs about medication, the intervention improved adherence with 10% more doses taken on schedule for the intervention group compared to the control group.³⁴¹ A study examining adherence among stroke patients following a pharmacist delivered intervention offering detailed information about medications, found significant differences between the intervention and control group for adherence to antithrombotic drugs (83.8% v 91.9%) and statin therapy (69.8% v 87.7%).³⁴²

Nevertheless, a systematic review of stroke interventions involving 10,292 patients over 18 studies, found that only five of the 18 studies (28%), three using cognitive behavioural interventions and two using an educational based intervention, showed statistically significant results, concluding that most interventions for stroke showed no statistically significant improvement in adherence.³⁴³ Another review exploring self-management interventions in stroke found that these were effective in improving short term adherence to stroke medicines, but benefits were not maintained in the long term.³⁴⁴

Lawrence and colleagues (2015) conducting a systematic review and meta-analysis of secondary prevention behavioural interventions for stroke and TIA identified some benefits for the use of multi-modal interventions on medication taking including a significant difference in adherence for patients taking antithrombotic and statin medication; however, no significant difference was found for adherence to antihypertensives.³⁴⁵

The lack of evidence in support of medication adherence suggests that robust and well-designed interventions to improve adherence to medication among stroke survivors are needed. An update of a Cochrane Review reported that current methods to improve adherence to medication in chronic health problems had limited effectiveness with suboptimal adherence to medication resulting in poor health prognosis, ineffective treatment and poorer long term outcome.^{300 338} The authors of that review concluded that innovative strategies were urgently needed to assist patients to meet medication requirements and to follow prescriptions for long-term medical conditions. Elsewhere a review of interventions to enhance patient adherence to medication prescriptions found that current methods were complex in their design and not predictably effective with only 49% resulting in a statistically significant increase in medication adherence.³⁴⁶ Medication nonadherence is a multifaceted healthcare concern. With multiple factors predicting adherence and multiple barriers to medication adherence identified across the literature, bringing into question the suitability of a “one size fits all” approach to addressing the adherence problem, patients may benefit from the development of interventions that are tailored to the cause of adherence and to the needs of the specific patient group.³⁴⁷

1.5 The role of the caregiver in medication taking behaviour

Caregivers, such as family members or unpaid care providers are playing an increasing role in providing support to patients with multiple chronic conditions who require help with managing complex medication regimens.^{264 348} As patients get older, physical or cognitive impairments become more prevalent, impacting on their ability to function independently and increasing their dependence on others. A significant proportion of patients with chronic disease also have multiple co-morbidities that require treatment with a large number of preventative medications. Furthermore, they may be disabled and therefore less likely to be able to manage their own treatment or take their medication effectively. As a result, the role of the caregiver has become increasingly important in the management of chronic disease. Research shows that informal carers such as family members play a role in medication taking activities including ordering medicines and ensuring medicines are being taken.³⁴⁹ Informal caregivers are uniquely placed to assist with patient medication taking practices. Caregiving duties related to health care provision are known to include health monitoring, managing the patient's medications and maintaining patient relationships with a healthcare provider. Nevertheless, caregivers have reported difficulties with administering medicines across a variety of health conditions.³⁵⁰

In England alone there are thought to be around 5.4 million caregivers, who provide care for another family member or friend.³⁵¹ Caregivers are thought to contribute around £132 billion a year to the UK economy.³⁵² More than half of stroke survivors are left dependent on others, such as caregivers.³⁵³ Survivors of stroke report unmet needs in many everyday activities.³⁵⁴

There is a growing awareness of caregiver participation in long-term stroke management and they are thought to play a key role in patients' medication taking activities, however, the precise role of unpaid caregivers in the management of stroke medication has not been widely explored. Involving the caregiver and the wider family in medication related activities and decisions among stroke survivors who are physically impaired could lead to better medication related outcomes.³⁵⁵

Caregivers have identified significant needs of the stroke survivor, including concerns around administrations of medication.³⁵⁶ With around two thirds of survivors who leave hospital known to have a disability³² and therefore requiring assistance with post-stroke care,

the caregiver may have a considerable role to play in the medication taking activities of stroke survivors.

To date, stroke research has largely focused on those patients who are independently capable of managing their own medication schedules. As a result, less is known about those patients who need help with medication activities, such as those stroke survivors who are disabled and whose needs may be less well known. Some stroke survivors are faced with communication difficulties, experience difficulties swallowing and have problems with memory and thinking³⁵⁷ which have the potential to contribute to poor medication taking behaviour. Understanding the role of informal caregivers in the medication activities of stroke survivors can help to inform the development of interventions aimed at improving the medication taking behaviour of this patient group in the future.

1.6 A strategy for cardiovascular medication taking: fixed-dose combination polypill

Fixed dose combination (FDC) therapy for the treatment of cardiovascular disease (CVD) first received attention at the beginning of the last decade when a scientific meeting convened by the World Health Organisation (WHO) set out to address the growing burden of non-communicable disease in low to middle income countries.³⁵⁸ This meeting became the early inspiration for a unique treatment approach for the prevention of CVD which proposed the combination of several separate medications into a single component pill. Inappropriate medication use, under prescription, low adherence and side effects associated with polypharmacy have increased the calls for an alternative combination therapy for the prevention of cardiovascular disease.

Evidence for fixed-dose combination treatment improving compliance with chronic disease medication has been reported previously with one meta-analysis of 68 studies consisting of 11,925 patients showing that FDC therapy led to a 26% reduction in noncompliance overall.³⁵⁹ In another meta-analysis the use of FDC's of antihypertensive agents was associated with significantly better compliance compared with the use of the free drug combinations (OR: 1.21 [95%CI: 1.03 TO 1.43]: P=0.02) and also nonsignificant benefits in systolic and diastolic blood pressure of 4.1 mmHg and 3.1 mmHg , respectively.³⁶⁰

1.6.1 A Polypill approach

The term 'polypill' was first coined by Wald and Law in their seminal article published in the British Medical Journal-“a strategy to reduce cardiovascular disease by more than 80%’ This

radical population based strategy envisaged treating everyone over the age of 55 with a single pill consisting of six individual components without the need for assessing risk factors including blood pressure or cholesterol levels.³⁶¹ The authors identified age as the only discriminatory factor on the basis that risk of CVD events increases with age. They further claimed that administering this single polypill irrespective of risk status had the potential to reduce blood pressure, levels of LDL-C and decrease cardiovascular events including ischaemic heart disease and stroke by 88% and 80%, respectively.

Over the last decade the focus of research on polypills has moved on from the population approach posited by Wald and Law. A growing body of research has now emerged in support of a fixed-dose combination polypill approach for primary and secondary prevention of cardiovascular disease.^{362 363 364 365} Comprising a single pill of multiple components of proven efficacy, a fixed dose combination polypill consists of aspirin and antihypertensive with or without statin, designed to treat modifiable CVD risk factors including high blood pressure and high cholesterol. By reducing pill burden leading to improved medication adherence, a polypill strategy for the prevention of cardiovascular disease aims to improve risk factor control and potentially lower the likelihood of a future cardiovascular event through the delivery of a cost effective medication intervention.³⁶⁶

1.6.2 A fixed dose combination polypill for primary prevention

A meta-analysis of polypill trials reported that fixed-dose combination therapy was both feasible and tolerable and improved risk factor control including blood pressure and lipid levels in patients at low risk of CVD.³⁶⁷ A series of trials for primary prevention have demonstrated that a cardiovascular polypill is well tolerated and associated with significant risk factor reduction. In the India Polycap Study, users reported no serious adverse effects and polycap led to reductions in cholesterol and blood pressure that would broadly be anticipated from using the combined agents separately.³⁶⁸ Elsewhere, another trial reported significant but modest reductions in SBP, DBP and LDL-C in the polypill group compared to the control group with a polypill well tolerated and few significant adverse events reported.³⁶⁹ Significant reductions were reported with SBP reduced by 9.9mmHg (95% CI: 7.7-12.1; $P < 0.001$) and LDL-C reduced by an average of 0.8mmol/L (95% CI: 0.6-0.9; $P < 0.001$) in the group receiving a polypill compared with the placebo group, translating to an estimated 60% reduction in both coronary heart disease (CHD) and ischaemic stroke.³⁷⁰ A placebo controlled

crossover trial demonstrated significant reductions in cardiovascular risk including SBP, DBP and LDL-C for the polypill group compared to the placebo group.³⁷¹

1.6.3 A fixed-dose combination polypill for secondary prevention

Support for a polypill for secondary prevention has grown out of concerns towards this treatment approach for primary prevention.³⁷² With proven cardiovascular therapies not being prescribed to all who may benefit and nonadherence to medication a growing problem, a fixed-dose combination polypill for secondary prevention has received increased attention.³⁷³

In a meta-analysis of polypill trials, significant improvement in medication taking, SBP and LDL-C levels, were reported among patients on a polypill compared to those on standard care.^{374 375} Trials of fixed-dose combination polypill for secondary prevention have demonstrated that a polypill has the potential to significantly improve adherence to medication in the primary care setting among patients with cardiovascular disease including stroke.³⁷⁶⁻³⁷⁸

1.6.4 Perceived advantages and disadvantages of the polypill approach

The polypill approach advocated by Wald and Law has provoked debate due to concerns around its true efficacy, potential for adverse effects in healthy individuals and the ethical implications surrounding medicalisation of a large proportion of the population^{379 380},

Detractors of the polypill have further argued that treatment is not conducive to medication titration, there is a lack of evidence on reduced mortality, a risk of users viewing the polypill as a ‘silver bullet’ replacement for other health behaviours.^{362 381} Uncertainty over composition, compatibility of components and the potential cost have been highlighted^{364 373} as well as the loss of benefits in all medications if one component is discontinued.³⁸² Concerns around this treatment approach have led to the suggestion that a polypill should be part of a wider strategy of CVD prevention to be used in conjunction with a healthy lifestyle.^{362 383}

1.6.5 Attitudes towards a polypill

Acceptability of a polypill approach for secondary prevention is likely to be considered as part of any decision to implement a polypill approach in the future.³⁶² The attitudes of patients and health care professionals towards a theoretical polypill have been reported in series of qualitative and quantitative investigations. In a study of UK patients’

attitudes³⁸⁴, greater convenience and likelihood of improved adherence were highlighted, while concerns around inflexibility in adjusting dosage and ingredients, potential side effects, pill size and consequences of missing a polypill were reported. Greater convenience with a more simplified regimen, treatment safety due to less confusion, and reduced pill burden were reported in another study, however the potential efficacy of treatment, lack of published evidence and equivalence with current care, likely adverse effects, stability of medications and inflexibility of dosage, also raised concerns among cardiovascular patients.³⁸⁵

A number of concerns including difficulties identifying responsible components, prescribing a polypill alongside existing medical conditions, inability to titrate medication dosage, lack of evidence for effectiveness and side effects were expressed by GPs in a UK study in primary care study.³⁸⁶ GPs also supported regular monitoring and a preference for a secondary prevention polypill and suggested that the indication of risk, cost, ability to monitor, reassurance around safety and effectiveness as well patient support would ultimately influence their decision to prescribe a polypill.³⁸⁶ In a study investigating the views of physicians who prescribed a polypill to patients with no known CVD, almost half (49.1%) said the degree of CVD risk reduction was the most important factor in determining their decision to prescribe with only 13.8% and 6.9% saying they wouldn't prescribe it for primary and secondary prevention, respectively.³⁸⁷ A survey among US healthcare professionals, reported cost, degree of CVD event risk reduction and side effects as the most important factors associated with a polypill. 41% said they would 'definitely' prescribe a polypill and an equal number said they 'probably' would if it was found to halve the risk of cardiovascular events.³⁸⁸

A study of pharmacists identified reduced confusion around generic medicines and the practice of substituting brands, simplifying explanations on side effects, improving compliance, and reducing CVD burden, as important advantages of a polypill. However perceived efficacy and safety, inability to titrate doses, difficulty identifying components responsible for side effects and fears that a 'cheap' polypill could jeopardise pharmacy profits raised concerns. Evidence of clinical efficacy and polypill safety were needed with a polypill approach thought to suit patients on stabilised medication regimens only.³⁸⁹

Additionally, attitudes towards a real world polypill have also been highlighted with practitioners reporting inflexibility, identification of components causing side effects and suitability of a polypill for those on a complex treatment plan as important concerns.³⁹⁰ In

light of the inflexibility of a polypill and its low dosage form, practitioners also considered polypill more suited to high risk primary prevention patients with stabilised treatment and patients with a high disease burden for CVD.³⁹¹

In another trial in primary care, participants felt that better medication adherence favoured the polypill approach, convenience of a simplified regimen was associated with better adherence and among competent adherers polypill made adherence easier. Polypill convenience was attributed to lower frequency of pill taking and needing fewer pills. Although health professionals within the trial anticipated improved adherence with a polypill, inflexibility of treatment was a concern.³⁹⁰ Elsewhere 53% of polypill patients found taking medication ‘very easy’ compared with 46% in the usual care group, while GPs described FDC as either satisfactory or very satisfactory for beginning treatment (91%) and regarding tolerability (81%) and considered better adherence the greatest advantage (57%) and inflexibility the greatest disadvantage (37%) of the polypill approach.³⁷⁷

1.6.6 Further research exploring patients’ and practitioners’ attitudes to Polypill

Acceptability of a cardiovascular polypill by patients as well as endorsement and uptake by health care professionals and other health bodies is likely to be important to implementing this treatment approach in the future.³⁹² Research on a polypill has demonstrated that this treatment approach has a number of strengths and limitations.³⁹³ While studies to date have predominantly focused on the acceptability of a polypill among cardiovascular patients and healthcare providers, attitudes towards a polypill approach for secondary stroke prevention have not been examined previously. Furthermore, qualitative research on polypill acceptability has overlooked the views and perspectives of patient caregivers, who are known to play a key role in the medication taking practices of stroke survivors.²⁶⁴ Understanding the views of stroke patients, along with caregivers may also provide some insights around this treatment approach among patients who are dependent on others for their medication, and who may traditionally struggle with medicine taking due to physical disability.

A polypill for stroke prevention represents a potential strategy to improve medication taking among survivors of stroke and transient ischaemic attack. Exploring patients’ and practitioners’ attitudes towards a polypill as well as the perspectives of caregivers, can contribute to our understanding of this treatment approach and the development of robust strategies which could be used to inform future interventions aimed at improving medicine taking in stroke.

Chapter 2

Barriers to medication adherence for secondary prevention care among survivors of stroke or transient ischaemic attack: A narrative review of the literature

Survivors of stroke or TIA are known to face considerable barriers to adherence to secondary prevention medication. In order to better understand the extent and nature of these barriers, a narrative review of the literature was undertaken.

2.1 Introduction

Although there has been significant progress in identifying stroke and in reducing the associated risks, stroke remains a significant health concern. At the individual and population level the burden attributed to stroke is considerable, affecting more than 900,000 people living in England alone, with half of these dependent on other people for help with everyday activities.³⁹⁴ As a result of the significant burden associated with stroke, in 2007, a national stroke strategy was developed by the Department of Health (DoH) with the aim of outlining the diagnosis, treatment and management of stroke.³⁹⁵

Guidelines on the identification and management of stroke recommend the importance of a patient centred approach focusing on individual needs, with each patient making informed decisions about their own treatment and care, in collaboration with a healthcare professional and with the contribution of family and caregivers.³⁹⁶ Success of preventative measures and the reduction in risk requires implementation of lifestyle factors and medication immediately after the event and continuing over the long term.¹²⁴

There is a considerable body of evidence recommending the use of key pharmacotherapies to control important risk factors for stroke including high blood pressure, high blood cholesterol, glucose intolerance, diabetes and atrial fibrillation.^{50 56 69 66} Research shows that the risk of recurrent stroke is greater following a first ever stroke or transient ischaemic attack.^{397 398} Early implementation of effective secondary prevention measures aimed at reducing blood pressure and lipid levels is recommended to reduce the risk of

further stroke events.^{140 141 154} Antithrombotic treatment such as antiplatelet medication is one of the most important methods for addressing stroke risk with research showing a reduction in the odds of a vascular event including stroke of around 22% in patients who had a previous stroke or TIA.¹³⁷ Overall, a considerable body of existing evidence highlight the benefits of preventative therapy such as cholesterol lowering and blood pressure lowering medicines following a stroke event.^{140 164 399 400} Despite the growing evidence on the effectiveness of pharmacotherapies for the treatment and prevention of stroke, medication, nonadherence among stroke survivors remains a concern, with the use of secondary prevention medicine known to decline in the early post stroke years.^{253 401}

Multiple factors are known to be associated with adherence to stroke medications including cognitive issues^{402 403}, understanding the importance of medication⁴⁰⁴, disability²⁵⁵, education and being provided with the appropriate medicines⁴⁰⁵, cost⁴⁰⁶ as well as the type of secondary prevention medicines being taken.^{251 407}

The implementation of effective secondary prevention strategies is associated with a significant reduction in the risk of a recurrent stroke or vascular events⁷⁰ with poor adherence to medication associated with adverse outcomes.²⁵⁰ Understanding the challenges patients face can inform the development of strategies and interventions designed to improve adherence to cardiovascular medication and ensure treatment success.²³⁸

Adherence to medication among stroke survivors is known to be sub-optimal. In one A study examining anti-thrombotic medication taking in stroke survivors, adherence fell from 92.6% to 84% between 3 and 12 months and from 85.2% to 77.4% for anti-coagulation medication across the same time period.⁴⁰⁸ Another study found that the proportion of stroke patients taking anti-hypertensives and statins declined progressively in the two years post discharge.²⁵³ In a study assessing compliance with secondary prevention medication, 87.6% of stroke survivors were still on antithrombotic medication at 1 year and 70.2% were being treated with the same agent.²⁵⁸ In a study looking at nonadherence to secondary prevention medications after ischaemic stroke, 18.7% and 11.9% of patients were nonadherent to aspirin or anticoagulants, respectively, specifically due to supposed adverse effects with 11.2% of patient on anticoagulants nonadherent as a result of the inconvenience of visiting the clinic.⁴⁰⁷

Research on improving medication adherence in stroke patients suggests that simple interventions including those which establish medication routines and modify patient beliefs

have the potential to increase adherence among stroke survivors.³⁴¹ Factors known to predict adherence to medication in stroke include the number of drugs prescribed and use of medication pill boxes²⁵⁵, using aspirin at high dose⁴⁰⁷ and severity of the stroke incident.²⁵⁸ Medication side effects⁴⁰⁹ and concerns about medication as well as beliefs about medicines²⁷¹ have been found to predict nonadherence to medication in stroke.

Understanding the challenges stroke survivors face has the potential to inform the development of effective strategies to address nonadherence to medication in stroke. A focused review of the literature was undertaken to describe potential barriers to secondary prevention medication adherence among survivors of stroke and transient ischaemic attack.

2.2 Methods

2.2.1 Data sources

To identify articles a computerised literature search was undertaken of medical and social science databases including Medline, PsycINFO, Embase and Cinahl from inception until August 2017. The reference lists of identified articles were also searched. The scope of the narrative review was limited to English language, peer reviewed, original full text publications. Abstracts, conference proceedings, commentaries or protocol papers were not considered.

2.2.2 Study eligibility criteria

There was no restriction on study design with both qualitative methodologies (e.g. focus groups and interviews) and quantitative methods (e.g. surveys/ questionnaires) considered. The primary focus of the review was to identify barriers and also facilitators of adherence to medication for secondary prevention in stroke. Eligibility criteria included 1) patients who experienced stroke or transient ischaemic attack 2) identifying barriers or facilitators of medication taking 3) in the English language and 4) published in a peer-reviewed journal.

2.2.3 Search strategy and Identification of studies

A search of electronic databases was conducted using precise search terms and appropriate variations. The search used in Medline (PubMed) was ‘stroke’ or ‘transient ischaemic attack’ AND ‘barriers’ or ‘facilitators’ AND ‘prevention’ with this strategy adapted to suit each electronic database. The search strategy used can be found in Appendix 1. All retrieved articles were imported into the reference management system EndNote and duplicates were

removed. Titles and abstracts were initially scanned and articles representing conference abstracts or reviews were excluded. All remaining titles were read to identify articles for potential inclusion in the review. Where a lack of clarity prevented identification through the abstract, the full text of the article was retrieved. Bibliographies of included studies were also searched to identify any additional relevant papers. The search was performed independently by two researchers and any disagreements were resolved through discussion. The search identified a further two studies which were not included in the final review. Both studies were carried out as part of this thesis and are described in detail in Chapters 3 and 4.

2.2.4 Data extraction

The following information was extracted from the review studies: 1) Title of study, including authors and year of publication, 2) Aim of study, 3) Characteristics of participants including sample size, gender and age, 4) study location, 5) design of the study, 6) study methods 7) main outcome findings including barriers and facilitators of medication adherence.

2.3 Results

Identification and selection of articles for inclusion in the review are displayed in table 1. A total of 817 articles were identified through the electronic database search. This included 242 articles in Pubmed, 421 in Embase 106 in PsycINFO, and 49 in Cinahl. Altogether 6 articles meeting all of the inclusion criteria were selected for review. Table 2.1 displays the key characteristics of studies reported in the review.

Characteristics of studies included in the review are reported in Table 1 below. The number of participants ranged from 17 in one of the qualitative studies to 600 in the quantitative survey study. 103 participated in the mixed methods study. Across the qualitative studies, male survivors ranged from 40% to 75%. Participants in the mixed methods study were predominantly female (64%), and fewer survey participants were male (40.6%).

One study reported a quantitative cross-sectional design⁴¹⁰, one was mixed methods incorporating a qualitative and quantitative methods⁴¹¹ and 4 were qualitative investigations, consisting of 2 semi-structured interview studies^{412 413}, and two focus group studies.^{414 415} Studies were conducted worldwide including South Africa⁴¹¹ UK⁴¹³ France⁴¹² and the USA.

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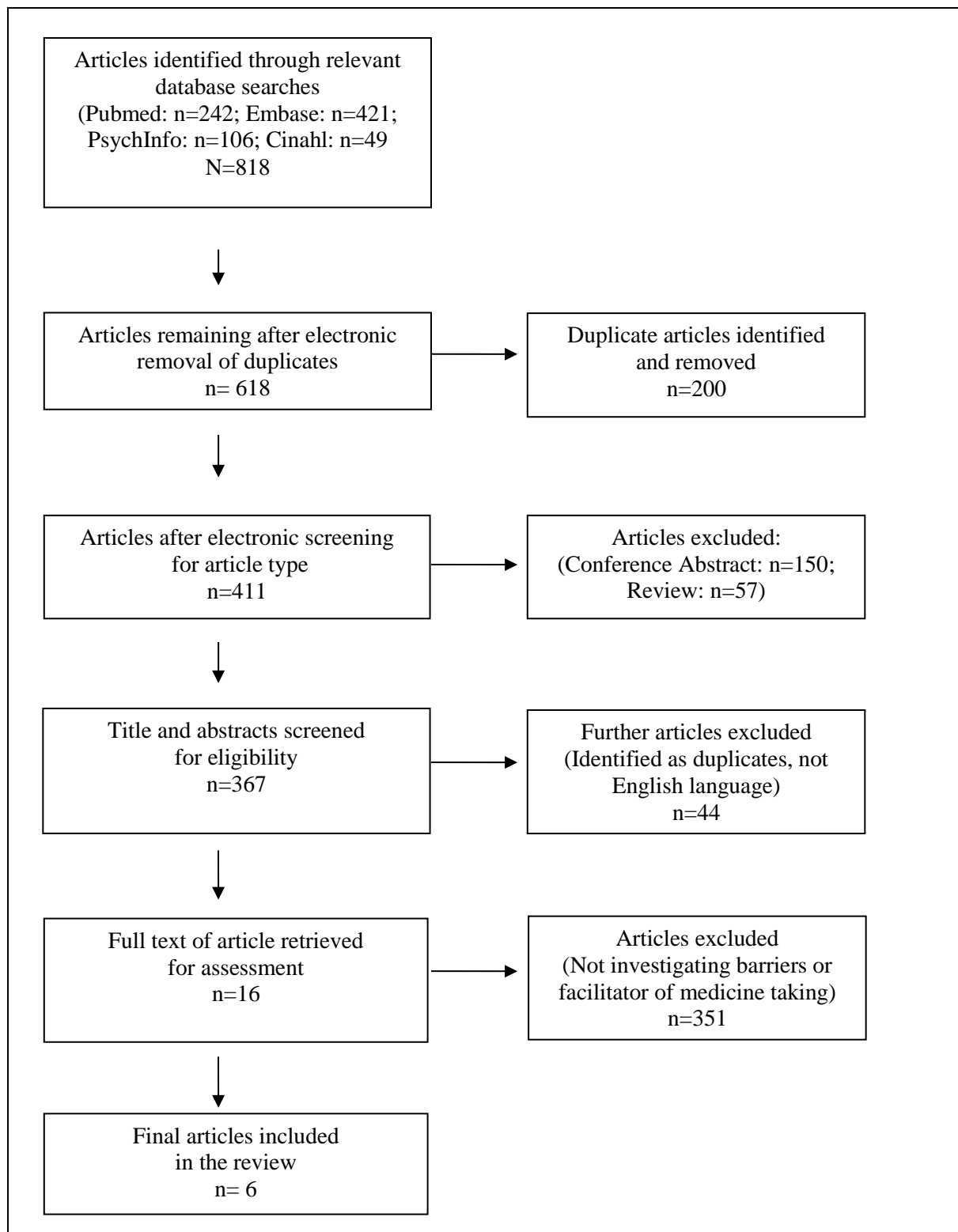
Studies reported the views and opinions of survivors^{410 411} survivors and caregivers together,^{413 414} stroke survivors, caregivers and healthcare professionals⁴¹² or a combination of stroke survivors, family members, emergency personnel, healthcare providers and community leaders.⁴¹⁵

Recruitment of stroke survivors took place within a hospital neurological unit⁴¹² acute stroke rehabilitation centre⁴¹³ a combination of primary care clinics, a specialist stroke care program, tertiary stroke unit and public libraries⁴¹⁴ community centres or churches⁴¹⁰ among inhabitants of rural villages⁴¹¹ or from across the community setting.⁴¹⁵

Inclusion criteria of stroke survivors included diagnosis of stroke,^{411 413} stroke with no significant neurological deficit or cognitive disorder^{410 412}, confirmation of TIA in previous 12 months⁴¹⁴ or having had a stroke within the previous 5 years.⁴¹⁵

The focus of included studies was: barriers to medication adherence,^{412 410} concerns and barriers to medication adherence⁴¹³, barriers and facilitators of stroke treatment⁴¹⁵, prevalence of stroke factors and medication barriers⁴¹¹ or barriers to stroke care and recovery.⁴¹⁴ With study heterogeneity making direct comparison difficult, we tabulated and provided summary descriptions of each study. (see Table 2.1)

Figure 1. Flowchart summarising selection of papers included in the review.



Study (Title/Author/Year)	Study objective	Patient characteristics (n, gender, age)	Location	Design	Methods	Main outcomes
Optimisation of secondary prevention of stroke: a qualitative study of stroke patients' beliefs, concerns and difficulties with their medicines. Souter et al, 2014 ⁴¹³	To explore stroke patients' and carers' beliefs and concerns about medicines and identify barriers to medication adherence for secondary stroke prevention	Total (n=30) Survivors: n=30 Male, n=15 Age: Median: 69 yrs (Caregivers contributed to 8 interviews (details unknown))	Scotland	Qualitative semi-structured interviews	Stroke patients and caregivers participated in qualitative semi-structured interviews. Analysis was conducted using the framework approach.	Negative beliefs influenced commencing medications. Perceived consequences and adverse events influenced medication behaviour, Importance of carer role acknowledged. Desire for more information was reported. Lack of contact after discharge reported.
Barriers and facilitators for medication adherence in stroke patients: a qualitative study conducted in French neurological rehabilitation units. Bauler et al, 2014 ⁴¹²	To describe the perceptions of French patients, caregivers and healthcare professionals on stroke and secondary preventive medications.	Total (n=26) Survivors: n=8 Male, n=9, Age: Median= 53.4 yrs Caregiver, n=6; Male, n=5. Age: Median: 60 yrs Health Professional: n=12: (4 physicians, 8 nurses) Male, n=3 Age: Median: 33.5 yrs	France	Qualitative semi-structured interviews	Stroke survivors, caregivers and health professionals were interviewed around 4 topics: stroke, secondary prevention, patient experience and relationship between the survivor/caregiver and the healthcare team.	Barriers to adherence, in patients: difficulties taking medications, inadequate knowledge on stroke and medication benefits, fear of overmedication. In caregivers, doubts about generic drugs. In HP's, lack of knowledge, absence of clinical symptoms. However HP and care support essential for compliance. Fear of further stroke was a facilitator of compliance

Stroke recovery and prevention barriers among young African-American men. Potential avenues to reduce health disparities Blixen et al, 2014 ⁴¹⁴	To assess post stroke care barriers among younger men and their care partners (in order to inform the development of acceptable and effective improvements in post stroke care)	Total (n=17) Survivors: n=10 Male: n=10 Age: Median: 53 yrs Caregivers: n=7 Female: n=7 Age: Median: 54 yrs;	USA	Qualitative focus groups	Community dwelling survivors within 1 year of stroke and carers participated in focus groups. Thematic analysis using the constant comparative method was used to identify self-perceived barriers and facilitators of stroke care.	Barriers to secondary prevention included: <i>knowledge</i> : associated with risk factors and stroke; <i>medication</i> : side effects and disliking tablets; <i>lifestyle</i> : adopting a healthier diet; <i>functional</i> : getting dressed and memory problems; <i>self-identity</i> : barriers resulting in the failure to promptly seek care; <i>family</i> : lack of support and caregiver stress; <i>health system</i> : poor clinician relationships, inadequate communication and difficulties with appointments.
Key barriers to medication adherence in survivors of stroke and transient ischaemic attack Kronish et al, 2013 ⁴¹⁰	To identify key barriers to medication adherence among stroke and transient ischemic attack (TIA) survivors	Total (n=600) Male: n=244 Age: Median: 63.4 yrs	USA	Quantitative cross-sectional study	Cross sectional survey study undertaken with inner city stroke and TIA survivors over the age of 40. Barriers were explored using validated questionnaires and medication adherence was measured.	Poor adherence associated with increased concerns, low trust in GP, communication difficulties, problems accessing care, poor continuity of care. Concerns and perceived discrimination remained barriers after adjusted analysis.
Secondary prevention of stroke- results from the Southern Africa stroke Prevention initiative (SASPI) Study Thorogood et al, 2004 ⁴¹¹	To describe the prevalence of risk factors and experience of interventions in stroke survivors, and identify barriers to secondary prevention	Total (n=103) Male: n=37 Age: Median: 60 yrs	South Africa	Qualitative in-depth interviews	In depth interviews were conducted in the homes of 35 stroke survivors diagnosed by a clinician in a rural community. The impact of stroke and health seeking behaviours following stroke were examined.	35 interviewed and 29 reported being prescribed anti-hypertensives after stroke. Barriers to secondary prevention included cost of treatment, reluctance to use pills, difficulties accessing drugs and lack of equipment to measure blood pressure.

<p>A Community-Engaged Assessment of Barriers and Facilitators to Rapid Stroke Treatment</p> <p>Nemeth et al (2016)⁴¹⁵</p>	<p>To identify barriers, facilitators, and implications to improve acute stroke care and (b) to develop a community model to improve care for stroke patients</p>	<p>Total (n=52)</p> <p>Community members n=39</p> <p>Patients, n=16,</p> <p>Family members, n=16,</p> <p>Community leaders, n=7)</p> <p>Male, n=11</p> <p>Ages unknown</p> <p>HCP (n=13)</p> <p>Male, n=7</p> <p>Ages unknown</p>	<p>USA</p>	<p>Focus groups</p>	<p>A qualitative approach was undertaken using a focus group methodology to identify barriers and facilitators to improve stroke care</p>	<p>Six themes were identified from the focus group analysis including lack of trust in healthcare system and healthcare providers; relationships and poor communication; low health literacy; financial limitations related to health care; community-based education; and faith.</p>
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Table 2.1: Characteristics of studies included in the narrative review

2.3.1 Details of included studies

Souter and colleagues (2014) conducted a qualitative semi-structured interview study to explore secondary prevention medication concerns among survivors and caregivers.⁴¹³ Interview questions focussed on issues thought to compromise medicine taking, including side effects, treatment worries, and inconvenience of stroke on lifestyle, information provision and post-stroke support. Four main themes emerged including: 1) *Beliefs and concerns about medication and stroke*; including the protective function of medication, concerns around self-monitoring and potential adverse events. 2) *Strategies and barriers related to medicine use*; including the caregiver role and importance of routines, difficulties accessing medications and swallowing tablets. Forgetting tablets was associated with night time medicines and lower perceived importance. 3) *Information needs and level of understanding*; including lack of information provision 4) *Delivery and impact of healthcare*; including lack of contact with GP or pharmacist, differences in the care provided between doctors. Patients acknowledged the important role of the pharmacist but expressed dissatisfaction with follow-up treatment and monitoring.

In a French study exploring barriers and facilitators of medication adherence among survivors, caregivers and health professionals, semi-structured interviews were undertaken to examine four areas of stroke prevention.⁴¹² These included beliefs about stroke, medication issues, patient experiences, and relationships with health professionals (HP). Stroke survivors expressed surprise at being diagnosed with stroke despite knowing the risk factors and concerns around side effects, difficulties taking tablets and scheduling medication into a daily routine. Survivors praised the relationship with their HP and considered the pharmacist's role important in administering medication. Caregivers had an understanding of stroke, reported seeking health information from the Internet and felt the HP provided correct information in an easily understandable manner, but were concerned about the potential for over-medication. HPs believed understanding of stroke was linked to severity of the event and provided information in simple terms while acknowledging the lack of information and time needed to deliver this. The potential for nonadherence due to absence of symptoms was recognised, while other concerns included fear of recurrent stroke and experience of adverse events

associated with medication. Involving the caregiver in secondary prevention was recommended.

In a US study, Kronish and colleagues⁴¹⁰ explored barriers to medication adherence and also assessed adherence using the 8-item Morisky Medication adherence questionnaire. Questionnaire measures assessed barriers in relation to patient interactions, the health care provider and health care system and included a measure of perceived concerns and necessity of medication- assessed by the Beliefs about Medicines Questionnaire (BMQ)³³², disease knowledge and trust in doctors. Reported barriers included poor knowledge of prevention therapies (77%), low trust in doctor (34%), medication difficulties due to cost (32%), discrimination by health care system (30%) and discrimination due to race (25%) or education/ income (22%). Increased concerns about medication, low trust, communication difficulties, accessing health care and poor continuity of care were most closely associated with nonadherence.

A mixed methods study was undertaken to describe the prevalence of risk factors and barriers to secondary prevention treatment with discussions centred on the impact of stroke and ways of coping.⁴¹¹ Separately, workshops with nurses focused on knowledge on the causes and treatment of stroke and hypertension as well as problems with the provision of secondary prevention care. Participants spoke of a 'reluctance to use pills' and stopping medication because it wasn't considered helpful, made them feel worse, because BP levels had reduced or because they ran out of pills. Availability of medicines at the clinic was also problematic. Consultation costs and transport costs to visit a doctor were a barrier, as was availability and maintenance of equipment, contributing to inadequate supplies and poor functionality. Negative views also surrounded the use of injection and tablets, with the belief that these could endanger life.

Blixen and colleagues completed focus groups to assess barriers to stroke recovery and secondary prevention among a sample of African-American men and their caregiver partners⁴¹⁴, exploring personal, family and provider factors associated with post stroke care, as well as perceptions around barriers to risk factor reduction and stroke/TIA recovery.

Stroke survivors identified personal, family and community and provider and health system barriers to stroke care. Personal barriers included anger and stress as a result of stroke,

barriers associated with knowledge including lack of understanding of stroke terminology and confusion around the purpose of medications and the dissatisfaction experienced due to side effects. Functional barriers consisting of difficulties with motor skills and mobility problems as well as self-identity barriers included needing to be strong and therefore being reluctant to seek medical help following a stroke. *Family and community level barriers* included the lack of support received from family caregivers and negative impact stroke had on the family. *Provider and health system barriers* included the patient/ clinician relationship and GP communication as well as difficulties accessing appointments and having enough appointment time.

In a focus group study conducted within a community setting in the USA, 52 participants took part in 8 focus groups to identify barriers and facilitators to improve stroke care in the community.⁴¹⁵ Two groups consisted of stroke patients, 2 were with family member of stroke survivors, one was with community leaders, one with emergency department professionals, one with emergency medical services providers and one with community health care providers.

Four of the 6 themes identified were considered barriers. *Lack of trust*: stroke survivors and family members expressing mistrust in the physician, reducing patient enthusiasm to attend the doctor or hospital. Participants expressed distrust in themselves to make the right decisions while healthcare providers did not always trust their recommendations were followed. *Weak relationships associated with poor communication*: Better relationships between the emergency medical services and patients and family members and having open lines of communication were considered important while difficulties in the patient doctor relationship were recognised. *Low health literacy* was problematic with some patients lacking clarity in knowledge understanding and decision making with patients not understanding the importance of the time needed to treat stroke from the onset of symptoms. A lack of ownership of stroke symptoms was also reported with many patients in the community not taking their prescribed blood pressure medications. Lack of stroke knowledge in the community was also considered an issue. *Financial limitations*: Visiting health care providers was problematic for some stroke survivors with limited health insurance and costs considered a burden. Money to pay for medication was a further concern

while primary care physicians and other emergency healthcare professionals admitting that many patients did not take their medicines as a result of financial barriers.

2.4 Discussion

A narrative review of the literature to identify and evaluate studies reporting barriers as well as facilitators of medication adherence in stroke was conducted. Six studies were identified, reporting the attitudes and perspectives of stroke survivors, caregivers and healthcare professionals.

Summary of findings

Stroke survivors highlighted barriers including concerns around medication side effects, difficulties scheduling medication as well as difficulties taking medicines, concerns around previous medication taking experiences. Others highlighted a reluctance to take medicines, including stopping medicines when the pills ran out or upon confirmation of risk reduction. Availability of drugs and costs were also mentioned by survivors. Barriers to medication adherence among patients also included negative medication beliefs, inadequate knowledge of medication and dissatisfaction around contact with the healthcare professional.

Caregivers reported confusion around the purpose of medications, concerns around the impact of adverse effects on medication adherence, fears about overmedication, concerns around pharmacy use of generic drugs, frustrations around the impact of stroke, the need for more information and clarity in patient-practitioner communication.

Health professionals recognised the need to provide more information to stroke survivors that was easily understood, to adapt intake through decreasing the quantity of medications, to introduce combination therapy where possible and to acknowledge that patients stopped taking medicines in the absence of clinical symptoms. The importance of family involvement as a facilitator was recognised, medication follow ups encouraged compliance and the role of the caregiver in the management of care was acknowledged while advice on the risk of recurrent stroke was offered in line with increased risk. Other barriers highlighted included lack of patient knowledge, absence of stroke symptoms, complex

medication regimens and pill burden which contributed to poor adherence and increased concerns around taking medications. Facilitators of medication adherence included recognition of the necessity of treatment, having a good relationship with the healthcare professional, following medication taking routines and the positive effects of the caregiver role.

Strengths and limitations

This review has a number of strengths. The findings are an important addition to the field of stroke research and highlight potential strategies that may be used to inform the development of future interventions aimed at addressing medication adherence in stroke. Findings are reported from across a range of health care settings is reported. A further strength of the review is in representing the attitudes of stroke survivors, caregivers and health professionals as well as the wider community, offering a broad account of secondary prevention medicine taking behaviour from different perspectives within the stroke domain.

However limitations of these findings should also be considered. The review was restricted to English language papers only. This may have impacted on the generalisability of the findings to other non-English speaking countries. With relatively few studies reported in the literature including only one UK study, it is unclear whether the findings reported here are representative of the views of all stroke populations. Grey literature including unpublished papers was not investigated but may have uncovered further insights into what is a relatively narrow research focus. Due to the heterogeneity of studies identified, it was not possible to directly compare across studies.

Only three studies sought the opinions of caregivers, despite the influential role they are considered to have in managing stroke medication and facilitating adherence. In one study, caregivers were unrelated to selected stroke survivors. Given the prominence of the caregiver role in managing medication and their unique knowledge of the stroke survivor's medication taking behaviour, exploring the barriers among this group in the wider context of patient compliance is warranted. It is not clear to what extent barriers and facilitators reported here represent the concerns of stroke survivors who may be disabled and have different medication needs. Further investigations would benefit from understanding those stroke survivors with significant physical and cognitive deficits who are largely dependent on the

support of others and likely to be faced with their own unique set of barriers to treatment and medication adherence. The views of healthcare professionals were also underrepresented. General practitioners play a key role in administration and prescribing of stroke medication and future research should seek to explore their views and opinions also. With the GP/patient relationship and communication known to have an important influence on patient medication taking behaviour, a greater understanding of the healthcare professional perspective is warranted.

Comparisons with existing literature.

Medication nonadherence has been attributed to multiple factors in cardiovascular disease, requiring a broad approach to meet the challenges patients face.⁴¹⁶ Barriers to medication adherence identified in this review are in line with difficulties reported previously in the literature. One review of adherence to cardiovascular medications identified poor knowledge of medicines, side effects and negative perceptions about medicines as common predictors of poor adherence among patients.⁴¹⁷

Previous research has identified medication side effects as having perhaps the most significant effect on patient adherence.²²⁷ A focus group study exploring patient perspectives around taking statins found that patients' concerns about adverse side effects were an important factor in their decision to reduce statin use⁴¹⁸, while experiencing side effects or the fear of experiencing side effects were reasons for stopping statin therapy in patients at high risk for cardiovascular events.⁴¹⁹

An interesting observation of this review was the level of agreement between the views of stroke survivors and caregivers concerning information needs and lack of knowledge as well as importance of support with medicine taking. This suggests the importance of adopting strategies that can inform interventions targeting both patients and their caregivers. A Cochrane review to assess the effectiveness of information strategies on improving the outcome of stroke survivors and their caregivers found that information improved knowledge of stroke and patient satisfaction.⁴²⁰ In a 2017 analysis of posts to an online stroke forum, stroke survivors sought practitioners' advice mainly on side effects and reassurance and this advice varied with regard to its impact on treatment.⁴²¹

Associating medication taking with a familiar routine or environmental cue was an important facilitator of adherence. Support for the role of routines when taking medicines and improving adherence is in line with previous research particularly among older adults^{422 423} including those prescribed cardiovascular medications.⁴²⁴ In a randomised trial to improve adherence to stroke medication specifically, establishing a brief medication taking routine increased adherence to medication among stroke survivors.⁴⁰³ An investigation to identify potential barriers and facilitators of adherence underpinning interventions to improve medication adherence, identified forgetting, prioritising medicines, following medication routines and encouragement through support for others.⁴²⁵

Unintentional nonadherence is a key facet of adherence associated with missing medication as a result of forgetting. Forgetting to take medication, possibly as a result of cognitive impairment due to stroke, was identified by survivors. In fact forgetting has been reported for cardiovascular patients more widely, with a systematic review of anti-hypertensives identifying remembering and forgetting as a key patient related barrier to medication.⁴²⁶

Intentional nonadherence is known to be associated with the individual's perceptions of the benefits and concerns around medications. Research has shown that distinguishing beliefs attributed to intentional and unintentional nonadherence may be important for the development of interventions aimed at addressing medication nonadherence, as patients who intentionally chose not to take medicines had higher levels of concern around taking medication compared to those who were unintentional non-adherers.⁴²⁷

Patients' beliefs about stroke and medications as well as concerns around taking medicines were highlighted by both survivors and caregivers as important barriers to adherence. Beliefs about medication are widely considered to be an important factor contributing to patient adherence and have been found to be more powerful predictors of adherence than clinical or socio-demographic factors.³²⁵ There is some evidence for the relationship between beliefs and adherence to medication in stroke, with a longitudinal study exploring predictors of nonadherence across UK stroke survivors finding that patient concerns and perceived benefits of medication were strongly associated with poor adherence at baseline and at 6 weeks follow up.²⁷¹ In a questionnaire study conducted with a sample of

Swedish stroke survivors reporting important associations between beliefs and adherence, nonadherent patients scored lower on positive beliefs and higher on negative beliefs.⁴²⁸ This evidence suggests that developing interventions that target patient beliefs and concerns around medication may be an important step in addressing the burden of nonadherence among patients including stroke survivors.

Although few studies explored barriers from the perspective of the caregiver, the significance of the caregiver role was recognised. Caregiver responsibilities are wide ranging⁴²⁹ and they are known to be instrumental activities such as in controlling and administering medications, co-ordinating health care and acting as an advocate for the patient. However, the precise nature of the caregiver role in facilitating medication taking, particularly among those who may have suffered a more disabling stroke, is not widely understood.²⁶⁴ In a study of cardiac patients, those who reported having or planning to have a caregiver were found to be 40% less likely to be nonadherent to medication compared to those who didn't have a caregiver.⁴³⁰

In helping with the management of medication and self-care among stroke survivors in the community, caregivers can also contribute to reducing the likelihood of readmissions after stroke.⁴³¹ Stroke survivors with disabilities may be particularly vulnerable to difficult experiences with medicines including handling tablets, filling pill boxes, remembering to take tablets and being capable of collecting prescriptions. However, caregivers can play a key role in these activities as well as acting on behalf of the stroke survivor in their dealings with health professionals. Research indicates that in clinical practice, the role of the caregiver is often underestimated by health care professionals, although they have an important role to play as a patient advocate and in shared decision making.⁴³² Efforts to address barriers to medication adherence should focus on developing interventions to improve adherence with the caregiver role in mind. A qualitative assessment of adherence to anticoagulant medication reported caregiver support as an important facilitator of adherence.⁴³³

The doctor/patient relationship facilitating good communication was recognised as being an important facilitator of medication taking, permitting the effective delivery of information on stroke and medication. It is known that patients' beliefs about the doctor-patient relationship have a significant impact on their decision to adhere to medication.⁴³⁴ The

level of agreement within the patient-physician relationship has also demonstrated a significant effect on medication taking behaviour, with one study reporting 1/3 greater medication compliance for consultations demonstrating higher levels of concordance between patients and practitioners.⁴³⁵ Results from a meta-analysis showed that the level of communication between the physician and the patient correlated significantly with medication adherence to the extent that for physicians who communicate poorly, the risk of nonadherence was 19% higher than among those patients with whom physicians communicated well.⁴³⁶ A patient-practitioner relationship facilitating effective communication has the potential to improve the delivery of information around stroke and medication, enhance trust in the health care professional and provide reassurance to the patient and address medication concerns. Drawing on these strengths could help to inform future interventions to improve adherence to stroke medication.

A lack of knowledge, information, and understanding around stroke and secondary prevention medications was recognised as an important barrier to medication, which was frequently highlighted. Inadequate information has been reported previously as an important factor influencing patient medication taking behaviour. In one systematic review, considerable unmet information needs among stroke survivors and caregivers were identified including inadequate information on stroke prevention and post- stroke management.⁴³⁷ A separate investigation of patients' problems with new medications for conditions including stroke and coronary heart disease found that there was a substantial need for additional information in 61% of patients still taking their medications at 10 days and 51% of those still taking their medications at 4 weeks. In a survey investigation of unmet needs among stroke survivors, one of the highest unmet needs reported by survivors (54%) was for information related to stroke.³⁵⁴

Difficulties among caregivers and survivors in accessing information is not new, with poor accessibility to information, suitability of information and quantity of information key impediments to the delivery of important stroke information and knowledge.⁴³⁸ Lack of information around stroke is also a concern for long-term stroke survivors.⁴³⁹ However, health care professionals can play an important role in communicating the importance of medication to patients and caregivers, ensuring stroke survivors are informed about their secondary prevention medications.

In a review examining the relationship between medication barriers and adherence in elderly patients, patient related factors such as knowledge and medication related factors such as adverse effects and the patient-physician relationship were important.²⁶⁸ Understanding the association between level of adherence and barriers to medication that patients face can help to tailor strategies that can inform the development of adherence interventions in stroke. Chambers and colleagues (2016) examined medication adherence in stroke survivors from the point of view of low versus high adherers. They found that high adherers adopted medication taking strategies, received support from family, had confidence in their medication and were more likely to persist with medicines compared with low adherers who were more likely to alter and stop medicine without the doctor's advice, less likely to seek out information, and showed a lack of awareness and knowledge of medication.⁴⁰⁴ Examining the potential association between medication barriers and how these relate to actual adherence among stroke survivors could be an important area for future research.

This narrative review uncovered few relevant studies reporting barriers and facilitators of medication adherence in stroke. In light of the paucity of research, further investigations were undertaken as part of this thesis to examine this behaviour within the UK stroke population. This has resulted in the completion and publication of a further two research studies which are described in Chapter 3 and Chapter 4 of this thesis, reporting barriers and facilitators of adherence to medication among survivors of stroke and TIA. These studies used two independent sources to collect qualitative data- traditional semi-structured interviews⁴⁴⁰ and a novel approach using an online stroke forum.⁴⁴¹

Implications for clinical practice

Effective interventions are needed to address the barriers stroke survivors face in adhering to secondary prevention medication. Highlighting barriers will also enable health care professionals to focus resources in support of stroke survivors in the community. Caregivers are well placed to understand barriers to medication that stroke survivors face, and health care professionals should draw on this knowledge to develop strategies that can facilitate medication adherence. Practitioners should also place greater emphasis on understanding the needs of those stroke survivors with cognitive and physical difficulties who may be less

likely to participate in traditional research and who may have unique medication needs. Multicomponent interventions delivered in the clinical setting can incorporate components that both challenge negative medication beliefs while also facilitating effective medication taking practices, such as the use of pill boxes or medication taking routines.

Through educating patients and their caregivers on medication, practitioners can promote a better understanding of secondary stroke prevention which can encourage more effective medication taking practices and ultimately improve health outcomes after stroke.

The pharmacy represents an important opportunity to deliver a brief intervention to stroke survivors. The pharmacist can offer support with medication taking and address patients' concerns as well as provide advice on medication taking aids and devices to improve pill taking. Future research should aim to explore this role further.

Conclusions

Adherence to medication among stroke survivors is known to be problematic. This review highlights the multiple barriers to medication adherence and secondary prevention care faced by survivors of stroke and transient ischaemic attack. This knowledge can inform efforts to challenge poor medication taking behaviour and the development of interventions aimed at improving adherence to secondary prevention treatment in stroke.

Chapter 3

Barriers to Medication Adherence for the Secondary Prevention of Stroke: A Qualitative Interview study

This chapter of the thesis describes an investigation exploring barriers to adherence to medication for secondary stroke prevention in UK general practice. Adherence to medication is known to be problematic among stroke survivors, however, the reasons why UK stroke patients do not take medicines as prescribed are not well known. Available evidence from research studies demonstrates that patients struggle with their medicines. Moreover stroke survivors are known to face multiple patient and medication related barriers to taking medication for secondary prevention. However difficult medication taking experiences are often mitigated by facilitators which can encourage positive medication taking practices.

It is therefore important to identify and to understand the barriers and facilitators of adherence stroke survivors face if we are to address the challenge of suboptimal adherence and improve the long term outcomes of stroke survivors.

As well as exploring the perspectives of survivors, understanding views of unpaid caregivers (i.e. family members) and healthcare professionals, all of whom are known to play an important role in the patient's medication taking behaviour, is important. While an acute stroke event is often treated in hospital settings in the UK, secondary prevention treatment is primarily delivered in the primary care setting. Therefore exploring barriers from across these different perspectives in the general practice setting provides an understanding of this important health concern and can inform the development of potentially effective strategies and interventions to challenge poor adherence in the future. Adopting a semi structured interview approach also allows the researcher to explore the area in depth and enables participants to provide rich descriptions on important aspects of the topic.

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This work was undertaken in collaboration with other researchers. James Jamison conceived of the study and its design, formulated the aims and methods, conducted all of the interviews with study participants, undertook the qualitative analysis, wrote up this chapter and prepared the manuscript for publication. Dr Ricky Mullis assisted with the protocol development, Dr Jonathan Graffy contributed to interpretation of the findings, Professor Jonathan Mant contributed to the study design and Professor Stephen Sutton double coded interviews and advised on all aspects of study development and delivery. All co-authors assisted with reviewing the final manuscript.

3.1 Background

Reducing the burden of stroke and risk of further cerebrovascular events can be achieved through implementing a medication regimen which includes cholesterol lowering and blood pressure lowering therapies.^{442 65 180} However success in stroke prevention is dependent on the survivors adherence to medication. Estimates suggest that up to 50% of patients with chronic disease do not take their medicines as prescribed²²⁶ resulting in negative health outcomes.²²⁷

Adherence to medication among survivors of stroke and TIA is known to be sub-optimal.^{258 407} A systematic review on adherence to cardiovascular therapies found a significant proportion of people did not adhere to cardiovascular medications and this was attributed to as much as 9% of all CVD events in Europe.²⁴² Furthermore, trials of medication adherence on blood pressure lowering among stroke largely excluded patients with any significant cognitive deficit and did not account for the caregiver role in the lives of stroke patients.⁴⁴³

Barriers to medication adherence in stroke have been explored previously. Research has shown that concerns about medication and knowledge of stroke prevention

therapies were important barriers among people with stroke.⁴¹⁰ Another study highlighted beliefs about medication, medication side effects and lack of information as important adherence barriers.⁴¹³ Further evidence on factors affecting adherence after stroke can address the poor uptake of these medications. The aim of this investigation was to explore barriers to secondary prevention medication adherence in UK general practice among survivors of stroke and TIA.

3.2 Methods

3.2.1 Design and participants

Interviews were conducted with patients on stroke registers of 5 GP surgeries together with their carers where relevant, and one GP from each practice. A list of patients over 55 with a history of stroke or TIA was compiled and sent to the GP for review. Anyone considered unfit to participate in the research (i.e. was seriously ill or terminally ill) was excluded and not approached by the practice. To achieve a maximum variety spread of age, socio-economic status (Indices of Multiple Deprivation (IMD) score⁴⁴⁴), gender, and disability (using modified Rankin scale⁴⁴⁵) purposive sampling was undertaken. Initially 25 patients from each practice were approached by letter. Positive respondents were phoned to confirm attendance and the presence of a caregiver at the interview. The final number of interviews was determined by data saturation, the point at which no new themes emerged.

Table 3.1: Qualitative interview study topic guide

<u>Qualitative Interview Topic Guide</u>	
Patient	
1.	Can you tell me about your health since you had your stroke? <ul style="list-style-type: none"> • How would you say your health has changed? • In what way, if any, has the stroke changed your relationship with the carer? • Is there anything you find particularly difficult since you had your stroke?
2.	Can you tell me about the stroke medication you currently take? <ul style="list-style-type: none"> • What are your general feelings towards taking your current stroke medication? • Do you know understand what the medications you take are for? • How is your medication managed? Who is responsible? How does this work? • Would you like to manage your own medication? Do you think its important?
3.	Taking your medication: <ul style="list-style-type: none"> • Do you always take your medication when you're supposed to? • Do you experience any other problems taking medication? Can you tell me a bit more about these problems? (e.g. quantity/size of meds). • How do you think the medication taking process could be improved?
Caregiver	
1.	Can you tell me about your experiences as a caregiver? <ul style="list-style-type: none"> • What is this like day-to-day? • How has this changed your relationship with the patient? • What is the most difficult about this experience of being a carer?
2.	Can you tell me about your role managing medication? <ul style="list-style-type: none"> • Have you always managed their medication? If not, why? • How important would you consider the role of managing this medication? • How good is the patient at taking his/her medication? • What are the difficulties around taking stroke medication? What do you think is the main concern the patient has? (E.g. size, quantity, forgetting). • How do you think the medication-taking process could be/improved?
GP	
3.	What do you think of current treatment for secondary prevention? <ul style="list-style-type: none"> • How do you think current stroke treatment could be improved? • Do you think current regimens are easy for patients to understand/manage? • Can you think of any limitations of current secondary prevention regimens?

3.2.2 Semi-structured interviews

Semi-structured interviews provided an opportunity for in-depth investigation of people's personal perspectives, using an open-ended line of questioning which defined the area to be explored.⁴⁴⁶ A topic schedule guided the line of questioning and prompts encouraged further discussion. The topic guide is shown in Table 3.1.

Two survivors piloted the patient topic guides and recommendations were incorporated. A clinical researcher provided feedback on the GP topic guide. Interviews were conducted in the patient's home or the practice. Discussion topics included attitudes to secondary prevention care, medication beliefs, adherence to treatment, carer role, GPs attitudes towards current practice and barriers to uptake. Interviews were conducted between June 2013 and February 2014, lasted 1 to 1.5 hours and were audiotaped and transcribed.

3.2.3 Data analysis

To ensure reliability of interpretation, transcripts were initially read and inaccuracies resolved by listening to the recordings. Nvivo 9⁴⁴⁷ (QSR Intl, Melbourne, Australia) was used to organise, code and manage the data. Transcripts were entered into the program and coded followed a constant comparative analysis⁴⁴⁸ approach in which key points were identified from the data and coded individually. An iterative process of data collection and data analysis was undertaken.

Initially, chunks of data were coded. Codes were then grouped into similar concepts and themes and categories were formed. (see Appendix 3). A process of identification and refinement of categories followed. As groups were compared further, more abstract categories developed until the core themes emerged. To strengthen the validity of findings and ensure rigour, 20% of all interviews were double-coded by a second researcher. Inconsistencies were resolved through discussion with a third author until a consensus on the final themes was reached.

3.3 Results

Thirty-three interviews were completed in total. Twenty-eight were with stroke survivors, 14 of whom had a caregiver present and 5 were with GPs. Practice response rates varied from 6 % to 24%. Twenty-two out of twenty-eight stroke survivors (78%) were male and 50% reported having TIA (n=14). The mean age of stroke survivors was 74 years with a quarter of the sample over 80 years of age. Eighteen out of twenty-eight survivors (64%) had a stroke within the last 5 years, 4 of whom were in the last 12 months. Participants were predominantly White (97%, n=27), and the time since a stroke occurred varied across the sample with 35% reporting a stroke within the previous 2 years, 29% had a stroke 3 to 5 years previously, 18% had a stroke between 6 and 10 years previously while 18% of the sample had experienced a stroke or TIA over 10 year previously. Approximately one third of the sample reported having diabetes (32%), and the majority (54%) had never smoked. Out of the 14 caregivers interviewed, 12 were the patient's spouse and 2 were the son or daughter of a stroke survivor. Three of the GPs interviewed were male and two were female. The characteristics of survivors are presented in Appendix 2.

Two key themes were identified: The first theme was *Patient level barriers* and the second them was *Medication level barriers*. Details of the key categories and themes identified in the interviews are reported in Appendix 3 and Appendix 4.

3.3.1 Patient level barriers

This theme included the sub-themes, ability to self-care, how seriously people take stroke and knowledge of stroke and medication. Patient level barriers are described in Table 3.2 below.

Ability to self-care.

GPs admitted that being housebound was a significant barrier compromising patients care and affecting adherence.

If somebody is stuck at home, a total five hours they have got contact with somebody, the rest of the 365 days they are by themselves.. their outcome is likely to be worse...their care can be low. If they're depressed they won't take their tablets (GP05, male).

For many survivors however dependence on a caregiver for their knowledge and managing medication was important.

My wife sorts it out and that's why I don't know so much about it you see she [taps].She puts them there, I take them and that's it (Pt04, Male, 80 yrs)

How seriously people take stroke

Survivors and carers frequently trivialised stroke and the significance of symptoms, often due to a lack of knowledge and expectation around the condition.

I knew there was a problem but I thought perhaps it would go away. So you sort of erm bury your head in the sand (Pt20, female, carer).

Within sort of half hour, hour at the most I felt I was ok again. The fact that we drove home the next day without seeking medical attention, it's silly but I did it because I didn't think anything else about it, it's gone whatever it is (Pt09, male, 68 yrs).

I wouldn't take them because I still, to me, blood pressure and cholesterol tablets to me I don't see what they're doing for me (Pt24, Male, 75yrs).

In the absence of symptoms the need for medication was also frequently underestimated, as GPs confirmed.

If they don't see or it didn't leave any residual effect on them, then they tend to forget

these things. Out of the sight, out of the mind. (GP02, Female)

Knowledge of stroke and medication

Inadequate information on stroke prevention and recovery was frequently cited by stroke survivors and caregivers.

No, I don't think we've got hardly any information. We haven't ever really had a lot of information about it have we? You just sort of get on with it...I mean perhaps I haven't ever asked enough but.. I think you should be, told in advance, (Pt14, Male, carer)

In addition, level of knowledge varied with several survivors admitting to being well informed, while others felt confused about tablets and the reasons they needed to take them.

The importance of taking these exactly on time is trivial. I would probably survive for a week, if I didn't take the. For a month I'd probably survive. It would not make any difference in two days. (Pt03, Male, 86yrs)

I don't know why I take them but it tells you on each one you know what it's for [] I wouldn't say I know what they're for.. (Pt16, Female, 82 yrs)

GPs agreed survivors lacked medication knowledge but that many took tablets because the doctor told them to.

I would say 50% of patients know what medication they are taking but erm 50% of patients doesn't know, they think the doctors have prescribed me this medication and I have to take it and that's why they are taking it (GP02, Female)

Table 3.2: Patient level barriers to medication adherence reported in interviews

3.3.2 Medication level barriers

This theme included the sub-themes, beliefs about medication, taking secondary prevention medications, medication routines, changing medication, regimen complexity and pill burden.

Medication level barriers are described in Table 3.3 below.

Beliefs about medication.

Patient's beliefs about medication frequently dictated adherence to some drugs.

I think aspirins good for you. That's the only one I fancy. Well it thins the blood and I think well by thinning the blood it flows better and that stops any clots so I do like to take it. I just don't see why I'm taking other medication, I'm not fat or anything like that. I don't get very high blood pressure and well cholesterol, what is cholesterol, (Pt24, Male, 75yrs)

I refused it and.. I said well... it's not because it's rat poisoning. If you tell me I've got warfarin I must be ill and if I take aspirin I can't be that ill (Pt22, Female, 71 yrs)

Some survivors questioned the need for any medication, expressing doubts despite experiencing a stroke.

I mean I'm taking them because they know better than I do, but at the same time at the back of my head I'm thinking I, I shouldn't have to take those (Pt10, male, 66yrs)

Other survivors focussed on conditions with a greater impact on everyday health.

To me the most important thing for her is controlling her diabetes...because I don't want her passing out having a diabetes wobbly (Pt08, male, 87 yrs)

Taking secondary prevention medications

The importance of taking stroke medication was widely acknowledged, however, complete adherence was a minor concern for many stroke survivors.

I'm sort of, a little bit annoyed that I've missed them but, no it doesn't worry me. It would worry me if..I missed them for three or four days but a day, no (Pt10, Male, 66yrs).

Although most stroke survivors considered themselves adherent, many reported forgetting to

take their night medication.

Well now and again I forget the cholesterol because that's the one at night and it's the only one I take at night (Pt15, Male, 67yrs)

For some survivors, not taking medication was a conscious decision and GPs acknowledged they needed to respect this.

We do have to respect their autonomy at the end of the day it's their bodies and some of them say to me look, for goodness sake I'm 94, I don't want to take these tablets, it makes me feel ill. I do have to respect that. (GP01, Female)

Nevertheless, survivors and caregivers reported they were generally happy to follow the advice of their GP.

So if the doctor says take ten pills a day, I'll, I'll do it...he makes the decision and erm he, he's the boss man as you might say, who knows what he's up to (Pt08, Male, 87yrs).

Patients also identified practical barriers including difficulties accessing medications and the size of tablets.

The big ones, I, do actually feel I have to swallow two or three times to get them down (Pt10, Male, 66yrs)

Some of the, the pills are a hell of a trouble, you know the bubble wrap, flipping them out especially with my hands not as strong as they should be (Pt08, Male, 87yrs)

Medication routines

Many patients admitted following a medication taking routine, without which they would have difficulties with medication adherence.

I only remember to take the others be- if I take them out of the cupboard the night before and leave them on the top. If I didn't take them out, I, I, would probably forget..because it isn't the first thing that I think of...you know when I, when I first get

up (Pt10, Male, 66 yrs)

The use of medication blister boxes was also beneficial and improved the experience of taking tablets.

(Taking medication) that was a lot more hit and miss then...when you pop 'em open if one flies on the floor I think nah leave it..Sweep it up later on. It's like a pleasure doing it now (Pt06, Male, 61yrs)

Changing medications

Stroke survivors described how medications were frequently changed, leading to disruption in pill administration and unwanted treatment side effects.

I did have a bad run because they changed the looks of the tablets oh god and I was taking four gout tablets a day and no diabetes ones and that put the old sugar up (Pt13, Male, 70yrs)

They changed his medication to cheaper cholesterol and Dean was physically ill. He couldn't cope on it at all so he went back and the doctor said 'oh well it was just to try and they put him back on the others (Pt24, carer, Female)

Regimen complexity and burden of medications

Survivors frequently expressed concerns around pill burden with several describing how visiting the GP often resulted in additional medications.

I have to take 10 a day now altogether but I went up there (to the practice) to say can I get off some of these tablets, and I come back and I was on an extra one so I've not been up since (Pt13, Male, 70yrs)

Others felt that the increased burden only contributed to their lack of understanding around stroke medications.

I've got yards of them. I don't know half the names I'm just told when to take them.

That's one thing I'd like to do away with (Pt11, Male, 73 yrs)

GPs acknowledged pill burden also and the contribution to patient's negative attitudes towards taking medication.

Most of them are more unhappy about the number of tablets... from a patient's perspective its usually it's just physically a lot of tablets you have to swallow (GP03)

Among the elderly, increased burden often led to a choice being made between which medications to take.

70% of patients are fully compliant but some of them are not compliant with these medications especially the elderly group of the patients because they think they are taking too many medications and sothey keep missing out the medications (GP02, Female.

Table 3.3: Medication level barriers to medication adherence reported in interviews

3.4 Discussion

Summary of key findings

A qualitative interview study with stroke survivors, caregivers and GPs was undertaken to explore barriers to medication adherence in stroke, within the UK general practice setting. Two key themes were identified. The first, *Patient level barriers*, included the sub-themes, ability to self-care, knowledge of stroke and medication and survivor's tendency to trivialise stroke. The second key theme, *Medication level barriers*, included the sub-themes, beliefs about how pills work, importance of taking medication, attitudes to missing tablets, difficulties taking medications, changing medications and pill burden.

Strengths and limitations

An important strength of the study was the inclusion of caregivers and GPs alongside patients, providing greater diversity of opinion. Employing a semi-structured interview methodology allowed participants maximum scope to dictate the direction of conversation and permitted an in-depth assessment of the topic area. This study offers a unique perspective on medication adherence barriers through the perceptions of stroke survivors, caregivers and GPs. However limitations of this research should also be recognised. Due to the small number of GPs it is unclear whether these views are representative of health professionals. Recruitment across five practices may also limit the potential to generalise these findings to the wider stroke population. Survivors were predominantly White, few were significantly disabled and none had substantial cognitive impairment. Future research however could include patients with aphasia who are dependent on others and those from ethnic minorities among whom cardiovascular disease is known to be more prevalent.

Comparisons with existing literature

Similar investigations from France and UK also reported that lack of symptoms and knowledge were important barriers to adherence.^{412 413} Poor knowledge contributed to misunderstanding, with stroke frequently trivialised and its symptoms ignored. This is perhaps not surprising given that half our sample reported experiencing a transient ischaemic attack or mini-stroke, where symptoms usually disappear within 24 hours. Indeed, this absence of symptoms has often been identified as an important reason for the lack of urgency among survivors seeking help following stroke onset.⁴⁴⁹ Elsewhere a systematic review of qualitative studies on patients understanding of hypertension and medication taking identified side effects and a dislike of medication as key reasons for not continuing treatment.⁴⁵⁰

Lack of knowledge, doubts about treatment efficacy and prioritising medications are in line with previous work in which poor adherence was linked with being likely to question the purpose of medication, having a poor understanding of therapy and concerns around the lack of information provided by the health professional.⁴⁰⁴ Prioritising medications due to perceived importance and treating the most salient symptoms corresponds with patients performing a risk benefit assessment in which condition severity and knowledge of medication influence the decision to use treatment.⁴⁵¹ The potential for positive beliefs on

medication to influence subsequent behaviour suggest that exploring beliefs among stroke survivors should be considered in an effort to improve medication adherence.⁴²⁸ The lack of knowledge identified among stroke survivors and caregivers suggests a need for improved education around stroke and treatment of the condition. Although education is a key component of providing stroke care, both survivors and caregivers face considerable barriers to information.⁴³⁸

This investigation confirms previously reported barriers including difficulties swallowing or accessing medication²²⁷ frequent changing of medication⁴⁵² use of storage devices³⁴¹ treatment complexity and the influence of co-morbidities.²⁸⁶ Complex medication regimens are important factors in adherence to chronic conditions including hypertension and cardiovascular disease.²⁹² While reducing the daily medication dose can improve adherence to anti-hypertensives⁴⁵³, recent research has suggested a fixed-dose combination (FDC) polypill approach can improve adherence to medications⁴⁵⁴ and has the potential to address barriers reported here.

These findings add to the growing body of literature on barriers to medication adherence in stroke. The failure of patients to act on stroke symptoms may represent a broader lack of knowledge associated with experiencing a TIA. Research into behaviour following a TIA indicates that a delay in seeking treatment is not uncommon, attributed not only to the recognition of symptoms but also the role of others and interactions with the health care provider.⁴⁵⁵ This study highlights the important role of the caregiver in providing information and facilitating medication taking behaviour. Further work exploring the role of the caregiver is therefore warranted. Inadequate stroke knowledge and information provided by the GP has been reported previously, indicating there are significant unmet needs within this group.⁴³⁷ While the measurement of adherence was beyond the scope of the current study, exploring how the beliefs and perspectives of survivors reflect actual levels of adherence should also be considered. Determining how the barriers identified here relate to actual adherence may help determine where secondary prevention efforts should be focussed in the future.

Implications for clinical practice

These findings provide an important basis from where effective adherence interventions to improve stroke care may be developed and implemented in clinical practice. Interventions are needed to address barriers to medication adherence among stroke survivors and ultimately improve stroke outcomes within this population. Increased efforts to improve awareness of stroke and secondary prevention medication is warranted. Given their potentially significant role in managing medication, it is important that caregivers are fully engaged with efforts aimed at addressing barriers and improving adherence to stroke medication. Furthermore, it is likely that caregiver support may be important for maintaining adherence among those survivors with cognitive limitations, who were largely overlooked in the present study and who may themselves face considerable barriers to adherence.

Adopting a collaborative approach between the patient, caregiver and practitioner as well as the wider primary health care team of practice nurses and pharmacists, who can also play a role in facilitating adherence, should also be considered and can be a focus for future work in this area. Finally, developing the patient practitioner relationship and facilitating better communication can enhance survivors understanding and knowledge of stroke and medication, while encouraging better adherence through challenging barriers to treatment.

Conclusions

This investigation identified important barriers to medication adherence among UK stroke survivors. Interventions are needed to address challenges associated with sub-optimal adherence including the provision of inadequate information, the role of the caregiver, recognition of stroke symptoms, patient beliefs about medication and the burden associated with taking pills. This investigation provides insight on the perspectives of general practitioners, caregivers and stroke survivors, highlighting the complex and multifactorial barriers to stroke medication they face.

Chapter 4

Barriers and facilitators to adherence to secondary stroke prevention medications after stroke: Analysis of survivors' and caregivers' views from an online stroke forum

This chapter of the thesis also examines barriers and facilitators of medication adherence in stroke, however the focus of this investigation is from an online perspective and the analysis of posts stroke survivors and caregivers contributed to a UK Internet based stroke forum.

This largely underreported methodological approach to qualitative data collection represents a unique perspective through which the concerns of stroke survivors and caregivers can also be investigated. Analysis of an online forum can provide a broader understanding of stroke survivors' and caregivers' concerns around secondary prevention medication for stroke.⁴²¹ In addition the online forum approach can provide a wider understanding of medication taking behaviour of stroke survivors who are younger and enables the participation of caregivers, allowing users to offer information and support as well as share their own experiences around stroke.⁴⁵⁶ Undertaking qualitative research within an online forum provides the opportunity to understand behaviour that traditional qualitative research studies may not capture.⁴⁵⁷ Forum users may be less likely to participate in traditional data collection practices and may be less well understood. The forum provides an opportunity to potentially understand the views and concerns of survivors who may have significant cognitive difficulties or be physically disabled and who are reliant on an unpaid caregiver or family member to manage medication and their behalf.

This is the first investigation of its kind to explore barriers and facilitators of medication adherence from the perspective of survivors and caregivers contributing to an online stroke forum. The investigation provides an opportunity to shed further light on

adherence in stroke and the barriers and facilitators to medicine taking stroke survivors face. Exploring and identifying the concerns of survivors and caregivers online may uncover new aspects of medication taking behaviour and identify potentially important barriers and facilitators that traditional qualitative methodologies for data collection such as interviews, may overlook.

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This work was undertaken with other collaborators as part of a research team. James Jamison formulated the aims of the study, conducted the qualitative analysis, wrote this chapter and prepared the manuscript for publication. Dr Anna de Simoni double coded a proportion of the online forum findings and contributed to the data analysis. Professor Stephen Sutton contributed to and advised on all aspects of the study and Professor Jonathan Mant offered critical appraisal of the study write up. All co-authors assisted with reviewing the final manuscript.

4.1 Background

Secondary prevention medicines are considered important in reducing stroke recurrences in patient who have already experienced a stroke or transient ischaemic attack.^{133 458} Reported practical barriers to medication adherence after stroke include forgetting medication, difficulty swallowing tablets and difficulties handling packaged medications.⁴¹³ A key factor decreasing patients' motivation for taking secondary prevention medications is having concerns about tablets, such as becoming dependent on them or worrying about their long term effects.⁴¹⁰ Difficulties with taking medication, lack of information on stroke and medications and patient's fears of medicines are important barriers, while support from caregivers and worrying about further stroke are facilitators.⁴¹²

Severe stroke related impairments make it difficult for survivors to participate in research. Perhaps for this reason there is little evidence available on factors affecting adherence to medications in patients with more disabling strokes (at least a third of stroke survivors).^{459 264} Studying factors affecting adherence can be difficult because of self-presentational bias, i.e. patients may perceive that a certain behaviour, e.g. adherence to treatment, is one of the duties expected of the 'good patient' and may be reluctant to admit a different behaviour, or reactivity bias, i.e. if patients are aware that their adherence is being monitored, this might increase adherence simply by drawing attention to it.⁴⁵⁷ De Simoni and colleagues used an online forum to explore adherence to inhaler treatment in asthma adolescents according to a framework, gaining fresh insights on factors affecting adherence in this patients' group.⁴⁶⁰

This exploration of adherence barriers differs from previous literature by assessing survivors and caregivers attitudes to medication from a viewpoint that has not been previously explored. The online forum offers users the opportunity to discuss issues that may be considered sensitive and that they are less willing to address using the traditional face to face approach.

Caregivers of elderly patients experience difficulties with tablet administration.³⁵⁰ As patients' dependency on caregivers for medicine taking increases, caregivers' factors also become relevant in determining patients' adherence.²⁶⁴ An interview study⁴⁴⁰ highlighted the importance of caregivers in adherence to secondary prevention medications. Elsewhere an investigation of patients with CVD found those with a caregiver were more likely to be adherent to medications.⁴³⁰ There is a need to investigate adherence to secondary prevention medications after stroke avoiding self- presentational and reactivity biases, including patients' with severe disabilities and caregivers' factors.²⁶⁴

Online health forums are accessible around the clock in the form of asynchronous communication that is convenient to the user. This medium offers anonymity and encourages honesty. Individuals with health-related difficulties can communicate in confidence about what matters to them.⁴⁵⁷ TalkStroke is an online forum where survivors and their families discuss information and provide support to one another. Recent investigations using this forum showed that a wide variety of themes were discussed online, including secondary prevention medications.^{456 421} Caregiver views were well represented and most of them

(70%) looked after patients with severe disabilities. Among forum users who were stroke survivors, 30% were suffering from severe impairments.⁴⁵⁶ Therefore data from the archives of this forum have the potential to shed light on adherence issues for these hard to reach groups.^{461 421}

The aim of this investigation was to understand barriers and facilitators of medication adherence among survivors of stroke and their caregivers through evaluating posts written in an online stroke forum, using a framework based approach.

4.2 Methods

4.2.1 Design

A qualitative analysis of posts to the TalkStroke online forum was undertaken in line with the Perceptions And Practicalities Approach (PAPA) theoretical framework.²³³ According to the framework, nonadherence is viewed as a variable that can change over time and treatments. Nonadherence is known to be intentional or unintentional. Unintentional adherence is linked to practical factors and resource limitation, e.g. forgetting to take medications because of lack of prompting or experiencing difficulties with swallowing tablets. Perceptual factors or beliefs affect intentional adherence, i.e. how patients consciously make decisions that influence their medication taking behaviour.²³⁰ This occurs when patients deliberately choose not to follow recommendations and where beliefs about medications influence motivation to begin and to continue treatment.

The PAPA framework was chosen as it is specifically designed to identify and classify factors affecting adherence to medications. Results have the potential to inform the development of behavioural interventions aimed at improving adherence and their subsequent evaluation according to causal pathways. The framework posits that patients make a choice to take medication based upon judgement of their personal need for the medication, relative to their concerns about the possible consequences of taking it.²³³ The PAPA approach seeks to understand adherence through addressing both perceptual (beliefs and preferences) and practical (capability and resources) factors which influence patients commencing and continuing treatment. The forum archives were searched using a set of pre-defined keywords,

in order to identify barriers and facilitators of adherence to secondary prevention medications. Posts were written by stroke survivors or family members/ caregivers.

4.2.2 Setting

Analysis was performed on the archives from TalkStroke, a UK based online forum hosted by the Stroke Association website, consisting of 22,173 posts written between 2004 and 2011 by 2,583 unique usernames.⁴⁵⁶ Talkstroke was an online resource through which stroke survivors and caregivers could seek and/or offer information and support. Forum users could discuss any topics, develop their own conversation threads and there was no restriction on the subject discussed. Participants could read the subject of the thread being discussed and decide whether they wished to contribute. Differentiating survivors and caregivers was done by reading the text of the post: survivors talked in first person about themselves, while caregivers were talking about a stroke survivor in the third person, e.g. ‘my father had a stroke’.

Stroke survivors with severe disabilities were amongst the users of the forum. Caregivers could register as users independently from patients. Within the forum, 60% of users were in fact caregivers.⁴⁵⁶ It is possible that some caregivers could have assisted patients in writing their posts, however the data was not available to quantify these occurrences.

4.2.3. Procedure and participants

A word list of unique terms of the archive file of Talkstroke was generated using the computer software, AntConc3.2.4.⁴⁶² Terms related to secondary prevention medications were selected (e.g. Amlodipine, statin, warfarin, ramipril), including misspellings (e.g. Asprin, simvastin), brand names (e.g. Lipitor, Plavix) and drug categories (e.g. statin, diuretics, blood pressure medicines etc.). Posts including any secondary prevention medication term were identified. In addition, the Talkstroke archive was searched using the keywords: ‘taking medication’, ‘pills’, ‘size’, ‘statins’, ‘side effects’, ‘capsule’, ‘box’, ‘routine’, ‘blister’, and ‘secondary prevention’. Keywords used were lay terms used by survivors and caregivers when talking about adherence to secondary prevention medications

as emerged from the transcripts of a previous interview study exploring barriers and facilitators of medication adherence in the general practice setting.⁴⁴⁰

Participants of the online forum included stroke survivors and patients talked about by caregivers, identified by usernames linked to each of the selected posts. Characteristics were retrieved from usernames, taking advantage of data from a previous study.⁴⁵⁶ Characteristics of study participants are shown in Table 4.1 below. All posts relevant to the research questions were copied and pasted into the computer software Microsoft Excel⁴⁶³ and NVivo 10⁴⁶⁴, to permit data analysis.

4.2.4. Ethics

Permission was granted by the Stroke Association to use the forum data for research purposes. As the online forum was inactive at the time of undertaking this research, it was not possible to obtain consent from forum users themselves. However, to protect the identity and intellectual property of forum participants⁴⁶⁵ *verbatim* quotes are not reported, despite this being normal practice in qualitative research. Instead, descriptions of quotes are provided throughout the text.^{456 461} Paraphrasing of the text reflected as closely as possible the original posts. The ethical aspects around conducting research on this forum have been discussed more extensively elsewhere.⁴⁵⁶

4.2.5 Data Analysis

A qualitative approach using thematic analysis was undertaken to explore forum posts.⁴⁶⁶ All posts retrieved through the search terms were read to aid familiarization. To strengthen the validity of findings and ensure rigour, 50% of all posts were double-coded by another researcher. During this process the coding structure was checked to ensure a high level of agreement in coding was maintained.

Queries arising from the coding process were resolved through discussions involving a third party where necessary, until a final consensus was reached. Nvivo 10⁴⁶⁴ was used to manage and organise the data. A set of codes representing key themes were initially developed from the forum to represent barriers and facilitators of medication adherence. These themes were refined, and sub-themes were identified and grouped together with similar concepts. A coding framework was formed and refined further as additional themes emerged.

Data saturation was reached with the recruitment of 84 individuals, beyond which no new themes emerged. Guided by the PAPA framework, forum posts were coded to identify practical and perceptual factors affecting adherence to medications. Identified themes were mapped onto the PAPA framework and sub-divided into barriers or facilitators of medication adherence. Clarification of themes through directly asking participants was not possible. Users could participate in forum discussions they were interested in, offering insights on barriers and facilitators to adherence that may be beyond the reach of interviews. A previous investigation comparing an online forum with qualitative interviews concluded that the forum could provide useful data for qualitative health research.⁴⁶⁷

Table 4.1: Characteristics of forum participants as identified in the study posts

Sample characteristics	N	Median Range
Total participants identified in posts	84	
Number of posts in the forum/ participant		16 (1-4932)
Number of posts about secondary prevention medications/ participant		1 (1-37)
Age at stroke		
Survivor		50 (32-72)
Patient by caregiver		66 (46-91)
Gender		
Male -Survivor	20	
Female- Survivor	26	
Not known - Survivor	3	
Male -Patient talked about by caregiver	20	
Female - Patient by caregiver*	12	
Unknown gender and unknown identity	3	
Identity person posting		
Stroke survivor	49	
Caregiver	33	
Not known	2	
Years since stroke		
(0-12 mths)	37	
(1-5 yrs)	25	
(6-10 yrs)	4	
(11-15 yrs)	2	
(15+ yrs)	1	
Unknown	15	
Caregiver identity		
Daughter /son	20	
Spouse	9	
Other (/in law/ sister)	3	
Unknown	1	
Legend: * <i>Patient talked about by a caregiver</i>		

Although there is evidence that inappropriate medical information or health behaviours in this online stroke forum were identified and corrected by participants in subsequent postings,⁴⁵⁶ consistent with what is reported elsewhere in a cancer patients' Internet support group,⁴⁶⁸ the threads of discussions were not analysed here. As a result, self-correction of quotes by users of the forum is not reported. The term caregiver refers to family members such as spouses or

children, and is not associated with paid caregivers. The analysis pathway to reach the final number of themes is reported in Appendix 5.

4.3 Results

4.3.1 Identification of posts

A search of the stroke forum resulted in 19,214 posts not associated with medication taking being excluded, leaving 2959 posts. Additional analysis excluded 2527 posts not about secondary prevention medications. Of the 473 remaining posts, a further 251 were removed as being duplicate or not directly associated with medication adherence. This yielded a total of 222 posts describing barriers and facilitators of adherence to secondary prevention medication, including 162 posts by stroke survivors, 57 by caregivers and 3 by individuals whose status as a survivor or caregiver could not be identified.

4.3.2. Characteristics of study participants

From 222 posts related to adherence to secondary prevention medications 84 individuals were identified. Approximately 60% of participants were stroke survivors posting about their own experiences with the remainder being caregivers, who were predominantly sons or daughters. Participants ranged from 32 yrs to 91 yrs of age, while similar numbers were male and female (n=40 vs n=38, see table 1). Majority of participants experienced a stroke within 12 months of posting on the forum. Around three quarters (73%) reported a stroke occurring within the last 5 years, with 44% having had a stroke within the previous 12 months. The mean number of years since stroke was 2 yrs 2 months for survivors and 10 months for patients talked about by caregivers. Several participants were prolific users on the forum and were instrumental in facilitating discussions and providing feedback on a considerable number of topics, offering a rich and in depth assessment of issues raised. One forum participant wrote 37 posts about secondary prevention medications, while another posted 15 times. The majority of participants (n = 44) posted only once, 19 participants twice and 6 posted three times. Sample characteristics of study participants are reported in Table 4.1.

4.3.3 Themes identified from the online forum

The range of themes comprising barriers and facilitators of medication adherence are reported in the Appendix 6 (Key themes highlighting survivors' and caregivers' barriers and facilitators to adherence to secondary prevention medications classified according to perceptions and practicalities). In line with the PAPA approach²³³ these are discussed according to the following two categories.

Perceptions- Necessity Beliefs and Concerns

In this section perceptual barriers and facilitators of medication adherence in stroke survivors and caregivers are explored, according to their classifications as necessity beliefs i.e. doubts about personal need for medication to maintain or improve current and future health, and their concerns about secondary prevention treatment.

Practicalities- Capability and Resources

In this section barriers and facilitators that stroke survivors and caregivers face around their capability of taking/giving medication and the resources available to undertake such behavior are explored.

Within each category themes are grouped into barriers and facilitators. For each of the emerging themes, where relevant, the caregivers' views are reported after patients' ones. Themes identified within the online forum are reported in Table 4.2 below

Perceptions - Necessity beliefs and concerns (PAPA)

Treatment Necessity

Theme 1: Lack of perceived benefits of medications

Sub theme: Doubts about high cholesterol as risk factor for stroke.

A few users expressed doubts about the role of cholesterol in stroke, questioning the need for taking any preventative medications at all.

A male survivor acknowledged statins controlled cholesterol, but believed strokes occurred regardless of cholesterol levels. He talked about the 'Cholesterol Myth' having researched the topic online and described feeling confused about taking statins when in reality they weren't needed. [Male, age 67, age at stroke 55, N.70]

Sub theme: Doubts about the added benefit of statins.

Doubts were also expressed about the benefits statin added to long term health outcomes

A female survivor read about the hype around statins and stated she still didn't have confidence in them. She had read a research paper on statins suggesting they only added an extra 9 months of life.[Female, age 56, age at stroke 56, N.66]

Caregivers' related views

Sub-theme: Respecting patient's medication choice.

Caregivers struggled with their role of ensuring patients' adherence. They felt survivors' decisions about choosing or refusing medications needed to be evaluated according to patients' preferences and not just in terms of what was clinically right.

A caregiver recognized it was hard to encourage her father to take medications. He suffered many side effects which made him feel less in control so he would choose to go without tablets. She said it was important to have a balance regarding what the survivor wanted, considering he stated he would be happier if he felt he was in control. She concluded that patient's choice had to be respected, even if she didn't agree. [Male, age unknown, age at stroke unknown, N.46]

Sub-theme: Awareness of stroke recurrences despite medications

The fact that survivors could suffer a further stroke despite taking secondary prevention medications and following a healthy lifestyle also raised concerns around the benefits of adherence to medications.

A caregiver described how after having a first stroke, her father changed his lifestyle completely by eating well, exercising more and taking medication to control his blood pressure. However one day his BP surged suddenly and he experienced a second stroke. [Male, age unknown, time since stroke 0 yrs, N.55]

Theme 2: Attributing importance to medications

Sub-theme: Secondary prevention medications are essential to prevent stroke recurrences

The importance of secondary prevention medication in reducing the risk of a stroke event was acknowledged by forum users. Prioritising secondary prevention tablets over other types of medications highlighted the significance survivors attached to adherence to these medications. These posts were often written in reply to users complaining of medication side effects.

A female survivor commented that it was better to take a few extra tablets from the GP than to experience another stroke. Tablets were provided to prevent a further stroke, and she stressed that they shouldn't be stopped except on professional advice [Female, age 51, age at stroke 51, N.17]

Sub-theme: Secondary prevention medications offer reassurance

Another survivor reported feeling reassured by medications, particularly warfarin.

A female survivor mentioned that although she had suffered 2 strokes in the previous year, none had occurred since commencing warfarin. She felt reassured about taking warfarin and she was now worried about coming off the medication as she had already experienced flashing in her left eye since she had started to be weaned off the drug [Survivor, female, age 42, age at stroke 42, N.35]

Sub-theme: Experiencing the consequences of nonadherence improves adherence.

Experiencing the consequences of medication nonadherence after having another stroke reinforced necessity beliefs about secondary prevention medications.

A survivor who had already suffered 2 strokes acknowledged it was impossible to ever fully recover from the stroke experience. He said after his first stroke he was prescribed tablets he didn't take and after suffering the second stroke he realised this was a big mistake. [Male, age 67, age at stroke 55, N.82]

A survivor refused statins after her first stroke because of side effects. However, after suffering a second one she was now worried enough to take them. [Survivor, female, age 68, age at stroke 67, N.14]

Caregivers' related views

Sub-theme: Not taking secondary prevention medications is risky

Caregivers generally held strong beliefs about the need for secondary prevention medications.

A caregiver (husband) advised that if patients don't take medications they're likely to become worse. He was amazed about how many people choose not to take their tablets, perhaps half of them, and few even did so when they knew they had a meeting with the consultant in the coming weeks. [Female, age 46, age at stroke 46, N.12]

A caregiver (daughter) mentioned that her father wasn't taking medication routinely. He had had a massive stroke just a few weeks earlier. She wanted to say to forum users that if stroke survivors follow a healthy lifestyle and are strict with medications, then there is no reason why a major stroke could not be prevented. [Male, age 55, age at stroke 55, N.6]

Concerns

Theme 3: Management of medication side effects

Sub-theme: Suffering from side effects contributes to suboptimal adherence

The experience of side effects led some users to intentionally alter adherence to the medications. This was done by ‘making a compromise’ with health professionals.

A male survivor described being suspicious of the number and variety of pills he was dispensed. He said that he had come to a compromise with his doctor about taking blood pressure tablets. He was on 2 tablets for blood pressure, of which one was a diuretic. Having got fed up of frequently running to the toilet, he decided to check his blood pressure every day and would skip the diuretic if blood pressure was fine [Male, age unknown, age at stroke unknown, N.63]

Sub-theme: Lifestyle changes *versus* taking secondary prevention medications

To avoid side effects, some stroke survivors took the decision to reduce cholesterol through changing diet, rather than medications, without mentioning whether this decision was taken with or communicated to healthcare professionals. However reducing cholesterol through diet rather than medication was recommended by the GP also.

A female survivor decided to reduce her cholesterol through diet because of unpleasant side effects of statins. Once symptoms disappeared, she wouldn't take the statins, but instead olive oil and a healthy diet to keep her cholesterol balanced naturally. She said she would continue aspirin as it didn't seem to cause side effects [Female, age 52, age at stroke 52, N.76]

A female survivor mentioned her cholesterol level was average. Her nurse suggested starting medication but her GP was against this, saying the level could be reduced through diet and exercise alone as these tablets were over prescribed. She added that statins were recommended when needed because of genetic makeup [meaning familial hypercholesterolemia]. [Female, age 49, age at stroke 48, N.21]

Depending on the exact clinical scenario, the decisions about statins in the last two posts could be medically appropriate or not, i.e. act both as barrier or facilitator to adherence to secondary prevention medications. Due to lack of details, no definite classification could be made. To reflect this, themes were reported under both headings in Table 2, but reported only here within the results, for simplicity.

Caregivers' related views

Sub-theme: Caregiver difficulties in acting as advocates of stroke survivors with healthcare professionals.

Caregivers assumed at times the role of advocates for their family members suffering from the side effects of medication and reported struggling in this role. Failure to be successful in obtaining a change in treatment led some survivors to stop taking medication completely.

A female caregiver described consistently trying to have her husband's 40mg statin dosage reduced by his GP. As a result of the high dosage he was chronically tired, so he stopped taking statins. [Male, age 54, age at stroke 52, N.68]

Theme 4: Impact of negative press attention on statin

Sub-theme: Influence of side effects on taking medicines

Side effects of secondary prevention medications raised important concern, and statins were frequently discussed by forum users. The negative press attention (e.g. in newspapers, television, radio reports) about statins was mentioned in relation to starting the medication and ongoing adherence. Participants discussed these concerns together with health care professionals.

A survivor wrote that despite her GP's recommendation she couldn't commence statins after reading in the press about side effects. She said she felt well and didn't want to jeopardise that, as she wasn't convinced she needed them. Although also her consultant disagreed with her decision and was keen for her to take them, he said she didn't necessarily have to take them. [Female, age 54, age at stroke 54, N.37]

Caregivers' related views

Sub-theme: Negative press attention making it harder for caregivers to encourage adherence
Reading information about statins and their side effects highlighted caregivers' struggle and made it more difficult for them to help stroke survivors be adherent.

A caregiver's mother had suffered 2 mini strokes and was now prescribed both aspirin as well as pills to lower cholesterol but was refusing to take these as she had read in the press about the bad side effects they caused [Female, age unknown, age at stroke unknown, N.74]

Theme 5: Questioning prescribing practices

Sub-theme: Problems with obtaining appropriate secondary prevention medication treatment
Disappointment was expressed when practitioners failed to start/change secondary prevention medications when the survivor judged their current treatment to be inadequate.

A survivor described feeling let down as he requested changes in medications because he didn't feel they [aspirin and clopidogrel] were beneficial. He'd lost confidence in the health care system after visiting several consultants and being sent home with unchanged medications. [Male, age 43, age at stroke 41, N.20]

Sub-theme: Concerns around incorrect prescribing

This was also apparent when the prescribed medication was perceived as being incorrect.

A stroke survivor recalled being on 75mg of aspirin as well as beta blockers, however, his nephew who was a consultant surgeon, suggested that had he been taking warfarin instead of the aspirin he may not have suffered a second stroke [Male, age 67, age at stroke 55, N.82]

Sub-theme: Inconsistent advice about medications prescribed

Receiving conflicting advice on medication practices caused further uncertainty and confusion, which might have indirectly affected adherence to secondary prevention

medications.

A survivor suffered increased bleeding while on warfarin was taken off it. He suffered another stroke shortly after, and was put back on warfarin for the bleeding to begin again. He felt confused at being told to stay on warfarin to avoid a potentially serious stroke. [Male, aged 72, age at stroke 72, N.10]

Caregivers' related views

Sub-theme: Questioning GP's motivation to prescribe

Caregivers also raised concerns about GPs prescribing, principally statins, for financial rather than medical reasons, which could indirectly affect adherence, especially in patients suffering from statin side effects.

A caregiver (sister) suggested that GPs shouldn't be paid for prescribing statins and that the decision should be based on clinical judgement alone. She suggested medication could be overprescribed as a result for financial reasons [Gender and age unknown, age at stroke unknown, N.78]

Sub-theme: Caregivers' difficulties as advocates of patients' medications

The caregivers' role as advocates for their family members came up in questioning prescribing practices, highlighting caregivers' awareness of guidelines and difficulties at times with obtaining treatment modifications on the behalf of patients. (This post does not reflect current practice as the cost of atorvastatin has dropped since the post was made on the forum).

A caregiver recommended being firm with GPs about being put on atorvastatin if simvastatin was not tolerated, as atorvastatin was a bit more expensive but recommended by NICE guidelines as an alternative [Gender and age unknown, age at stroke unknown, N.18].

Sub-theme: GPs' role advising about secondary prevention medications

Some survivors reflected on the role of GPs in their adherence. They felt that the GP's role was to provide advice. Getting support from family in medication related decisions was considered important.

A male survivor agreed to stop taking a blood pressure tablet with his doctor because of intolerable side effects, and his wife being a nurse made it easier. He felt strongly that doctors are there to advise not instruct. [Male, age unknown, age at stroke unknown, N.63]

Caregivers' related views

Caregivers also recognized the importance of medications and the need to continue taking tablets despite experiencing side effects. The importance of only stopping medication on GP's advice was highlighted.

A caregiver reported that because of side-effects her husband had voluntarily come off all the medication he was taking, except for aspirin which he continued to use. She said they had agreed to this together with the GP and stressed the importance of doing so before stopping tablets. [Male, age 54, age at stroke 52, N.68]

Theme 6: Management of medication side effects

Sub-theme: Medications didn't necessarily cause side effects

Survivors who did not experience medication side effects generally felt that taking medication was a positive preventative measure against stroke. Although threads of discussion were not analysed, these posts often were written in reply to users who complained about suffering from side effects.

A male survivor advised it was better taking tablets than risking another mini-stroke. He had a severe stroke himself and was prescribed aspirin and simvastatin. He never experienced side effects and also knew others on the same statin who didn't

experience any either. [Male age 67, age at stroke 63, N.52]

Sub-theme: Changing medications to avoid side effects

Forum users reported changes in secondary prevention medications being made by the health professionals to counteract negative side effects, which helped adherence.

A male survivor described that on a dosage of 8mg of warfarin he started to suffer migraines and bleeding, leading him to refuse the drug. After further conclusive tests, the consultant decided to take him off warfarin as he was taking persantin, which never gave him a headache or nosebleed. He acknowledged warfarin was an important drug, but didn't suit everyone. [Male, age 49, age at stroke 49, N.47]

Sub-theme: Perseverance with asking modifications to achieve optimal treatment

Doctors' and patients' perseverance in modifying medications was important to achieve optimal treatment.

A male survivor reported taking up to 7 different blood pressure tablets and that it was unusual for a stroke patient to only need a few. He recommended going back to the GP as necessary to keep changing tablets until the right combination was found [Male, age 52, age at stroke 52, N.64]

Caregivers' related views

Sub-theme: Treatment adjustments to avoid side effects

Reduction of medication dosage by doctors and elimination of side effects was reported as a successful strategy to aid adherence.

A female caregiver described her husband suffering from considerable side effects from simvastatin 40mg but when the GP changed to atorvastatin at a lower dose of 10mg he was able to cope. [Male, age 54, age at stroke 54, N.49]

Theme 7: Trusting healthcare professionals

Healthcare professionals had an important role in patients' trust in secondary prevention medications and consequently adherence.

A survivor described how he trusted his vascular surgeon who had changed his medication from warfarin to aspirin and statin. The survivor was happy to take aspirin and felt it would be good to continue as the surgeon also took it regularly, concluding it must be beneficial [Survivor, male, age 35, age at stroke 34, N.71]

Practicalities- Capability and resources

Theme 1: Problems associated with taking tablets

Sub-theme: Swallowing and handling medicines

Swallowing difficulties were reported when taking tablets, especially in relation to the medication dipyridamole, due to its size.

A male survivor described 'swallow panic', i.e. fear of choking when trying to take Dipyridamole capsules. The user reported it took around 3 months before he got over that. [Male, age 67, age at stroke 55, N.70]

Size of tablets also caused handling difficulties due to stroke related impairments.

A survivor agreed with another user about the problem with the size of dipyridamole tablets, which were getting stuck in the pill box organizer. [Female, age 46, age at stroke 45, N.30]

Caregivers' related views

Sub-theme: Treatment burden

Taking multiple tablets also contributed to treatment burden experienced by caregivers. One caregiver described how this added to the survivor's episodic refusal to take any medications.

A caregiver was asking advice on encouraging medication taking. He said his mother was on multiple tablets, up to 4 times a day, but was now refusing to take any at all and this did upset him. Persuading her to continue taking the most important tablets had taken hours to do. [Male, age 77, age at stroke 77, N.9]

Sub-theme: Attending routine appointments

Another practical difficulty was dealing with routine appointments which were considered burdensome, resulting in the survivors being non-adherent to medications.

A caregiver (wife) described how her husband was adamant that he was not prepared to take statins because he didn't have the time to keep going back to the GP for check-ups. The caregiver reported feeling helpless. [Male, age 55, age at stroke 55, N.24]

Sub-theme: Difficulties experienced by patients with disabilities

Caregivers of patients with severe disabilities such as aphasia and inability to communicate, made their job of ensuring patients' adherence a difficult experience.

A caregiver said she couldn't imagine what a stroke survivor was going through, with her mother unable to communicate following a stroke. She described her mother having difficulties with medications caused by previous changes in treatment. She felt her mother was giving up and wanted advice on dealing with aphasia. [Caregiver-daughter, age 52, age at stroke 47, N.54]

Sub-theme: Problems with using storage devices

Using Dosette boxes was sometimes a struggle for survivors with severe disabilities, and a source of worry for caregivers.

A caregiver mentioned that despite using a nomad tray, tablets were still being taken from the wrong day with several days' worth of tablets being taken in a single day. His father in law often didn't take the time to work out the days or to look at the calendar [Male, age unknown, age at stroke unknown, N.40]

Sub-theme: Seeking advice from pharmacists on managing medications

Another caregiver described having to seek advice on the best way to manage the stroke survivor's medications.

A caregiver said he went to the pharmacist and spent half an hour chatting about medications after which he bought a flip top multi-coloured medication box labeled with the days and doses. He also said it took him a while to establish the best way to fill the box without getting confused, eventually filling it a tablet at a time across the entire week, instead of a day at a time. (Male, age 82, age at stroke 82, N. 57)

Theme 2: Cost of medication

Survivors' highlighted difficulties faced with meeting the cost of stroke medications.

A female survivor described being prescribed both aspirin and simvastatin that she had to pay for. She reported having to take out a credit card to pay for her medications as she was unable to work and did not have any money coming or any benefits. [Female, age 59, age at stroke 59, N.72]

Theme 3: Storage devices and strategies for medication management

Sub-theme: Using medication aids

Stroke survivors also reported benefits from using medication aids including pill-boxes and medication wallets to facilitate medication taking behavior. These devices ensured the appropriate medication was being taken at the right time, while also allowing monitoring when boxes needed to be re-filled.

A survivor agreed the storage box was useful to view medication and her husband didn't have to keep asking her whether she had taken her tablets as he could also see. She said it was irritating to be constantly asked. The box helped her also with not running out of medications as she filled it weekly and could tell when it was time for a repeat prescription. [Female, age 46, age at stroke 45, N.30]

Caregivers' related views

Sub-theme: Using medication instructions

Caregivers highlighted how instructions were considered helpful in facilitating day to day medicine taking. Keeping track of medicines that had been taken was suggested as a method of ensuring good adherence.

A caregiver (son) described making a note on the pill box asking the survivor to turn it over after taking the pills as this would mean the morning pills were now taken. A second instruction invited the survivor to do the same when taking the evening tablet. He suggested to forum users that a simple chart tracking when each medication was taken was also helpful. [Caregiver-son, age 82, age at stroke 82, N.57]

Theme 4: Good medication taking routines

Sub-theme: Creating good medication routines

Linking daily tablet use to an everyday activity or placing tablets in a specific location which then acted as a cue to take the medication was described as helpful by several users.

A survivor suggested using a white board and having method in place helped. She remembered taking her own medications through repetition or linking tablet use to another everyday activity [Female, age 54, age at stroke 46, N.19]

Caregivers' related views

Sub-theme: Reminding survivors about taking tablets

Caregivers also played a key role in medication routines when survivors couldn't remember to take tablets.

A caregiver (wife) described regularly giving her husband his medication because stroke had caused short term memory loss and he would forget them or sometimes take them over again. She said she was now in total control of his medications which was fine because she was a nurse with experience of this. [Female, Age 46, age at stroke 40, N.5]

Table 4.2: Themes identified within the online forum: Perceptions and Practicalities

4.4 Discussion

Summary of main findings

Data from an online forum provided a rich source of information, illuminating on practical and perceptual barriers and facilitators to adherence to secondary prevention medications in stroke survivors and their caregivers. These data highlight several points. Concerns around the negative press attention on statins could result in stroke survivors being cautious about commencing/ continuing to take this medication, and opting for a change in diet as an alternative (potentially a not medically appropriate decision and without healthcare professionals' support). Survivors expressed concerns about being prescribed medications they considered inappropriate, questioned GPs' motivation to prescribe medications and at times realised when prescribing mistakes occurred.

Caregivers themselves reported some doubts about the effectiveness of tablets and difficulties in ensuring good medication adherence, while recognising that it is ultimately the survivor's decision whether or not to take medication, particularly when suffering from side effects. Indeed, not experiencing side effects from secondary prevention medications was an important facilitator of adherence. Health professionals successfully modifying treatment to

manage side effects and awareness that not everyone suffers from side effects were reported as increasing the motivation to take secondary prevention treatment. Believing that medications reduced stroke risk, feeling reassured by taking secondary prevention treatment and experiencing another cerebrovascular event as a consequence of nonadherence were important drivers of necessity beliefs and supported adherence.

Practical barriers included difficulties swallowing capsules, burden of multiple medications, stroke-related communication impairments (e.g. aphasia) causing patients' confusion with any treatment changes, difficulties meeting medication costs and managing storage devices. Caregivers' posts greatly contributed to these data. They reported that improved patients' adherence was linked to using medications storage devices, getting help from pharmacists in organising medicines, assuming full control of their family members' medication taking, and having previous experience and knowledge about medications and their administration.

Strengths and limitations

This study has a number of strengths. Firstly, the method of data collection where descriptions by forum users capture unprompted thoughts is unlikely to be affected by self-presentational bias. Information came from patients over a wide geographical area and included patients who might not take part in traditional research because of severe disabilities, communication impairments or in the case of caregivers, because of lack of time.⁴⁵⁷ The forum creates a natural environment facilitating exchange in opinions and in-depth discussions around several topics including secondary prevention medications. The important presence of caregivers in online discussions is a further strength, offering a unique viewpoint on medication taking behavior of survivors with severe disabilities. Given that patients with significant disabilities may not traditionally participate in health research, the online forum may represent a potentially important method of data collection in which these patients' views may be heard through their caregivers.

These findings however should be interpreted with caution. A key limitation of this research was that forum data was from the years 2004- 2011 and therefore the findings reported here may not reflect current practice in primary care. Lack of details about the underlying clinical scenarios described in some of the posts made it difficult classifying

emerging themes as barriers or facilitators to adherence. In addition, barriers and facilitators were limited to those identified from the pre-defined search criteria. Different keywords may have uncovered additional barriers to medication adherence that we failed to identify, or revealed issues related to medications in general rather than specifically secondary prevention ones. All forum posts were examined by a moderator prior to being published online which may have restricted the views of some users. Finally, with the majority of forum users under the age of 70, it is possible that this method of data collection overlooks a significant proportion of the older stroke population.

Comparisons with existing literature

This investigation shed light on the significance stroke survivors and caregivers attributed to the negative press attention on statins, which impacted on their adherence. This agrees with a recent investigation concluding that negative statin related news stories was associated with early discontinuation of statin and increased risk of death by cardiovascular disease.⁴⁶⁹ Furthermore, people already taking statin were found to be more likely to stop this medication following high media coverage,¹⁵⁷ or when side effects were not tolerable despite GP's attempts to modify treatment.⁴²¹ Beliefs about secondary prevention medications differed at times between survivors and caregivers. Some stroke survivors decided to stop medications because of intolerable side effects, despite their caregivers' believing optimal adherence was important to prevent stroke recurrences. In the context of medication side effects, caregivers believed in their role as patients' advocates with healthcare professionals (including GPs and pharmacist) and often discussed and sought advice from other users in the forum on the matter. Findings from the present study also highlight the difficulties experienced by stroke survivors using blister packaged medication and dosette boxes, despite at the same time outlining their benefit in terms of adherence. Evidence from a systematic review has demonstrated significant improvement in adherence for those in the group using reminder packaging⁴⁷⁰ as well as using pill boxes and blister packs in packaging interventions in cardiovascular disease⁴⁷¹ while the use of reminder packaging may be a simple way of improving adherence to medication.⁴⁷² With older people known to experience difficulties taking medication, developing interventions that seek to combine the use of

medication management devices with caregiver co-operation may be one way of addressing the practical challenges they face.

This study highlights a couple of interesting findings. Survivors reported making decisions about taking or not secondary prevention medications sometimes independently from their GPs, despite considering GPs' support important. Collaborative decision making involving caregivers, clinicians or pharmacists may however empower stroke survivors to make better informed decisions about secondary prevention medications. Understanding how patients make decision about medications is important⁴⁷³ and GPs may benefit from enhancing caregivers' role in the decision making process about medications.

Barriers to caring for the stroke survivor post hospital discharge have included a lack of collaboration with the healthcare team and a lack of community support for the caregiving role⁴⁷⁴ as well as insufficient knowledge and skills to care for the survivor in the home.⁴⁷⁵ This study highlighted the struggle caregivers face in their role as advocate of patients, on one side engaging with healthcare professionals for ensuring that recommended secondary prevention treatment is received, and on the other side wanting to support and respect patients' decisions about taking or not taking medications. Caregivers facing this dilemma could benefit from greater support by GPs and pharmacists. Caregivers could play an important role in bridging the gap between health professional and stroke survivor in primary care and deserve more research and clinical attention. Developing interventions that seek to encourage active caregivers' engagement in stroke survivors' and healthcare professionals' shared-decision making, can help to address more comprehensively barriers to adherence as well as delivering a care program tailored to the individual needs of patients.⁸

Barriers highlighted here are in line with those reported by another qualitative study, where negative or erroneous beliefs about tablets, doubts around the effectiveness of medication and concerns about the consequences of not taking tablets were associated with being low adherers.⁴⁰⁴ Greater emphasis on informing stroke survivors and caregivers about secondary prevention medications in primary care is therefore needed. In a recent randomised trial evaluating an educational package for stroke survivors and caregivers, participants who received tailored information along with verbal reinforcement reported a greater satisfaction with medical and practical services.²⁹⁷

Survivors' concerns around the need for secondary prevention medications may reflect a wider pattern of misunderstanding about the benefits of such drugs. In an assessment of attitudes towards taking cardiovascular medications, caution expressed around medications was linked with how great their risk to health was perceived to be.⁴⁷⁶ A meta-analysis examining the necessity-concerns framework across a range of conditions found that experiencing the consequences of nonadherence reinforced the subsequent need to take tablets, acting as a driver of medication adherence²⁷², in agreement with what is reported in this study by both stroke survivors and caregivers.

Although statins are known to reduce the risk of stroke by as much as 25%,⁴⁷⁷ benefits are undermined by suboptimal adherence. In a previous examination on patient perspectives around statin therapy, compliance with statins was associated with information provided during the practitioner consultation as well as the beliefs about cholesterol and current health status.⁴⁷⁸ This concurs with the findings in the current study. An investigation exploring nonadherence and patient's perceptions towards statins found that up to three quarters of participants doubted the necessity of statins, lacked knowledge about this medication, and concerns around side effects were significantly associated with intentional nonadherence.⁴⁷⁹

This online forum provided evidence that stroke survivors establish routines and use cues to facilitate medication taking. This is in agreement with findings reported elsewhere, including a pilot trial in which a plan to establish a medication routine resulted in significantly greater adherence among survivors.³⁴¹ Providing support to establish medication taking routines particularly among older patients with stroke can be beneficial.⁴²³ Challenges to adherence with warfarin therapy, including beliefs about the need for this treatment have been highlighted previously, suggesting the benefit of a more collaborative patient - practitioner approach, focusing on education around anticoagulant therapy.⁴⁸⁰

These findings also add to current literature by providing an assessment of adherence from users of an online forum. There has been little research on this approach to data collection conducted to date. The study identifies adherence concerns of younger stroke survivors who may be less likely to participate in traditional research studies and whose attitudes to medication may be less well known. The results reported in this study shed light

on the dynamic interactions between the stroke survivor, caregiver and healthcare professional and the extent to which this influences medication adherence in stroke. .

Implications for clinical practice

Results show there is a need to address barriers to adherence in secondary prevention medications within clinical practice. Improving patient-caregiver and caregiver-practitioner communication through more effective clinical consultations has the potential to benefit patients and encourage a greater understanding of the importance of secondary prevention medications. This approach could contribute not only to shaping patients' beliefs about medications but also to improving confidence around taking them. Challenging negative medication beliefs and adopting practices that implement simple medication taking routines and appropriate use of tablet storage devices, particularly for those patients with more severe disabilities as a result of stroke, can increase adherence and ultimately improve health outcomes.⁴⁷⁹

Both primary and secondary healthcare professionals should seek to engage the family of survivors and their support network to challenge concerns around taking tablets, offer reassurance on the benefits of medications, discuss the need for treatment in light of side effects, and even support patients' informed decision to refuse medications.

Interventions using 'expert patients' or 'expert caregivers' providing support to stroke survivors and caregivers in the primary care setting hold potential.⁴³⁰ Internet forums for stroke patients offer a potentially important resource through which survivors and caregiver's attitudes towards medication use can be better understood.

These findings provide new insight to clinicians about younger stroke survivors' concerns and the struggles caregivers might face in their role as patients' advocates. Awareness of these factors will improve consultations about secondary prevention medication with both younger survivors and stroke survivors' caregivers. Stroke survivors with severe disabilities and their caregivers experience significant practical barriers to adherence. Greater focus on such practicalities by healthcare professionals would be beneficial.

This study highlights caregivers' unique position in overseeing patients' medications. Exploring the stroke survivor-caregiver dynamic can shed light on potential barriers to

adherence to secondary prevention medication and ways to address them, eventually improving patients' outcomes.

Future research

This study suggests that caregivers play an important role in bridging the gap between patient and practitioner with regard to informing and facilitating the medication taking process. Future research should therefore further explore their role in stroke survivors' medication taking and systematically incorporate them into adherence interventions.

Given the strong focus of forum users on statins, understanding why stroke survivors choose not to take statins as prescribed and suggesting to healthcare professionals effective ways of dealing with this issue should be a key focus for research in this area. With adverse events the most common reason for poor adherence to statin therapy, improved patient understanding of this medication through greater communication with the practitioner can help to address ongoing concerns.⁴⁸¹

Future interventions should aim at further improving medication taking routines after stroke, using cues to prompt tablet taking. Advances in technology could facilitate delivery of such interventions. One novel approach to improving adherence particularly with regards to multiple medications is the use of fixed-dose combination therapy 'polypill approach'.⁴⁵⁴ Indeed a recent systematic review of barriers and facilitators of adherence to secondary prevention medications within cardiovascular disease found fixed dose combination (FDC) therapy to be an important facilitator associated with high adherence.⁴⁸²

Conclusion

This study identified barriers and facilitators to medication adherence for stroke through analysing data from an online forum using a framework approach. Developing interventions which build on these results according to the PAPA framework has the potential to improve medication adherence and ultimately reduce the burden of stroke. Greater efforts are needed to meet the growing challenges faced by stroke survivors and their caregivers and to enable primary care clinicians to effectively address the burden of nonadherence to secondary prevention medications.

Chapter 5

Online stroke forum as source of data for qualitative research: insights from a comparison with patients' interviews

This chapter of the thesis examined the potential of an online forum as a valid source of data for conducting qualitative research by comparing results derived from two independent data sources examining barriers to medication adherence for the secondary prevention of stroke- semi structured interviews and an online forum.. The online forum approach (see Chapter 4) was compared to a traditional face to face interview approach (see Chapter 3), to identify key methodological and characteristic differences. While the qualitative interview approach is a well-established research methodology, the potential of the online forum as a medium through which qualitative data may be collected and analysed is largely unexplored. Analysis of both of these data collection approaches, through comparing the methodologies, can offer reassurance that an online stroke forum may be a valid source of data in its own right, despite the inability to verify online forum participants' characteristics including identity and stroke diagnosis. This study will also provide an assessment of the representativeness of findings from the online forum when compared with a more traditional research approach such as interviews. Identifying important differences between these two approaches could be advantageous to researchers when deciding which of the two approaches is better suited to a particular research question. Moreover, comparing both approaches using the same research question has the potential to uncover new and interesting insights into medication adherence that may not be uncovered by a single approach or may be beyond the reach of traditional data sources such as semi-structured interviews.

Comparing these approaches will provide a wider understanding of the potential for using online forums as a tool to explore patient concerns and perspectives on medication in stroke.

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Other collaborators contributed to the investigation. James Jamison conceived of and devised the study, undertook the statistical analysis and prepared the manuscript for publication. Dr Anna de Simoni, Professor Stephen Sutton and Professor Jonathan Mant advised on the study direction, offered critical appraisal and assisted with reviewing of the final manuscript.

5.1 Background

In recent years participation in online forums has increased dramatically out of a need for patients to know more about the health care conditions they face.^{483 484 485 486 487} With the use of online health forums steadily increasing, greater efforts are being made to understand this mode of data collection for qualitative research.^{488 489} Online patient communities represent an important source of information, offering access to hard-to-reach groups who are often excluded (or exclude themselves) from traditional research studies.^{457 461}

Internet use across the UK has grown considerably. A recent report on Internet usage report found that in the first quarter of 2017, approximately 89% of adults used the Internet, increasing from 52% in 2011 to 78% in 2016 for those between the ages of 65 and 74.⁴⁹⁰ 42% of those 75 years and older of all genders are now Internet users.⁴⁹¹ It is estimated that one in four people with a chronic condition who use the Internet go online to find others with similar health concerns.⁴⁹² Patients engage with the Internet to access health information⁴⁹³ and manage chronic illness.⁴⁹⁴

Patients are becoming more informed about their health through using the Internet.⁴⁹⁵
⁴⁹⁶ Around 70% of Europeans who access the Internet, using it to obtain health

information.⁴⁹⁷ In the UK, digital technology has recently emerged as a key vehicle for the delivery of health and social care.⁴⁹⁸ A review of the use of technology in healthcare confirmed that social media were increasingly used to communicate health information among public, patients and health professionals.⁴⁹⁹

As a method of capturing data on health attitudes and behaviour, the online forum offers considerable advantages, including access to large numbers of prospective participants with the potential for open and honest discussions.^{500 456 457 461} Such forums have been used previously in health care research⁵⁰¹ across a range of health domains.^{502 503 504 505}

In the face of increased technological change, there is a growing need to understand the potential for online sources of qualitative data⁵⁰⁶ and their advantages and disadvantages compared with traditional data collection techniques.^{507 508}

The interview is an important qualitative data collection technique widely used in health care research.⁴⁴⁶ This method permits face to face contact with respondents, flexibility to adapt the direction of conversation and the scrutiny of physical cues such as body language, adding greater meaning to the discussion.

There is a growing body of literature exploring the potential for online forums as a source of data collection compared with traditional qualitative techniques as well as a greater understanding around using each of these methods. Nevertheless, difficulties verifying participants' identity and medical condition (i.e. are forum users real patients with stroke?) as well as the inability to interpret visual cues and seek clarification to questions, suggests that it may be necessary to confirm results with more established data sources, such as qualitative interviews.^{446 413} Confirmation of data may be deemed necessary in order to explore whether forum findings are representative of issues experienced by patients with stroke, and whether differences between the two sources could be used to decide which is better suited to addressing a particular research question. In an investigation comparing an online forum with qualitative interviews among cancer patients, the authors concluded that the forum offered useful data for qualitative health research.⁴⁶⁷ Similarly, comparison between an online forum and face to face focus groups in people with multiple sclerosis concluded that forum results were comparable.⁵⁰⁹ Comparison of characteristics of online versus face to face approaches have been reported more frequently with respect to focus groups.^{510 511}

Drawing on a realist evaluation perspective⁵¹² the objective of the present study was to explore differences across two approaches to qualitative data collection- interviews⁴⁴⁰ and an online stroke forum⁴⁴¹ by seeking to understand the attributes that underpin each data source, exploring the context within which each data collection occurs and comparing barriers and facilitators of adherence to secondary prevention medication classified thematically according to the Perceptions and Practicalities (PAPA) framework.²³³ The overall aim was to offer a structured way to systematically explore the differences between these two data collection approaches and highlight the characteristics of an online stroke forum as a source of data for qualitative research, which may be of use to other researchers.

5.2 Methods

5.2.1 Design

Comparison of themes around barriers and facilitators of adherence to secondary prevention medications after stroke in two independent studies, qualitative semi-structured interviews and an online forum. Although one author initially coded the data in both studies, a subset of each data set was double coded by a different author in each of the studies; therefore thematic analysis was independently validated. As interviews are a widely accepted method in qualitative research,⁵¹³ this approach was used as the standard against which to compare forum data. Differences and similarities in the data were examined, and results were compared and contrasted to explore the potential of the online forum as a data collection source.

5.2.2 Interviews-dataset

Interview participants included stroke survivors recruited through five general practice surgeries in Eastern England, along with their caregivers, as described previously.⁴⁴⁰ In brief, purposive sampling was undertaken, patients were approached by letter and positive responders were contacted to confirm attendance. All interviews were guided by a topic schedule, with written consent. They were conducted in the stroke survivors' own houses together with caregivers and lasted approximately one hour. Twenty percent of the interviews were double coded by another author to enhance rigour and strengthen the validity of

findings. The interview study was granted ethical approval by NHS Research South Yorkshire Ethics Committee (Ref 13-YH-0067).

5.2.3 Online forum- dataset

Methods are reported in greater detail in Chapter 4. Briefly, the source of data was the archive file of an online forum, Talkstroke, hosted by the UK charity Stroke Association, between 2004 and 2011. This was a moderated forum, set-up as part of the charity website with the scope of facilitating online communication between stroke survivors and caregivers, sharing information about any aspect of stroke and offering emotional support.

Barriers and facilitators of adherence were identified through analysis of a set of pre-defined keywords related to secondary prevention and stroke. Forum posts were explored using thematic analysis. Key themes were developed, representing barriers and facilitators of medication adherence. As these themes were further refined, subthemes were identified and a coding framework was developed. Forum posts were coded to identify practical and perceptual factors affecting adherence to medication, guided by the PAPA framework. In the final stage of the analysis, themes that were identified were mapped onto the theory and then subdivided to represent barriers or facilitators of adherence. To ensure rigour, another researcher who was not involved in coding the interviews, double coded half of all the forum posts identified. With respect to ethical approval, the Stroke Association granted permission to use the stroke forum data for research purposes before analysis of the data commenced. Informed consent was not sought from forum participants although forum users were aware that by participating in a public forum, their responses were available for others to view online. Verbatim quotes posted in the online forum were not used to protect the identity and intellectual property of participants, despite this being normal practice in qualitative research, only descriptions of quotes were used throughout the text.^{456 461} To minimise the risk of interpretation bias, the paraphrasing of text reflected as closely as possible the original forum posts. The ethical aspects of conducting research on this forum have been discussed more extensively elsewhere.^{456 465}

5.2.4 Procedure and analysis

To enable direct comparison of the analyses from the interviews and an online stroke forum, transcripts of the interview study were re-analysed in NVivo 10⁴⁶⁴, using a thematic analysis⁴⁶⁶ according to the PAPA framework (see the section Procedure and Analysis).^{233 230}

5.2.5 Comparison of attributes of the two data sources

The literature was explored to isolate characteristics associated with face to face and online forum approaches to qualitative data collection.^{467 510 511 488 489} The evidence was discussed with experts in qualitative research methods, and subsequently 10 attributes identified as representing the key characteristics of both methods of data collection. Attributes were categorised according to the domains of realistic evaluation – context, mechanisms and outcomes. The classification of attributes into context, mechanisms and outcomes was discussed until a final consensus was reached.

The key attributes that were considered to represent important aspects of each data source were subsequently applied in the context of collecting/interpreting research data from each source.⁵¹² Context included the attributes location and sampling; Mechanisms included the attributes participation, dynamic of interaction, contribution, timing, guidance and communication; Outcomes included activities and reporting. Table 5.1 below displays the attributes identified and the key difference within these attributes reported in the qualitative interviews and the online stroke forum.

5.2.6 Comparison of themes using PAPA thematic analysis

Key themes arising from the data were classified according to the Perception and Practicalities Approach (PAPA)²³³ and interpreted according to the following two categories of the PAPA framework.

Perceptions: Necessity Beliefs and Concerns.

Perceptual barriers and facilitators of medication adherence in stroke survivors and caregivers were explored within both sources of data, according to their classifications as necessity

beliefs i.e. doubts about personal need for medication to maintain or improve current and future health, and concerns about secondary prevention treatment.

Practicalities- Capability and Resources.

Barriers and facilitators that stroke survivors and caregivers face around their capability of taking/giving medication and the resources available to undertake such behaviour.

	Attribute	Online forum Recognised feature identified in the Literature Versus <i>Feature identified in the Present study (italics)</i>	Semi-structured interviews Recognised feature identified in the Literature Versus <i>Feature identified in the Present study (italics)</i>
Context	Location	Respondents from across a wide geographical area, can participate at own convenience. ⁵¹⁴	Interviewees geographically restricted.
		<i>Any location with Internet access: UK</i>	<i>Patient's own home: East of England</i>
	Sampling	Voluntary participation/ self-selection. Recruitment does not require collaboration between clinical sites or support of professional staff. ⁵¹⁵	Purposive recruitment in health care settings, guided by sampling techniques based on population demographics including age, gender and disability.
		<i>Voluntary self-selection by participant: no sampling criteria, no restriction on age. Verification of stroke/TIA diagnosis not possible. Most participants taking part within the first 5 years since the cerebrovascular event</i>	<i>Purposive sampling: GP screened pre-defined criteria to achieve maximum spread of gender and disability. Age: 55 years and over. Confirmed stroke/TIA diagnosis</i>
Mechanisms	Participation		
		<i>Multiple participants per conversation thread: stroke survivors or caregivers. Conversation possible between survivors, survivors and caregivers, or caregivers with other caregivers</i>	<i>Max 2 or 3 participants per single interview conversation: Researcher, stroke survivor and caregiver</i>
	Dynamic of interaction	Discussion conducted remotely. Relative anonymity can encourage users to feel uninhibited. ^{487 516} Likelihood of expressing honest opinions about sensitive issues.	Engagement can be actively encouraged. Face to face approach enables development of rapport between interviewer and participant. ⁵¹⁷

		<i>Less knowledge of participants, participants remain anonymous. No influence of researcher on participation.</i>	<i>Researchers gain knowledge of interviewees, development of researcher-participant rapport, active encouragement of participation</i>
Response contribution		Longer conversations allow for a broader understanding of the subject matter and potential for greater depth. ⁵¹⁸ Discussion threads generate reflection and greater description among users. ⁵⁰⁹	Probing questions from researcher seeking clarification or to pursue a more detailed response. ⁵¹³
		<i>Potential for significant individual contribution. Responses shaped by other peer contributors. More opportunity for self-reflection. More frequent comments.</i>	<i>Maximum of two individual contributions (patients and caregiver). Responses shaped by researcher interaction. Less opportunity for self-reflection. In depth comments encouraged by researcher.</i>
Timing of event		Users can post repeatedly and frequently on many topics over a long period of time.	Interview is a single event occurring at one point in time Maximum of 2 contributors to the interview discussion.
		<i>Single or multiple participation over time. Ability to contribute to discussion on multiple occasions/topics.</i>	<i>Single participatory event. Contribution fixed to a single time period.</i>
Guidance		User freedom to choose what to discuss, and how frequently to contribute to free-flowing discussion threads. ⁴⁸⁷ Posts created through peer to peer communication, without professionals' involvement and influence. ⁵¹⁹ Response shaped by contribution of other survivors or caregivers.	Follows a pre-defined line of questioning. Several key questions define the area to be explored. ⁵¹³ Researcher oversees the direction of conversation.
		<i>Free or peer-guided discussions.</i>	<i>Guided conversation: responses to pre-defined questions in topic guide</i>

	Communication	Permits broad accessibility and asynchronicity with online communication. ^{487 520} Restricted to those with Internet access. ⁵¹⁰	Direct face to face, synchronous communication
		<i>Indirect communication, via computer, no physical proximity, asynchronous</i>	<i>Direct communication, face to face, synchronous</i>
Outcomes	Activities	No physical transcription is required; user contributions printed automatically, improving credibility of data. ⁴⁸⁹ Potential for inaccurate interpretation through misunderstanding nuances in the data may still exist. ⁴⁸⁹	Transcription is key to representing the individual and dependability of data. Transcription opens data to misinterpretation or misunderstanding. ⁵²¹ Rigour and accuracy in transcribing is integral to the analysis process, influencing the degree of dependability of data. ⁵²¹
		<i>No audio recording. Automatic transcription printed directly from forum No field notes.</i>	<i>Interviews are audio recorded and interviews are transcribed. Potential for ambiguity through inaccurate transcribing Field notes taken during interviews</i>
	Reporting	Forum posts are moderated before appearing online, effect on the data collected is relatively unknown. Moderation processes can influence engagement in online communities. ⁵²²	
		<i>Third party moderation leading to possible exclusion of data</i>	<i>No exclusion of data prior to analysis</i>
Footnote: Location: Geographical area of the research. Sampling: Sampling method used to recruit participants. Participation: Individuals participating in conversations Dynamic of interaction: Knowledge of participant determined by level of engagement. Response contribution: Level of contribution to the conversation by individuals. Timing of event: Frequency of participation over time. Guidance: Level of conversation guidance and level of freedom to discuss Communication: Face to face versus distance communication. Activities: Need for audio recording and transcription activities. Reporting: Moderation of data before analysis			

Table 5.1: Theoretical attributes and key differences identified between the online forum approach and the interview approach to data collection.

5.3 Results

Details of participant characteristics are reported in Table 5.2. Of the 42 interviewed participants, two thirds were stroke survivors and one third caregivers. The median age of interviewed survivors was 72 years (range 61-92 years) and the majority were female (21/28; 75%). The majority of interviewed caregivers were the stroke survivor's spouses. Sixty-four per cent of stroke survivors experienced a stroke within the previous 5 years, 22% in the last 12 months. 50% suffered from a stroke, predominantly ischaemic, 50% from a TIA. Interview participants were recruited from a single UK region.

Of the 84 online users, 58% were stroke survivors and 39% were caregivers. Forum survivors were on average aged 50 years (Range: 32-72 yrs). The median age of stroke survivors talked about by caregivers on the forum was 66 years (Range 46-91 yrs), and 57% were female. 62% of caregivers in the online forum were daughters or sons, 28% spouses and the remainder was family members such as siblings or in-laws. 90% of forum participants, who reported time since stroke, experienced it within the previous 5 years, 53% within the previous 12 months. It was not possible to determine the type of stroke experienced by users in the online forum. A small number of participants in the forum were prolific, commenting frequently and offering encouragement to other participants. Forum users came from all over the UK.

Despite the differences between the two sources of data as highlighted in Table 5.1, all key themes about barriers and facilitators to adherence to secondary prevention medications that emerged from the interview study could be matched with corresponding themes from the online forum. The comparison of themes in the two data sources was facilitated by their classifications according to the PAPA framework and details are reported in Appendix 7. Three additional themes were identified in the forum, which did not emerge from interviews. First, stroke survivors openly discussed the influence of negative press attention on medication taking, in particularly around statins. Second, forum users raised concerns around healthcare professionals' prescribing practices and financial incentives to prescribe. Third, caregivers' difficulties with ensuring adherence to secondary prevention medications and acting as advocates for patients with healthcare professionals.

	Interviews	Online forum
Sample characteristics	N [Median] (Range)	N [Median] (Range)
Total participants	42	84
Age		
Survivor	[72] (61-93)	[50] (32-72)
*Caregiver	-	
Gender		
Male -Survivor	7	20
Female- Survivor	21	26
Not known - Survivor	-	3
*Caregiver of Male Survivor	4	20
*Caregiver of Female Survivor	10	12
Unknown gender and unknown identity	-	3
Identity person posting		
Stroke survivor	28	49
Caregiver	14	33
Not known	-	2
Years since stroke		
(0-12 mths)	4	37
(1-5 yrs)	14	25
(6-10 yrs)	6	4
(11-15 yrs)	2	2
(15+ yrs)	2	1
Unknown	-	15
Type of stroke		
TIA	14	-
Ischaemic stroke	13	-
Haemorrhagic stroke	1	-
Caregiver identity		
Daughter /son	2	20
Spouse	12	9
Other (/in law/ sister)	-	3
Unknown	-	1
Number of posts about secondary prevention		
		37(1 participant)
		15(1 participant)
		1(44 participants)
		2(19 participants)
		3(6 participants)
Legend: * Refers to ‘caregiver’ in interviews and ‘Patient talked about by caregiver’ in the forum discussions		

Table 5.2: Characteristics of participants of the online forum and interview study

To understand attributes in the context of data source, their relationship to the themes identified within the two studies was examined. Table 1 also shows the description of the two sources according to the data collection attributes identified.

The forum facilitated access to participants' views from across a wide geographical area compared to the views of a small group of survivors within a specific context (i.e. Eastern England GP practices). This may have limited interview participants' views, with the forum drawing on more varied and wide ranging healthcare setting experiences.

The sampling of participants in the forum was reflected in the theme '*How seriously people take medicine for secondary prevention of stroke*', with online users being familiar with negative press on statins from across a variety of information sources, including research papers and online sources. Older interview participants recruited through GP practices instead might not be able to access this as easily, as reported in the '*Knowledge of stroke and medications*' theme. Within this theme, interviewed stroke survivors reported looking for medicine information in leaflets inside drug boxes, with forum participants seeking information mainly from resources such as healthcare professionals or online peers. Forum participants seemed keener to adopt a joint approach for medication taking with health professionals, which included patient-clinician shared decision-making about stopping medications.

Participation in the online forum meant that users had the possibility of taking part in multiple discussion threads. Despite the inability to ask clarification questions or to probe participants of the forum, survivors and caregivers could read and reply to each other's' posts in an asynchronous way, with online discussions allowing an in-depth exploration of themes about barriers and facilitators to secondary prevention medication taking. The '*ability to self-care*' theme is an example: survivors perspective of handing over all responsibility of medications to caregivers was enriched by caregivers' posts describing how they were acting at times as advocates for stroke survivors with health professionals. As has been highlighted in previous research in the field⁵⁰⁹, the caregiver/survivor discussion dynamic among forum participants permitted conversations across and within patient and caregiver groups. Stroke survivors who were forum users offered advice and suggestions about medication as well as seeking reassurance and support. At the same time they were providing advice to caregivers on medicine taking or dealing with medication refusal, as reported in the themes on *regimen complexity and burden of treatment*.

The relative anonymity during online forum discussion and the absence of researcher's influence favoured openness among forum participants. For example, forum users were more likely to make frank admissions about decisions to refuse medicines, particularly statins, and about GP role in advising on medicines, as shown in the '*Taking medication*' theme. While the younger age of forum participants may have contributed to this, interviews with stroke survivors were conducted in the presence of the caregiver and this may have encouraged a level of self-censorship. Discussions around this theme went as far as including clinicians' financial motivation behind prescriptions and questioning whether this was prioritised over health benefit. This contrasted with the dynamic reported by interview participants who reported that they were willing to do as the GP said.

Forum users had multiple opportunities for participation, with an open line of questioning guided by other survivors developing the conversation and widening the scope of the discussion. This contributed to data richness and important insights around the practicalities of medication taking, including difficult experiences with practical aspects of '*taking medications*' such as experiencing 'swallow panic'. The collaborative discussions between survivors and caregivers on the forum meant that users were likely to offer each other practical medication taking strategies such as "using a whiteboard" on which to write reminders to take medication. Caregivers in the online forum could communicate with other online caregivers separately from stroke survivors, manifesting their own opinions and attitudes towards secondary prevention medications. This did not emerge from interviews, when caregivers and survivors were interviewed together.

5.3.2 Comparison of themes in the interview and online forum studies

Online forum data offered an unprecedented access to exploration of patient-caregiver dynamics in respect to barriers and facilitators to adherence to secondary prevention medications. Themes identified in the interviews and the forum's corresponding themes are reported briefly in Table 5.3 below and in more detail in Appendix 7

Theme 1: How seriously people take stroke medicines:

This theme describes the survivor's attitude to taking medication and their thoughts on the importance of taking these medicines.

"I wouldn't take them because I still, to me, blood pressure and cholesterol tablets to me I don't see what they're doing for me"(Interview participant-Male, 75 yrs. N.24).

A corresponding theme was also referenced in the forum:

"A female survivor didn't want to jeopardise feeling good by taking medication which she wasn't convinced she needed" (Forum participant- Female, Age 54, N.37)

Theme 2. Knowledge of stroke and medications:

This theme discusses how having incorrect or inadequate knowledge influences medication taking.

Whenever I've got a new pill or anything I'd read the instructions only because they've made a mistake before now, like for instance they gave me one which I'm allergic to... So I keep check of what I'm taking now. (Interview participant-Male, Age 80, N.04).

A corresponding theme was also referenced in the forum:

A stroke survivor recalled being on 75mg of aspirin as well as beta blockers, however, his nephew who was a consultant surgeon, suggested that had he been taking warfarin instead of the aspirin he may not have suffered a second stroke (Forum participant-Male, Age 67, N.82)

Theme 3. Doubts about medicines

This theme reflects doubts around the need for medications following a stroke and the patient's confusion around needing medication that was considered unnecessary.

I just don't see why I'm taking the other medication. I'm not fat or anything like that. I don't get very high blood pressure and well cholesterol, what is cholesterol. (Interview participant- Male, Age 75, N.24)

A corresponding theme was also referenced in the forum:

A survivor talked about the 'Cholesterol Myth' having researched the topic on the Internet. He said he was feeling confused about the value of statins and taking these when in reality they weren't needed (Forum participant- Male, Age 67, N.70).

Theme 4 Realisation of the importance of medicines.

This describes the patient's acceptance of needing to take medication following a stroke and the realisation that if they didn't their health could be in danger.

At one time I wouldn't take a pill, I wouldn't even take an aspirin. Now I take it because I understand it keeps me alive. I just think its fate, that's the way I look at it. If I stop taking medication I might as well lie down in the fast lane (Interview participant- Male, Age 67, N.12)

A corresponding theme was also referenced in the forum:

A male survivor already suffered 2 strokes and said it was impossible to ever fully recover from the experience. He said after his first stroke he was prescribed tablets he didn't take and he realizes this was a big mistake. (Forum participant- Male, Age 67, N.82)

Theme 5 Ability to self-care.

This theme reflects the help by caregivers and the patient's dependence on the caregiver when taking stroke medication .

My wife sorts it out and that's why I don't know so much about it you see she [taps].She puts them there, I take them and that's it (Interview participant- Male, Age 80, N.74)

A corresponding theme was also referenced in the forum

A caregiver stated she was providing the stroke survivor with all of his medication due to his poor memory as a result of the stroke. She was now in complete control of his medication which she was happy but it was difficult as he was a loved one and something she had no training for. (Forum participant- Male, Age 46, N.05)

Theme 6. Taking medications

This theme reflects nonadherence of stroke medications, with survivors both forgetting medicine and actively choosing not to take medicine.

Well now and again I forget the cholesterol because that's the one at night and it's the only one I take at night (Interview participant- Male, Age 67, N.15)

A corresponding theme was also referenced in the forum:

A male survivor said he was on 2 tablets for blood pressure and that he continued to take one every day. But the other was a diuretic and having got fed up frequently running to the toilet, he decided to check his blood pressure every day and would skip the diuretic if it was fine (Forum participant- Male, Age unknown, N.63)

Theme 7. Medication routines

This theme refers to regulate medication taking routines that stroke survivors follow to remind them to take their medication

I only remember to take the others if I take them out of the cupboard the night before and leave them on the top. If I didn't I would probably forget...because it isn't the first thing that I think of. (Interview participant- Male, Age 66, N.10)

A corresponding theme was also referenced in the forum:

A female survivor described keeping the pill box in a specific location in the house, such as by the kettle, which then acted as a reminder to check the medication box (Forum participant, Female, Age 60, N.52)

Theme 8. Changing medications

This theme is associated with stroke medication being changed, often without the knowledge of the patient, as well as the resulting consequences of this.

They changed his medication to cheaper cholesterol and Dean was physically ill. He couldn't cope on it at all so he went back and the doctor said 'oh well it was just to try and they put him back on the others (Interview participant- Female, age unknown, N.24)

A corresponding theme was also referenced in the forum:

A survivor described being on 80 mg of simvastatin which they were happy with but that upon leaving hospital the dose was halved by the consultant which had very bad consequences, resulting in daily angina turns for a week. In the end he had to go back to his GP and be put back on the 80mg dose. (Forum participant- Female, age 53, N.62)

Theme 9. Regimen complexity and burden of treatment

This theme described the complexity of medication taking regimens for patients and the implications for medication taking behaviour.

I have to take 10 a day now altogether but I went up there (to the practice) to say can I get off some of these tablets, and I come back and I was on an extra one so I've not been up since (Interview participant- Male, Age 70, N.13)

A corresponding theme was also referenced in the forum:

A caregiver (son) was asking advice on how to encourage medication taking. His mother was originally taking multiple tablets up to 4 times a day but that now she was refusing to take them all and he was upset by this. Persuading her to continue taking the most important tablets had taken hours to do. (Forum participant- Female, Age 77, N.09)

Table 5.3: Themes identified in the interviews and the forum's corresponding themes

5.4 Discussion

In this analysis, themes that emerged from an interview study with stroke survivors and their caregivers could be matched with corresponding themes from users of an online stroke forum. This was true despite key differences in the attributes of data collection and the lack of verification of participants' identity and stroke diagnosis. An online stroke forum can be considered a trustworthy source of data for qualitative research on patients' and caregivers' issues with medications after stroke. Perhaps because of the inclusion of a

younger and computer literate population and the opportunity of online discussions between survivors and caregivers, forum data offered additional insights such as the effect of negative press attention on taking medicines, issues about clinician prescribing, and easy access to caregivers' reflections on their caregiving role.

Strengths and Limitations

This is the first investigation in stroke research to compare results from two independent studies addressing the same research question using two different data sources, a traditional one (interviews) and a novel one (online forum). The results suggest that qualitative studies on online stroke forums are robust and represent a step towards establishing the validity of an online stroke forum as source of qualitative research data.

A further strength of these results consists in highlighting characteristics that could be used to decide which source of data is more suitable to a particular research question, e.g. an online stroke forum could be more suitable when the focus is on gathering qualitative data from young computer-literate stroke survivors and young caregivers (most forum caregivers are sons and daughters of stroke survivors) and within the first year after stroke. With online comments provided directly from participants, the potential for ambiguity or distortion of patient views through transcription is reduced. This investigation suggests that there is potential for an online forum to improve understanding of stroke survivors' issues with medications.

A limitation of this study is the inability to compare data from the two sources in respect to participants' characteristics like type of stroke, social class and geographic location. Body language, facial expressions and face to face interaction that were present in interviews could not be compared with forum data. Third party moderation of an online forum raises the possibility of an online discussion being ended prematurely and posts excluded before they are analysed and therefore themes being missed.

While interviewed participants contributed to one or more themes and were included in the interview study, several forum participants mentioning secondary prevention medications were excluded from the forum study because they did not provide enough details to allow the identification of a theme. Despite this, because of the wealth of information shared online and the high number of forum participants, the exclusion of several participants did not affect data collection within the forum study.

Comparisons with existing research

In agreement with our findings, investigations of online versus face to face focus group discussions concluded that both methods could be used to answer research questions, that online forum is more suited to communicate opinions and capturing participants' perspectives from a wide geographical area⁵¹⁰, and through anonymity discussions of more personal issues.⁵²³

Issues around the potential reliability of forum data in answering the research question may also arise out of concerns about whether the data are skewed toward a specific participant group. As the use of the Internet to conduct behavioural research grows, the representativeness of participants' samples and issues will remain challenging, in spite of the advantages of increased accessibility to otherwise hidden populations.⁵⁰⁰

An online forum as source of data collection offers the opportunity for cross communication and shared support among participants. Through this forum, users can also draw on a personalised support system based on peer experiences and built trust.⁵²⁴ At the same time, as shown in this study, online cross communication between participants can enhance understanding and add depth to the themes in qualitative research. With evidence that trust forms and develops on the online forum⁵²⁵, there is the potential for this methodology to become an accepted and valued source of health information.⁵²⁶

For researchers using an online forum as a data collection technique in health care research raises potential ethical concerns around anonymity, privacy, confidentiality and informed consent compared to the more traditional qualitative approaches such as semi-structured interviews. This outlines the importance of referring to a research protocol with appropriate ethical guidance to research using online sources.^{465 527}

Compared with face to face interviews where stroke survivors and caregivers were interviewed together, the forum offered a more neutral environment in which caregivers had the freedom to participate on their own. In this context, participants may be more willing to express deeply held personal opinions and to discuss sensitive issues more freely, as described by Allen and colleagues.⁴⁸⁷ The knowledge of such issues has the potential to inform and improve involvement of both patients and their caregivers in the decision making process, thus facilitating a collaborative approach around the use of medication, and encouraging effective medication taking behaviour.⁵²⁸ An interesting observation was that survivors who were interviewed were more likely to follow the GPs' instructions around

medicines whereas survivors in the forum reported a shared approach to decisions. This identifies an interesting dynamic around how elderly stroke survivors and their younger counterparts view the practitioner role. Indeed previous research confirms that older patients look to the GP for support and view the practitioner as trustworthy and an ally in making healthcare decisions.⁵²⁹

Implications for research

The online forum represents a source of data collection suited to capturing the views of a younger stroke population who have access to online resources and to information from press outlets, which can potentially influence their attitudes to medication. The presence of younger patients and caregivers in online stroke fora offer insight for the development of interventions targeted to these groups. Indeed research has shown that those who are younger with poorer mobility report most unmet needs, including in respect of medication taking.⁵³⁰

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Stroke survivors who struggle with face to face communication but can communicate using technology such as a computer or mobile phone can provide insight on their needs, informing clinical interventions designed to improve medication taking in this patient group.

In agreement with the work on cancer forums, our work shows that the potential of online communities as a source of data is only beginning to be realised. This comparison study suggests we can be more confident in using data from online forums. Online forum data also offers unprecedented access to the caregiver perspective and the dynamic of their relationship with the stroke survivor and other with respect to barriers and facilitators to adherence to secondary prevention medications for stroke.

Conclusion

Both interviews and online forums are rich and useful sources of data and knowledge, revealing similar issues about patients' core experience. In uncovering additional themes the online forum may represent an important adjunct to traditional qualitative data collection methodologies.

Chapter 6

Evaluating support stroke survivors get with medicines and unmet needs in primary care: A survey

This chapter of the thesis reports on a quantitative survey study, the aim of which was to evaluate the type of help stroke survivors get with taking their medicines in the community and to understand their unmet medication needs. The qualitative studies reported in the thesis have demonstrated there is a potential role for unpaid caregivers in facilitating medication taking behaviour among stroke survivors.

However the help survivors receive from caregivers to take medicines and those areas of medicine taking where stroke survivors have unmet needs, remains relatively unknown. Previous research on unmet needs in stroke has focussed primarily on information and everyday living. This study includes detail on the development and delivery of a new questionnaire designed to evaluate the help stroke survivors get with daily medication taking in the community, based on the views gathered from patients' and caregivers' through workshops.

The questionnaire is intended to highlight the effect of impairment due to stroke on the medication taking activities of stroke patients as well as predictors of medicine taking which effects medication adherence. This study has the potential to raise awareness of the needs of stroke survivors in the community around taking medicines and on the role of the informal caregiver in daily medication taking activities. Furthermore, results could also raise awareness of patients' needs among health care professionals. Identifying and quantifying the support stroke survivors get with taking their medication is important to challenge suboptimal medication taking practices and to improve medication taking behaviour in the future. This investigation focusses on stroke survivors in the community, with an emphasis on including those who have suffered a severe stroke and are likely to be disabled and may therefore be vulnerable to poor medicine taking practices and in need of help with medicines. This group of stroke survivors are often excluded from research.

By exploring unmet medication needs this study can inform strategies to increase medication taking practices among stroke survivors. Identifying aspects of medication taking in which patients need help can highlight areas in which resources to support medication taking may be best focussed. Strategies can inform the development of interventions delivered in the primary care setting to improve adherence to medications in stroke.

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Other collaborators also contributed to this research. James Jamison undertook development, design, data collection, analysis and prepared the manuscript. Dr Anna De Simoni, Dr Luis Ayerbe and Dr Gian Luca Di Tanna contributed to the data analysis, Professor Stephen Sutton and Professor Jonathan Mant provided input on the study direction. All co-authors contributed to critical assessment and assisted with reviewing the final paper.

6.1 Background

For many older adults remaining independent at home may depend on how well they can manage complex medication regimens.^{532 533} An estimated 25-74% of the 50 million stroke survivors worldwide requiring some assistance or being fully dependent on caregivers for activities of daily living (ADL's).⁵³⁴⁻⁵³⁶

There is evidence that being dependent for ADL's and impairment in mobility and communication decrease medication adherence in patients suffering from hypertension.⁵³⁷ Deficits in attention, cognition or working memory have been linked with nonadherence to medications in other patient groups.⁵³⁸ In a systematic review of medication adherence among patients with cognitive impairment, one third of studies showed that such patients were likely to have a caregiver to assist with medications and there was an association between taking four or more medicines and nonadherence.⁵³⁹ In patients taking cardiovascular medicines, multiple factors including cognitive problems, lack of social support, dosing regimen, as well as practical problems and difficulties accessing services, contribute to poor medication adherence.^{240 540} Low adherence to secondary prevention medication is associated with poor cardiovascular health.^{251 270 541}

Research on medication adherence in stroke has identified multiple barriers to medication taking among stroke survivors.^{413 440 441} However interventions developed to improve adherence have mainly concentrated on patients responsible for their own medicine taking.^{264 443}

In elderly patients in particular, cognitive deficits, taking large number of medicines and the complexity of medication regimens have been identified as barriers to medication adherence.^{265 269} Caregivers are known to play a key role in providing assistance to older people in a range of daily activities including medication taking and physician visits⁵⁴², and can help improve adherence in cardiac patients with memory problems.⁵⁴³ However, the proportion of community stroke survivors relying on caregivers for some, or all aspects of medicine taking, is not known.

Survivors of stroke have previously reported unmet needs including physical difficulties, cognitive and emotional difficulties, information needs and other unmet needs.^{354 544} However we know little about factors that influence medication taking among stroke survivors with disabilities living in the community (i.e. not in nursing homes), their unmet needs around the use of medicines or the proportion relying on caregivers for some or all aspects of medicines taking.

To date, survey instruments examining the unmet needs of stroke survivors have not focused on aspects of medication taking.

The aims of this investigation were to design an instrument to evaluate the help stroke survivors get with taking their medicines, characterise patients receiving help with medications, estimate the proportion who have unmet needs with daily medicine taking and who miss medications. A further aim was to identify predictors of missing medicines and of experiencing unmet needs with medications. This knowledge can inform the development of primary care interventions aimed at improving medication taking in this patient group.

6.2 Methods

6.2.1 *Questionnaire development workshops*

To develop the questionnaire, three workshops were conducted with 26 stroke survivors and 12 caregivers in the East of England. Recruitment was opportunistic and no purposive sampling was applied. The survey questions were developed through thematic analysis⁴⁶⁶ of workshops field notes.

A fourth workshop was conducted to gather feedback on the questionnaire using Patient and Public Involvement (PPI) exercise with 11 stroke survivors and 3 caregivers recruited through a local stroke group. Two stroke survivors from this group took part in subsequent 'think-aloud' interviews, which involved talking out loud as they read the questionnaire, continually verbalising what they were thinking.

6.2.2 Postal survey

General practices in primary care in the East of England and London were approached through the Clinical Research Network (CRN). Eleven GP practices took part in the Eastern region and seven participated in London. Patients with stroke and their caregivers were sent the postal questionnaire according to the following criteria

Inclusion Criteria

Patients: All patients aged > 18 on the practice stroke register with documented history of stroke. Caregivers: Anyone identified by the patient as being a caregiver and having a role helping with medicine taking.

Exclusion Criteria

Patients who had suffered a Transient ischaemic attack (TIA) but not a stroke; Palliative or end of life patients; Patients receiving institutional long term care (receiving total care in residential homes or living in nursing homes).

6.2.3 Survey participant identification

A list of prospective patients was compiled from the stroke register of each surgery by the practice staff. No restriction was placed on the recruitment of survivors experiencing who were dependent for ADL's or lacking capacity. The list was screened by a practice GP and anyone not meeting the inclusion criteria or whom the GP considered unsuitable for the study (e.g. terminally ill) was excluded.

6.2.4 Survey participant recruitment

Eligible participants were sent a study survey pack by practice staff between September 2016 and February 2017. Study recruitment packs included two invitation letters,

patient information sheets, questionnaires and postal version of Barthel Index⁵⁴⁵, one of which was for completion by the patient and the other by the caregiver. The Barthel Index provides a measure of functional independence and physical functioning and has been used in stroke research previously.⁵⁴⁶ Patients with Barthel score <20 were categorised as dependent for ADLs/disabled. If receiving help with medications, the patient was asked to pass to their caregiver the invitation letter and information sheet and invite him/her to complete their copy of the questionnaire, providing answers on the patient's medicine taking. Family members, friends or paid caregivers of stroke survivors who were severely disabled and/or lacked mental capacity were invited to fill and return the caregivers' questionnaires only on behalf of patients. The information sheets stated that consent was implied by returning the completed questionnaire. Participants were asked to return completed questionnaires to the research centre in the FREEPOST envelopes provided. A second mail out of the study invitation pack was sent to all patients as a reminder, two weeks after the first one.

6.2.5 Survey Analysis

Survey data entry was performed by Document Capture Company.⁵⁴⁷ Individual patients' characteristics (age, gender, time since stroke, number of daily medicines) were collected from the questionnaires themselves. Practice population, number of patients on stroke registers, deprivation score and ethnicity were taken from the National General Practice profiles (<https://fingertips.phe.org.uk/profile/general-practice>). The proportions of patients in each sociodemographic category, needing help taking medication, missing any medication in the previous 30 days, and reporting the need for more help taking medication, were estimated. When the survivor and caregiver questionnaires were both returned together, study data were collected from the patient's questionnaire only.

Multivariable logistic regression analysis was fitted to estimate associations between 'Unmet needs' and the variables: age < or \geq 70 years, gender, total number of medicines taken, dependence for ADL, years since stroke, and receiving help with medicines. In the model each domain of help with medicine was estimated individually and then combined. A second multivariable logistic regression examined the association between 'Missed medicines in the previous 30 days' and the variables: age < or > 70 years, gender, total number of medicines taken, dependent for ADL, years since stroke, help with medicines and unmet needs. Regression models were adjusted for age, gender and variable of interest.

6.3 Results

6.3.1 Questionnaire development

Taking medications emerged as an important issue in all three workshops: nearly half of patients stated that a family member or friend was supporting them with daily medicine routines especially in relation to prompting medicine taking. This was put down to effects of the stroke itself on memory retention rather than general memory problems that people without stroke also experience. They admitted missing doses due to forgetting. Only a small proportion of survivors were actually handling their own prescriptions and were relying on support from family and/or community services. In one workshop almost all survivors had Dosette medication boxes and agreed that taking medications out of safety bottles and blister packs was a problem due to physical disabilities.

Thematic analysis of workshop data revealed five main practical domains of support needed with medication taking: 1) Dealing with prescriptions and collection of medicines; 2) Getting medicines out of the box, blister packs or bottles; 3) Prompting 'It's time to take your medicine'; 4) Swallowing medicines; and 5) Checking whether medicines have been taken. The final study questionnaire (see Appendix 8) included questions relating to each of these five domains, one item related to adherence (missed medicine in the last 30 days) and an assessment of disabilities through completion of the validated postal version of the Barthel Index.⁵⁴⁵ The questionnaire was adapted for caregivers (see Appendix 9).

6.3.2 Questionnaire finalisation

On the basis of the fourth workshop and two 'think-aloud' interviews, survey questions were reworded (e.g. from 'Do you get help with' was changed into 'Is somebody helping you with') and a scale response used ('All the time', 'Often', 'Sometimes', 'Rarely', 'Never') for the first question of each of the five survey domains, which was originally conceived as a 'yes' or 'no' answer.

6.3.3 Survey-practice characteristics

Eighteen GP practices agreed to take part in the study, of which just over 1/3 were in London (n=7). GP practices were relatively large with an average population of 11,904 patients (SD = 4010) and a low to moderate level of deprivation (Index of Multiple Deprivation⁵⁴⁸ (IMD): Mean-7.05; SD-3.19). Out of 3066 patients on the stroke registers,

1687 stroke patients (55%) were considered eligible for the study and received the postal questionnaire. The average response rate of East of England and London practices was 42% and 27% respectively. The response rate varied between 16% and 53% across practices.

6.3.4 Survey- participant characteristics

596 participants returned a completed questionnaire [549 (92.4%) from patients, 45 (7.6%) from caregivers] showing a mean response rate of 35% (0.33-0.37). Participants were on average 72.7yrs old. 37.8% (n=210) of the sample were female and 62.2% male (n=346), see table 1. The mean number of years since stroke was 7.7 and participants took an average of 6 different medicines a day. There were a high proportion of White patients in the recruited practices which were on average 21% of mixed or ethnic minority background. Approximately 28% of study participants were completely independent for ADL, self-reporting a Barthel Index score of 20.

Participants getting any kind of help with medicines were on average 73.6 years old, two thirds were male, had a stroke approximately 8 years previously and were taking on average 1 extra medication a day. Only 19% of this group were completely independent for ADL. Participant characteristics are reported in Table 6.1.

	All patients				Patients who receive any kind of help				Patients with unmet needs				Patients who miss medication			
	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD
Age (years)	588		72.7	11.6	331		73.6	12.2	64		68.8		203		70.5	13.0
Female	210	37.8			112	36.2			18	28.6			68	35.6		
Male	346	67.2			197	63.2			45	71.4			123	64.4		
Time since stroke (years)	535		7.7	7.6	295		7.97	8.5	61		9.3	9.2	186		7.7	8.5
N of daily medicines	557		6.4	4	312		7.3	4.5	59		9.7	7.1	190		6.9	4.1
Independent for ADLs (BI=20)	139	28.3			53	18.9			5	9.8			45	25.7		
Moderately dependent for ADLs (BI=15-19)	231	47.1			130	46.4			17	33.3			84	48.0		
Severely dependent for ADLs (BI=0-14)	121	24.6			97	34.6			29	56.9			46	26.3		

Table 6.1: Characteristics of survey participants (*mean scores reported unless otherwise stated*). N represents the number of participants who completed the survey in respect to the different variables. BI: Barthel Index.

6.3.5 Support with daily medication taking

Table 6.2 shows the mean responses to the survey questions quantifying the help participants receive with medicines and unmet needs. Overall, 55.7% (95% CI: 51.7-59.7) of the participants received help in at least one aspect of taking medication, in that they ticked one of the options from 'all the time' to 'rarely' on one or more of the five questions related to medicine taking. 11.4% (95% CI: 8.8-13.9) of patients reported experiencing unmet needs and needing more help with at least one of the aspects of taking medication, in that they ticked 'yes' to the question "do you feel you need more help", on one or more of the five questions related to medicine taking.

Among participants help was needed to some degree with prescriptions and collection of medicines (49.7%), getting medicines out of the box or packet (27.9%), reminding to take medicines (36.4%), swallowing medicines (20.2%) and checking that medicines have been taken (34.2%). Being reminded to take medicines, dealing with prescriptions and collection of medicines and getting medicines out of a pack or bottle were the most commonly reported areas of unmet needs.

Almost two thirds of participants (65.3%) reported never missing medicines in the last 30 days. Out of the 34.7% of patients who said they missed taking medicine at any point in the previous 30 days, 23.9% said rarely, 9.3% sometimes, 0.8% often and 0.7% all the time.

	N	All the Time N (%)	Often N (%)	Sometimes N (%)	Rarely N (%)	Never N (%)	Yes N (%)	No N (%)
Question 1 Is somebody helping with prescriptions and collection of your medicines?	583	186 (31.9)	19 (3.3)	40 (6.9)	45 (7.7)	293 (50.2)		
Question 1a Do you feel you need more help with prescriptions and collection of your medicines?	551						33 (6.0)	518 (94.0)
Question 2 Is somebody helping you getting the medicines out of the box, bottle or blister pack?	578	85 (14.7)	15 (2.6)	31 (5.4)	30 (5.2)	417 (72.1)		
Question 2a Do you feel you need more help with getting the medicines out of the box, bottle or blister pack?	553						33 (6.0)	520 (94.0)
Question 3 Is somebody helping with reminding you when is the time to take your medicine?	577	78 (13.6)	22 (3.8)	59 (10.2)	51 (8.8)	367 (63.6)		
Question 3a Do you feel you need more help with reminding when is the time to take your medicine?	564						35 (6.2)	529 (93.8)
Question 4 Is somebody helping you with swallowing your medicine?	579	56 (9.7)	11 (1.9)	29 (5.0)	21 (3.6)	462 (79.8)		
Question 4a Do you feel you need more help with swallowing your medicine?	560						9 (1.6)	551 (98.4)
Question 5 Is somebody helping you with checking that you have taken your medicines	576	76 (13.2)	23 (4.0)	58 (10.0)	40 (6.9)	379 (65.9)		
Question 5 a Do you feel you need more help with checking that you have taken your medicine	558						20 (3.6)	538 (96.4)
Thinking of the last 30 days, how often did you miss taking your regular medicines?	594	4 (0.7)	5 (0.8)	55 (9.3)	142 (23.9)	388 (65.3)		

Table 6.2: Results summarising participants' responses to survey questions.

6.3.6 Factors associated with unmet needs

Being on a higher total number of daily medications (OR: 1.2, (1.1-1.3), $p<0.001$), severe dependence for ADLs (OR: 11.6 (4.2-32.4) $p<0.001$) and receiving any kind of help (OR: 5.9, (2.7-11.6), $p<0.001$) in relation to taking medication was associated with experiencing unmet needs. Getting help with swallowing medicines (OR: 6.8, (3.8-12.0), $p<0.001$), getting medicines out of a box, blister packs or bottles (OR: 6.6, (3.6-11.8), $p<0.001$) showed the strongest associations with experiencing unmet needs (see table 6.3). When the analyses were conducted with data from questionnaires filled by patients only, variables significantly associated with unmet needs were the same, apart from years since stroke (see table 6.5).

	Univariable analysis		Multivariable analysis	
Variable	N	Odds ratio (95% CI) p value	N	Odds ratio (95% CI) p value
Age ≥ 70	581	0.6 (0.4-1.1) $p=0.084$	544	0.7 (0.4-1.2) $p=0.180$
Gender (female)	544	0.7 (0.4-1.2) $p=0.137$	544	0.7 (0.4-1.2) $p=0.147$
Number of different medicines	542	1.2 (1.1-1.3) $p<0.001$	509	1.2 (1.1-1.3) $p<0.001$
Moderate Dependence for ADLs (BI: 15-19)	479	2.2 (0.8-6.1) $p=0.135$	447	2.7 (1.0-7.5) $p=0.068$
Severe Dependence for ADLs (BI: 0-14)	479	8.5 (3.2-22.8) $p<0.001$	447	11.6 (4.2-32.4) $p<0.001$
Years since stroke	522	1.0 (1.0-1.1) $p=0.078$	490	1.0 (1.0-1.1) $p=0.160$
Getting help with prescriptions and collection of medication	568	4.7 (2.5-8.8) $p<0.001$	533	4.6 (2.4-8.7) $p<0.001$
Getting help with taking medicines out of the box, bottle or blister pack	563	6.7 (3.8-11.8) $p<0.001$	527	6.6 (3.6-11.8) $p<0.001$
Getting help with reminding you when is the time to take your medicine?	562	4.7 (2.7-8.2) $p<0.001$	526	4.3 (2.4-7.6) $p<0.001$
Getting help to swallow the medication	565	6.7 (3.9-11.6) $p<0.001$	528	6.8 (3.8-12.0) $p<0.001$
Getting help by checking that you have taken your medicines	562	4.9 (2.8-8.6) $p<0.001$	526	5.9 (3.1-10.1) $p<0.001$
Getting any kind of help	574	5.9 (2.8-12.1) $p<0.001$	537	5.9 (2.7-11.6) $p<0.001$

Table 6.3: Results of the multivariable analysis showing the variables associated with unmet needs.
N: number of observations; ADLs: Activities of daily living; BI: Barthel Index.

6.3.7 Factors associated with missing medications

Being older (age ≥ 70) was associated with a lower probability of missing medication (OR: 0.6 (0.4-0.9) $p=0.006$). Being on a higher number of daily medicines (polypharmacy) (OR: 1.1 (1.0-1.1), $p=0.008$) and getting any kind of help with medicine taking (OR: 2.1 (1.4-3.0) $p<0.001$) were associated with higher probability of missing medicines. The more unmet needs stroke survivors had with taking medication, the more likely they were to miss their medicines (OR: 5.3 (3.0-9.4), $p<0.001$) (see Table 6.4). When the analyses were conducted with data from questionnaires filled by patients only, the variables significantly associated with missing medication were the same. (see Table 6.5)

	Univariable analysis		Multivariable analysis	
Variable	N	Odds Ratio (95% CI) p value	N	Odds Ratio (95% CI) p value
Age ≥ 70	594	0.6 (0.4-0.8) $p=0.003$	555	0.6 (0.4-0.9) $p=0.006$
Gender (female)	555	0.9 (0.6-1.2) $p=0.401$	555	0.9 (0.6-1.3) $p=0.498$
Number of different medicines	555	1.0 (1.0-1.1) $p=0.040$	520	1.1 (1.0-1.1) $p=0.008$
Moderate Dependence for ADLs (BI: 15-19)	490	1.2 (0.8-1.8) $p=0.468$	456	1.3 (0.8-2.0) $p=0.343$
Severe dependence for ADLs (BI 0-14)	490	1.3 (0.8-2.1) $p=0.342$	456	1.4 (0.8-2.4) $p=0.239$
Years since stroke	533	1.0 (0.9-1.0) $p=0.950$	499	1.0 (0.9-1.0) $p=0.971$
Getting help with prescriptions and collection of medication	581	2.0 (1.5-2.9) $p<0.001$	544	2.3 (1.6-3.3) $p<0.001$
Getting help to have the medicines out of the box, bottle or blister pack	576	1.4 (1.0-2.0) $p=0.089$	538	1.5 (1.0-2.2) $p=0.051$
Getting help with reminding you when is the time to take your medicine?	575	2.5 (1.7-3.6) $p<0.001$	537	2.7 (1.8-3.9) $p<0.001$
Getting help to swallow the medication	578	1.5 (1.0-2.3) $p=0.045$	539	1.7 (1.1-2.6) $p=0.022$
Getting help by checking that you have taken your medicines	576	2.4 (1.7-3.4) $p<0.001$	537	2.5 (1.7-3.7) $p<0.001$
Getting any kind of help	587	2.1 (1.4-3.0) $p<0.001$	548	2.1 (1.4-3.0) $p<0.001$
Unmet needs (participant reported more help needed)	580	5.3 (3.0-9.2) $p<0.000$	544	5.3 (3.0-9.4) $p<0.001$

Table 6.4: Results of univariable and multivariable analysis showing associations with missing medicines. N: number of observations; ADLs: Activities of daily living; BI: Barthel Index.

	Unmet needs		Missing medication	
Variable	N	Odds ratio (95% CI) p value	N	Odds ratio (95%CI) p value
Age ≥70	498	0.7 (0.4-1.2) p=0.248	508	0.6 (0.4-0.9) p=0.009
Gender (female)	498	0.7 (0.4-1.3) p=0.262	508	0.9 (0.6-1.3) p=0.576
Number of different medicines	465	1.2 (1.1-1.3) p<0.001	475	1.1 (1.0-1.1) p=0.015
Moderate Dependence for ADLs (BI: 15-19)	408	2.6 (0.9-7.5) p<0.075	417	0.3 (-0.2-0.7) p=0.289
Severe Dependence for ADLs (BI: 0-14)	408	10.9 (3.8-31.0) p<0.001	417	0.5 (-0.1-1.0) p=0.119
Years since stroke	446	1.0 (1.0-1.1) p=0.036	454	1.0 (0.9-1.03) p=0.725
Getting help with prescriptions and collection of medication	487	4.6 (2.4-8.9) p<0.001	497	2.6 (1.8-3.8) p<0.001
Getting help with taking medicines out of the box, bottle or blister pack	481	6.6 (3.6-12.2) p<0.001	491	1.7 (1.1-2.6) p=0.20
Getting help with reminding you when is the time to take your medicine?	480	4.7 (2.6-8.5) p<0.001	490	3.0 (2.0-4.5) p<0.001
Getting help to swallow the medication	482	7.9 (4.2-14.8) p<0.001	492	2.1 (1.3-3.4) p=0.005
Getting help by checking that you have taken your medicines	480	5.9 (3.2-10.9) p<0.001	490	2.8 (1.8-4.2) p<0.001
Getting any kind of help	491	5.6 (2.7-11.9) p<0.001	501	2.3 (1.6-3.4) p<0.001

Table 6.5: Predictors of unmet needs and missing medication, responses given by patients only (i.e. caregivers' filled questionnaire excluded). Multivariable analyses, all models adjusted for age and gender. N: number of observations.

6.4 Discussion

Summary of findings

From the workshops five key issues were identified that patients regarded as important with medication taking after stroke. These were converted into a five-item questionnaire that was distributed to people on stroke registers in 18 general practices. A response rate of 35% was obtained. Among respondents, 56% of survivors in the community were receiving help in some aspect of daily medication taking, 11% reported needing more help in at least one domain of medicine taking and 34% missed taking their medicines at some point in the previous 30 days. A higher total number of daily medicines, being severely dependent for ADLs and receiving help with medication were predictors of experiencing at least one unmet need in respect of medication taking. Stroke survivors who were younger, taking a higher number of daily medicines and experiencing a greater number of unmet needs were more likely to miss medications. This work identified issues from a population that includes patients severely affected by stroke, who are often excluded from research.²⁶⁴ Results presented here shed light on the effect of stroke-related impairments on practical domains and predictors of medicine taking, which are shown to have significant effects on overall adherence.

Strengths and limitations

A strength of this study is that the questionnaire was developed from patients' and caregivers' own views gathered through workshops. Although not recruited through purposive sampling, workshop participants suffered from a range of stroke related impairments, as highlighted by the reported use of Dossette boxes, dependence on others for aspects of medicine taking like prompting medication times, and dependence for ADLs such as collecting prescriptions and taking tablets out of boxes. In the postal survey, the inclusion of stroke survivors regardless of level of dependence for ADLs permitted investigating a population who are understudied²⁶⁴, yet may have significant unmet needs that can affect their adherence to medications. This investigation highlights caregivers' role in managing medicines in survivors dependent for ADLs.

However, study limitations should also be considered. The response rate across recruited GP practices was low and harder to reach stroke survivors may have been missed. Poor response rate is a source of bias that might affect these estimates. Interestingly, considering the average age at stroke in England (i.e. 74 for men and 80 years for women⁵⁴⁹), the participant population was slightly younger (73 years), perhaps reflecting the fact that patients receiving institutional long term care were

excluded from the study or that older people found it harder to take part in a postal survey. Through the Barthel score, cognition was not directly assessed directly, although low cognitive function is associated with poor adherence.⁵⁵⁰ As the Barthel focuses on physical disability it is not known to what extent study participants were cognitively impaired or suffered from communication difficulties like aphasia. In addition, dependency for ADLs could have been caused by existing co-morbidities other than stroke. Information on the use of blister packaged medication or devices to aid compliance was not collected, which could have influenced medication taking practices. Finally, this study examined all medicine taking and did not differentiate between stroke secondary prevention medications and other drug categories.

Comparisons with existing research

This is the first study that shows that more than half of all stroke survivors get help with some aspect of medicine taking and that those receiving help are more likely to have unmet needs. This provides some insight into why adherence to medication in stroke survivors may be poor.²⁴²

Moreover, the greater the number of medicines, the more likely stroke survivors were to miss medications. Addressing pill burden by simplifying drug regimens may be an important focus for future interventions. Indeed the polypill approach to medication taking has been shown to reduce cardiovascular as well as total pill burden in a primary care setting.⁵⁵¹ Simpler dosing regimens, are known to be associated with better medication adherence⁵⁵² while fewer medicines has been shown to be an independent predictor of long term medication persistence among stroke survivors.^{255 553} A recent trial incorporating a fixed-dose combination polypill approach to taking cardiovascular medicine demonstrated better adherence among patients receiving a single pill.³⁷⁸

Receiving help with prescriptions and collecting medicines was identified as the area where most help was received (49.7% of respondents). Stroke survivors who are dependent for activities of daily living may face considerable practical challenges accessing health care resources at the pharmacy and the GP practice. A recent study in the USA found that around 2/3 of caregivers were involved in at least 1 medication management activity of elderly patients and that high involvement in Instrumental Activities of Daily Living (IADLs) was associated with the caregiver providing the patient with assistance in ordering medicines.³⁴⁹ Filling prescriptions is also known to be an important factor influencing medication adherence.^{267 554} Indeed caregivers can play a significant role in ensuring appropriate medication taking. A recent interview study exploring potential barriers and facilitators of medication adherence in stroke identified the central role of the caregiver in medication adherence.⁴¹² Our evaluation of an online stroke forum also confirmed the important role

of the caregiver in facilitating medication adherence.⁴⁴¹ Monitoring prescription collections, liaising with the GP and pharmacy, increasing the time between prescriptions or arranging medication deliveries, may help to address prescription needs.

Around 11% of stroke survivors reported unmet medication needs. The study found that stroke survivors dependent for ADLs and receiving help with medicines were more likely to report unmet needs, which is in line with a recent study investigating stroke/TIA survivors in Australia, where greater functional ability was associated with fewer unmet needs, including those related to secondary prevention.⁵⁵⁵ In previous research on unmet needs among stroke survivors, a 44 item survey study by McKevitt and colleagues (2011) reported that 49% of stroke survivors had at least one unmet need³⁵⁴, while in a study of Australian survivors who completed a 58 item survey, the percentage was 84%.⁵⁴⁴ Both these studies however examined unmet needs over a variety of domains including health, work, leisure and everyday living, social support and finances, whereas this study focused on medication needs only.

Getting help to take medicines out of a box, packet or bottle was the area where the greatest proportion of stroke survivors needed help all of the time. The use of pill boxes and blister packed medication is known to be both a facilitator³⁵ and a barrier⁴⁴¹ to adherence among stroke survivors⁴⁴⁰ while interventions using blister packaging and pill boxes have been found to be associated with improved adherence.⁴⁷¹ Although electronic medication devices were considered potentially effective in improving medication taking behaviour among patients with cognitive impairment, success in using such devices was dependent on the patient having a good level of dexterity, while removing the medication from these devices was also found to be challenging.^{556 557 558} The need for further support in this domain, as reported in this study, suggests that handling medications remains problematic for stroke survivors.

An interesting finding from this survey study is that stroke survivors who missed medicines were younger. This is consistent with other research on adherence in stroke that found that younger age was predictive of poor adherence²⁷¹, and has also been described in patients taking medication for cardiovascular disease.⁵⁵⁹ The finding in the present study contrasts with the view that older patients are more likely to face difficulties taking medication^{560 407} which is frequently attributed to higher number of pre-existing comorbidities resulting in polypharmacy and increased complexity of medication taking regimens. The fact that older patients may less likely miss medicine might be down to the support they receive from caregivers. The findings reported here suggest that support needed with medications may be overlooked in younger stroke survivors.⁵³¹

In this study a significant proportion of patients admitted missing medications occasionally. There is evidence that improving adherence by one anti-hypertensive pill/week for a once-a-day

regimen reduces the hazard of stroke by 8–9 % and death by 7 %.⁵⁶¹ Each incremental 25% increase in proportion of days covered with statin medications is associated with a 0.10 mmol/L reduction in LDL-C.^{145 562} Nonadherence to cardiovascular medications is associated with increased risk of morbidity and mortality.⁵⁶³

Implications for clinical practice

A significant proportion of patients, particularly those who take large numbers of tablets, are disabled or receive help to take medication, have unmet needs and miss their tablets, which can increase risk of recurrent cardiovascular events. These particularly vulnerable groups of patients might benefit from focused clinical attention. Through understanding the needs of survivors and caregivers in different aspects of daily medication taking, we can help direct future resources to the areas of greatest need. For example, further exploration of medication packaging is warranted to understand the difficulties stroke survivors face handling medicines. Polypharmacy remains a difficulty for older patients. Therefore, exploring the use of combination pills and further efforts to reduce the burden of multiple medications among stroke survivors is warranted.

The questionnaire we have developed could be used to understand the challenges around medication faced by other patient groups. Unmet medication needs among UK stroke survivors have not been previously explored in the context of activities both survivors and caregivers consider important for taking medicines. Through understanding the extent of unmet needs as well as the areas in which these are greatest, strategies can be developed which address poor medication taking practices and therefore improve medication adherence.

Future research

Novel interventions focussing on the practicalities of taking medicines and aimed at improving stroke survivors' adherence to treatment are needed. These findings may inform the development of such interventions. Advances in technology have the potential to facilitate delivery of such interventions, e.g. electronic devices prompting medication taking times.^{564 565} Efforts to improve medication taking among survivors of stroke using technology are already underway and have shown promise.⁵⁶⁶

Chapter 7

Stroke survivors', caregivers' and GPs' attitudes towards a Polypill for the secondary prevention of stroke: A qualitative interview study

This chapter of the thesis explored the opinions and attitudes of survivors, unpaid caregivers and General Practitioners towards a new treatment which may improve medication taking behaviour among stroke survivors. This treatment, called 'polypill' and consisting of fixed-dose combination (FDC) therapy, has emerged over the last decade as a potential treatment for the prevention of cardiovascular disease. The potential for a fixed-dose combination polypill as a strategy to improve adherence to cardiovascular medications in primary care has been demonstrated through a series of clinical trials. The investigations reported here have shown that stroke survivors taking multiple medications face barriers to medication adherence including treatment burden and the complexity of the medication regimen, while GPs have admitted concerns around the quantity of medicines needed and the burden of medication resulting in survivors being selective about which medicines they take. A polypill for stroke prevention has the potential to address some of these concerns among stroke survivors and healthcare professionals.

Online stroke survivors also expressed concerns about incorrect prescribing of medicines while caregivers have highlighted the impact of treatment burden resulting in episodic medication refusal. Taking fewer medicines could reduce treatment burden and has the potential to improve medication taking behaviour. A FDC polypill approach may therefore be acceptable to stroke survivors and their caregivers through simplifying the drug regimen and reducing the number of medicines needed. This in turn may improve medication taking behaviour and consequently, adherence to secondary prevention medicines among stroke survivors.

To explore the potential of a polypill strategy for secondary stroke prevention in the primary care setting it is important to understand the attitudes of survivors, caregivers and health professionals towards this treatment approach. This study focusses on understanding perspectives

around a polypill approach to stroke prevention through the delivery of qualitative semi-structured interviews.

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Other collaborators contributed to this research. James Jamison conceived of the study and its design, formulated the aims and methods, conducted all of the interviews with study participants, analysed the data, and prepared this chapter as well as the published manuscript. Dr Ricky Mullis contributed to the protocol development, Dr Jonathan Graffy assisted with interpretation of the findings, Professor Stephen Sutton double coded interviews and advised on all aspects of study development and Professor Jonathan Mant contributed to the study design. All co-authors provided critical appraisal and assisted with reviewing of the final manuscript.

7.1 Background

The use of multiple medications to treat CVD is often associated with inappropriate medication use (e.g. under-use, or use of non-appropriate medicines), under-prescription and reduced adherence.²⁸² A polypill for the treatment of CVD³⁵⁸ has been proposed, consisting of cholesterol lowering and blood pressure lowering therapies, with or without aspirin, in a single fixed-dose combination pill.

Since the polypill concept was first introduced³⁶¹, a growing body of literature has developed around a fixed-dose combination (FDC) pill, for the prevention of cardiovascular disease.^{362 567} To date a number of qualitative studies have investigated the attitudes and perspectives of patients and healthcare professionals towards a fixed-dose combination polypill for the prevention of cardiovascular disease. The findings showed that cardiovascular patients considered a polypill to be convenient, but the inflexibility of this treatment approach was a concern.⁵⁶⁸ Healthcare professionals said they would consider prescribing it to those who needed secondary prevention medication if it was shown to be effective.^{386-388 569} With adherence to medication among stroke survivors known to be suboptimal³⁴¹ this patient group may be particularly suited to treatment with a fixed-dose combination polypill.

The aim of this study was to explore the attitudes and perspectives of stroke/TIA survivors, carers and GPs towards a polypill approach for the secondary prevention of stroke, including the benefits and consequences of using a polypill, factors likely to influence uptake, the caregiver role in managing medication and GPs' views and attitudes towards prescribing a polypill in the future.

7.2 Methods

7.2.1 Study Design and Participants

A qualitative study using semi-structured interviews was undertaken. The stroke registers of 5 GP practices in the East of England were searched. Patients over the age of 55, with a diagnosis of stroke or TIA and able to speak English were eligible. Based on these criteria, a list of prospective participants was generated by the practice administrator, screened by the practice GP and anyone deemed unsuitable, such as those unable to provide informed consent or who were terminally or seriously ill, was removed.

Purposive sampling was used to recruit stroke/TIA survivors. Survivors were sent a study information pack and invited to attend an interview. Caregivers were approached via the stroke survivor and were interviewed in the presence of the survivor due to time constraints. A GP from each practice was also interviewed. The number of interviews was determined by data saturation, where no new information emerged. Ethical approval was granted and consent was taken before any discussion commenced.

7.2.2 Data Collection

Data was collected through semi-structured interviews with open ended questions that defined the area to be explored.⁴⁴⁶ Topic guides were developed and informed by current literature in the field and expertise provided by a GP, a qualitative researcher and a stroke patient. To ensure ease of understanding and suitability, topic guides were piloted with two stroke survivors and checked by a GP. Any appropriate recommendations were considered and implemented. Data from the two pilot interviews was included in the final analysis. Topics discussed were perceived benefits and consequences of a polypill, factors influencing polypill uptake, caregiver views and GPs' beliefs and attitudes towards prescribing a polypill. Field notes were also taken by the interviewer. The topic guide is shown in Table 7.1 below.

Interview topic guide

Stroke survivor

Do you know what a polypill is?

- What do you think of being able to take a single pill (containing a combination of different stroke medications in one pill) instead of your usual medication?
- How do you think this would change the experience of taking medication?
- What would you consider to be the advantages of taking a polypill?
- Can you think of any reasons why taking a polypill might not be a good thing?
- Would you consider taking a polypill in the future?

Caregiver

Have you heard of the term polypill?

- What do you think of the idea of a 'polypill' to prevent stroke?
- What do you think of the patient taking a single polypill instead of their usual stroke medications?
- How do you think this would benefit patient's medication taking behaviour?
- Can you think of any reasons why taking a polypill may not be a good idea?
- How do you think a polypill would enable better management of medication?
- What do you think about a polypill being introduced in the future?

GP

Are you familiar with the idea of a polypill for cardiovascular disease?

- What do you know about polypill therapy for cardiovascular prevention?
- Are you familiar with this?
- What do you think about using a polypill for secondary prevention in stroke? Do you think it's feasible?
- What would be the difficulties (if any) with using a polypill for secondary prevention?
- What would be the benefits of a polypill?
- If a polypill became available for secondary prevention, is it something you would consider prescribing?

Table 7.1: Polypill topic guide for interview participants

The schedule of questions was refined and finalised after the fifth interview to include questions on the wider experience of stroke as well as understanding of the polypill approach and the GP relationship. Interviews were audiotaped, lasted 1- 1.5 hours and were transcribed verbatim to permit data analysis.

7.2.3 Data analysis

Following a constant comparative analysis approach⁴⁴⁸ key points emerging from the data were coded individually. A set of codes, representing initial themes, were developed from chunks of data. Codes were then further refined, and those representing similar concepts were grouped together to form categories. The identification and refinement of categories continued until the final themes emerged. Nvivo 9⁴⁴⁷ (QSR Intl, Melbourne, Victoria, Australia) was used to organise, code and manage the data. To assess inter coder reliability, 20% of the transcripts were independently double coded. Queries arising from coded transcripts were settled through discussion with further communication enabling clarification and refinement of categories until a consensus was reached.

7.3 Results

A total of twenty-eight stroke/TIA survivors participated. Fourteen were interviewed alone and 14 with the caregiver present, who was either a spouse (n=12) or family member (n=2).

Level of disability was assessed through the Modified Rankin Scale. Within the sample, 35% of participants had no symptom or reported slight disability, 35% were characterised as having slight to moderate disability and 29% identified with having moderate severe or severe disability. The sample was almost exclusively White (97%) 25% of participants were over the age of 80 and half (50%) reported having a minor stroke or TIA. Around one third of participants had diabetes and just over a half (54%) had never smoked. The characteristics of study participants are displayed in Table 7.2 below. Three male GPs and two female GPs were also interviewed. One GP was White British, one was Chinese and three were of South Asian origin.

Three key themes along with sub-themes were identified, reflecting the positive and negative aspects of the polypill approach as well its potential for future use. (See Appendix 10 for example polypill themes reported by interview participants).

Polypill benefits: This theme included greater convenience, with a single pill considered easier to remember, contributed to better compliance, reduced pill burden, ensured the correct medicines were being taken and provided potential cross-over treatment for other co-morbidities. Among caregivers, a polypill made medication taking itself less demanding and contributed to better

management of medication A further advantage of the polypill approach was that it offered the benefit of correct treatment in that a single pill ensured that all the appropriate cardiovascular medications were being taken and it offered confidence to the user that the components were both appropriate and safe.

Polypill concerns: This theme included concerns around the appropriateness of a single pill approach, suitability of a polypill strategy, potential side effects attributed to a polypill, ability to adjust medication, the size of a pill and the cost of the polypill and its implications for prescribing.

Polypill lessons for implementation. This theme suggested that the future use of a polypill was likely to be guided by a Polypill being recommended by the GP, patient satisfaction with their current stroke medication and a polypill being endorsed by the healthcare professional.

		N	%
Gender	Male	21	(75)
	female	7	(25)
Age (Mean: 74yrs)	60-69	10	(36)
	70-79	11	(39)
	80-89	7	(25)
Ethnicity	White	27	(97)
	Asian	1	(3)
Stroke classification	Stroke	14	(50)
	TIA	14	(50)
Time since stroke (yrs)	6m – 2	10	(35)
	3-5	8	(29)
	6-10	5	(18)
	>10	5	(18)
Diabetes status	Yes	9	(32)
	No	19	(68)
Smoking status	Non-smoker	15	(54)
	Ex-smoker	11	(39)
	Smoker	2	(7)
Interview status	Survivor with caregiver	14	(50)
	Survivor	14	(50)
Rankin score* mRS-9Q¹²⁰	No symptoms: (0)	6	(21)
	No significant disability: (1)	4	(14)
	Slight disability: (2)	6	(21)
	Moderate disability: (3)	4	(14)
	Mod/ severe disability: (4-5)	8	(29)
*Rankin score is derived from a scale that measures the degree of disability in the daily activities of people who may have suffered a stroke			

Table 7.2: Characteristics of stroke survivors participating in semi-structured interviews.

7.3.1 Polypill benefits

The concept of a polypill was broadly acceptable to survivors and caregivers. Greater convenience leading to better adherence, confidence that a polypill was providing the appropriate treatment, reduced treatment burden, ease of use, and improved medication management were all considered benefits. For GPs, a polypill facilitated medication taking and provided flexibility in treatment and convenience around prescribing practices. Polypill benefits are reported in Table 7.3 below.

Convenience

Survivors were enthusiastic about one tablet combining all stroke medication and reducing treatment burden through minimising the inconvenience of managing multiple medications.

That is the best thing I've read when it said you might have to take one pill to cover the lot. Super, because that is just a bugbear, it's a bugbear in life. (pp 11, Male, 73yrs).

A single tablet was considered easier to remember and likely to improve overall medication taking behaviour.

I think it's brilliant because erm I, I've got more chance of remembering to take one tablet than I have of remembering two different times of the day if you like. (pp10, Male, 66 yrs)

Caregivers also endorsed the view that a polypill improved compliance and that it ensured the appropriate medications were being taken.

It means that if you've taken that one you've taken them all. Whereas sometimes if you run short, you think oh I'll just take that one and forget about the other one until you go to the doctors and get the refill (pp02, Female, carer).

GPs also felt that a polypill had the potential to improve medication adherence.

I think that would reduce the pill burden to our patients and I think that's very good idea... I think he would be very compliant with it, because he is thinking that he is going to be taking 1 tablet and not 5 tablets....(GP 02, Female).

The potential for 'cross-over' treatment in individuals with multiple existing cardiovascular comorbidities was mentioned.

If you're giving polypill in the form of one pill, even with people with comorbidities (you're)

maybe reducing their number...and might improve overall compliance and it may have the side effect of improving their comorbidity as well (GP 05, Male).

For carers, the polypill approach made the medication taking process less demanding.

It's logic to me and I think it's an excellent idea if it could be done, certainly instead of [patient] fiddling about in a saucer trying to pick up tablets.. (pp28, Male, carer).

They also felt the process of managing medication was better, compared with multiple medications.

Well if it's only one tablet a day it would be quicker, wouldn't it? for a start. I mean I usually sit on a night-time and do that (pillbox) when I'm watching telly. There's a few times I've missed out the odd tablet or put a double in or put too many in so I mean that would be easier. (pp02, Female, carer)

Benefits of correct treatment

A polypill offered the benefit of correct medication and it ensured that the patient received their recommended medications.

It could protect, once you had polypills that contained a mixture of medications which are known not to have...contradictory side-effects...then you would feel very safe. (pp03, Male, 86 yrs)

And as long as it's whether it's one pill or four pills so you know this is my point of view I don't think it's going to affect I mean other people might oh yeah I could have four pills instead of one and they'll start worrying about it but no I erm I just accept that, that the people are doing their job properly and getting their facts right...as I say as long as the scientists have got it alright you know you've got to have faith in them (pp08, Male, 87 yrs)

There was also confidence that components were safe, tested and therefore provided the most appropriate treatment.

I'm all for these things....it might not be good for you, It might not, I don't know I can't see how because if they're now gonna put four different pills into one they musta investigated a, b, c and d to put them in one so therefore it's going to be beneficial to me and anybody else that wants those four in one (pp11, Male, 73yrs).

Table 7.3: Polypill benefits identified in semi-structured interviews

7.3.2 Polypill concerns

Survivors' and caregivers' concerns included polypill noncompliance resulting in missing all medications, inability to adjust dosage, whether a polypill could maintain the benefits of the survivors' current secondary prevention medication, timing of a polypill, identifying the source of polypill side effects and modifying treatment if a component was no longer required. GPs questioned whether a single pill could treat the entire stroke population, the cost implications of treatment and the wisdom in modifying a patient's stable treatment regimen. Polypill concerns are reported in Table 7.4 below

Appropriateness of treatment

Several survivors expressed concern that a polypill may not sustain equivalent therapeutic benefit of secondary prevention treatment.

As far as I'm concerned you've got one tablet with all the ingredients of the others... if I've got the same erm dosage of statin and if it didn't disturb my readings then yeah I mean erm what are the objections to it? (pp05, Male, 64 yrs)

Others also had concerns about the prospect of a 'pill for all', inability to alter dosage and being less amenable to dose titration, if that was required.

Would the polypill be in different strengths because like for blood pressure at the moment I'm taking...12 and a half, and then me cl- clopidogrel is 75, maybe six months down the line my blood pressure can reduce, what would that do with the polypill? (pp21, Female, 68 yrs)

Survivors accustomed to scheduled medication regimens also questioned how drugs could now be combined and taken at a single time point.

If you've got them altogether and you're supposed to take those tablets at different times of the day, how's it going to work? Is it going to upset your system? (pp22, Female, 71 yrs).

Suitability of the polypill strategy

Survivors questioned the ease of managing treatment if one or more components were no longer required.

Would it only be suitable for somebody who's taking four of that particular medication? But

what would happen if say the Dr said, you're not so bad so you don't need to take that particular tablet? (pp16, Female, 82 yrs)

A few expressed concerns around the inclusion of statins in any combination pill.

Yes has that got anything to do with statins? I've read a lot about statins and I'm afraid I feel I wouldn't want to take them. Because the side effects and everything.

(pp19, Female, carer)

GPs were cautious, suggesting a polypill could be better suited to those on similar medications whose treatment was well-established.

I think the right drugs in the right combinations there, it, would potentially be helpful for a cohort of people. I don't think it will be for everyone but there will be a cohort of people who will probably be on very similar drugs... (GP03, Male)

Survivors and carers were also concerned that poor adherence would lead to missing all their secondary prevention drugs.

If you're gonna give them a polypill that is three or four tablets and they don't bother taking that.. They're gonna be worse off (pp14, Male, Carer)

Given the unique needs of stroke survivors, some suggested that multiple polypills may be needed.

They don't give me three separate ones for no reason, there must be a reason for it. You can't do that with a polypill unless you have a hundred polypills all different medications and different combinations (pp18, Male, 88 yrs).

Polypill side effects

The likelihood of polypill side effects led many to question the suitability of single pill treatment.

The fine tuning takes a bit of doing so w- with the one pill I got my bit of a doubt that it might work for some people but it might not work for everybody you see (pp04, Male, 80 yrs).

For GPs, a further problem resulting from this was the potential difficulty in identifying the component of a polypill responsible for side effects.

My personal anxiety is about side effects when you club two, three medicines together, if one of them, one of the components is, is causing the side effect then you'll not know, you

may have to again change.. (GP 05, Male)

Medication adjustment

GPs questioned the benefit in altering established medication routines to accommodate a polypill in those who were already taking their medication as directed.

If you've got, as I said, a very motivated patient they are happy with what they are taking, then we don't probably have to intervene, but we may have to give to people who are not that motivated or compliant. (GP 05, Male)

They also expressed concern about the inconvenience of having to re-adjust future treatment if polypill components were no longer required.

If somebody has a problem ok well we'll just stop using the polypill and give them the individual ones but with that stopping and chopping and changing people will say they've changed my tablets again, that becomes an issue. (GP 04, Male)

However, inflexibility of a polypill and the inability to manipulate dosage was perhaps the greatest concern among GPs.

We do switch around quite a bit different brands, different sizes, statins and sometimes it may not be the right dose but you kind of slowly edge it in... It would be advantageous if it was a single pill but that would be maybe a bit difficult with polypill...It's the fine tuning that's difficult..(GP 01, Female)

Caregivers also expressed concern around the inflexibility of a polypill and the potential difficulties in adjusting dosage.

You would have to get the right strengths of each tablet. "Where you were on atenolol 50 you are now on 25". Sometimes they change the strength of the tablet. That's where it would be harder to change with the polypill (pp25, Female, carer).

Size of polypill

GPs raised concerns that a large pill could actually discourage medication taking.

Yeah is it a horse tablet?...that's going to have the other, the opposite effect on compliance that we want...People are going to start breaking it having half now and half twelve hours later (GP 03, Male).

The size was also highlighted by caregivers who expressed concerns around a prospective polypill being very large.

Not going to be horse pills are they.. as we call them, 500 mg. (pp07, Female, carer)

For some stroke survivors, a single pill was considered much easier given the potential problems associated with multiple medications which could be larger and more difficult to swallow.

If you can get it into one, it's so much better, you haven't got to put all these tablets down your throat. I mean like this might get stuck, and one of my tablets, if it gets stuck it burns my throat so much so the other week I lost my voice (pp06, Male, 61 yrs)

Cost of polypill

The burden of the polypill on NHS resources was also raised with a number of GPs suggesting that a more expensive pill could be difficult to prescribe.

If it is cheaper then there won't be an issue at all. if it comes out to be more expensive than the four tablets which you are giving individually to the patient then it comes to be an issue (GP 02, Female)

Cost implications for practices and pharmacies dispensing a polypill were also considered with GPs acknowledging the likelihood of reduced revenues associated with a single pill.

They get an item fee for each thing they prescribe so if you have 4 drugs you get a fee for each, if you put it in 1 pill that will account for one (GP 04, Male)

Table 7.4: Polypill concerns identified in semi-structured interviews

7.3.3 Polypill lessons for implementation

Survivors thought that whether they used a polypill in the future would depend on their doctor's recommendation, but they also questioned the need for a polypill given their satisfaction with current treatment. GPs acknowledged that their support was likely to be influential in the decision to use a polypill and believed the approach should be adopted if it was found to be beneficial to the patient. While stroke/ TIA survivors were generally positive about the polypill approach, many were non-

committal on its future use, largely due to the lack of existing evidence. Polypill lessons for implementation are reported in Table 7.5 below.

Polypill recommendations

Caregivers felt that whether they used a polypill in the future was likely to depend on their doctor recommending the treatment.

It sounds good but w- we've got to, we would have to weigh up, listen to what the doctors say and the consultants and see what history, because this polypill, from what we've hear. Very, very little, it's quite new, that's all we know. (pp22, Male, carer)

While GP's felt comfortable with the polypill approach, there was a preference for recommending a polypill to those who were already using the medication components.

I don't think I'd be comfortable saying here's a new stroke patient, just start them with a polypill as a starting point, I think I'd feel uncomfortable with that.

If I had patients that are on the four drugs that are in there erm I think I'd probably feel fairly comfortable saying well here's one tablet that's got all of those things you're on already (GP 04, Male)

Satisfied with current medication

Being content with their current medication also made survivors less enthusiastic about taking a polypill which may have unwanted side-effects.

Why take a tablet that perhaps will affect you. Plus the fact I'm perfectly happy with what I'm on, you know, at the moment anyway. Perhaps if I go a bit doo-lally or you know erm....I would consider it (pp01, Female, 71 yrs).

While a concern raised among some study participants was that there was as yet, little scientific evidence in support of a polypill approach.

No, I don't think I'd like to be a guinea pig with it though.... I don't know, I think I would rather continue with what I've got until it's absolutely perfected the polypill. Get somebody else (pp23, Female, 74 yrs)

Endorsement of the polypill

GPs agreed that if they endorsed polypill, stroke/TIA survivors were likely to accept it as a treatment for secondary stroke and commit to using it in the future.

I think the majority of our current patients if we told them we think this is the right thing to do would probably be happy with that. It's a fairly easy argument (GP 03, Male).

Furthermore, there was an obligation to try new and innovative treatments like the polypill, if its potential benefits were proven.

I welcome change and innovation I'm excited by it... you don't know until you've tried it... We have to try it if there was a potential benefit there for people (GP04, Male)

Table 7.5: Polypill lessons for implementation identified in semi-structured interviews

7.4 Discussion

Summary of main findings

Stroke/TIA survivors and caregivers felt a polypill offered greater convenience, reduced the burden of treatment and improved adherence to medication. A polypill also ensured that patients received the correct treatment and that medications were safe. However, survivors expressed significant concerns around the suitability of a polypill if not already using its individual components, the size of a polypill and the implication for using a polypill if any component was no longer needed. Other important limitations identified by participants included the potential for side-effects and the inflexibility of the single pill approach. GPs felt that a more expensive pill would be problematic and acknowledged that their endorsement was key to it being accepted. For survivors, the decision to use a polypill would depend on the GP's recommendation, but those who were satisfied with their current treatment regimen felt less inclined to change to a polypill.

Strengths and Limitations

A strength of this study is that it adds to a growing and important body of research on attitudes towards a cardiovascular polypill with a focus on secondary prevention of stroke. Secondly, the use of semi-structured interviews enabled an in-depth assessment of individual perspectives. A further strength is the inclusion of caregivers, who can make a significant contribution in the future

management of polypill treatment. Finally, being interviewed by a qualitative researcher rather than a health care professional may have encouraged survivors to be more open and to engage in discussion.

However the study has limitations that should be considered. The sample of GPs was small, with only one from each of 5 general practice surgeries. Although every effort was made to recruit a representative sample with varied disability, most survivors who responded to the request to participate were primarily able bodied with no significant stroke symptoms and independently managed their own medication. In addition, survivors were almost exclusively White British. With some ethnic groups, particularly south Asians, known to be at considerably higher risk of cardiovascular disease⁵⁷⁰, the study may have benefited from the including individuals who are considered to be at a greater risk from stroke and likely to be prospective users of polypill therapy. As a result, survivors may not represent the wider stroke population. Furthermore, with only five GPs interviewed, their opinions may not reflect those of the GP population at large. With all caregivers interviewed in the presence of a survivor, this may have contributed to individuals responding in a socially desirable manner and understating their true views on secondary prevention and the polypill. Investigating a polypill among survivors with significant symptoms and dependent on others to organise their tablets may be an area for future research in the field. Future research should also aim to include those harder to reach groups of survivors who may benefit most from a polypill approach.

Comparisons with existing literature

The inflexibility of treatment and the potential for side-effects were considered key challenges of a polypill approach. Concerns about side-effects have previously been identified as influencing medication taking behaviour³²⁵ and recognised as a significant barrier to adherence in cardiovascular disease medication.²³⁸ These findings are also in line with another investigation in UK primary care in which patients considered a secondary prevention polypill acceptable, but were concerned about components interacting and inflexibility of treatment.³⁸⁴ The inability to adapt polypill dosage and the suitability of fixed dose treatment was a key concern for GPs in this study and has been previously reported in studies exploring polypill attitudes among GPs elsewhere. A small survey of 17 practitioners in New Zealand reported that having no choice of polypill components or doses was the thing GPs disliked most about the concept of a polypill.⁵⁶⁹ In another UK study of primary healthcare professionals, inability to titrate dosage was considered a major disadvantage of the polypill.³⁸⁶

The GPs in this study agreed that cost was a potential impediment to prescribing a polypill in the future. Compared with free combination medications, FDC therapy has the potential to be

relatively inexpensive due to cheaper drug costs and reduced monitoring⁵⁷¹, and there is increasing evidence in the literature supporting the cost-effectiveness of a polypill strategy.^{572 573} With modest costs considered a cornerstone of combination therapy⁵⁷⁴, evaluations of the cost-effectiveness of using polypills is urgently needed.

Improved adherence was recognised as a key advantage of a polypill, and survivors acknowledged that a single medication episode was easier to remember. With frequent dosing regimens⁵⁵² and polypharmacy associated with poor patient compliance to cardiovascular medications^{227 575}, a polypill approach offering a simplified medication regimen has the potential to improve adherence in the treatment of cardiovascular disease.^{576 568} The findings in this study corroborate observations from a patient perspective on whether a polypill could improve adherence, which highlighted concerns around the efficacy of a polypill compared with current medications and the potential for side-effects.⁵⁶⁸

For caregivers, benefits of a polypill included simplifying the medication taking process and ease in organising pill boxes. In a study on factors that influenced caregiving and medication management, participants recognised complex medication needs as an impediment to care by increasing the demands placed on the caregiver.⁵⁷⁷ Caregivers in the present study recognised that a polypill approach was potentially more convenient for the pharmacy, an observation which has been confirmed in a qualitative investigation exploring pharmacists' views towards a cardiovascular polypill.¹⁸⁴

Stroke/TIA survivors expressed a reluctance to adopt a future polypill strategy, citing GP approval as a key factor. This not only supports the view that cardiovascular patients were inclined to do what their GPs told them⁵⁷⁸ but also highlights the key role GPs can play in promoting a polypill approach. Exploring the perspectives of those with direct experience of the polypill can contribute to the wider acceptability of a polypill strategy and should continue to be a priority of future research. While a polypill was acceptable to most patients of the UMPIRE trial, some felt that fixed-dose combination therapy was less tailored to individual patient needs.³⁸⁴ A recent investigation of the views of cardiovascular patients and providers who participated in polypill trials reported similar advantages and concerns to those identified in our study³⁹¹, suggesting that polypill perspectives translate to other regions and health care settings.

With research suggesting that health practitioners often fail to fully explain the important elements of medication when first prescribing treatment⁵⁷⁹, uptake of a polypill may depend not only

on the GP prescribing therapy but also on informing and encouraging acceptance of the approach among stroke/TIA survivors and their caregivers.

Implications for clinical practice

This study identified some positive aspects of a cardiovascular polypill for the secondary prevention of stroke. However greater efforts are needed within the clinical practice setting to reassure patients of the benefits of a polypill. Health professionals endorsement when prescribing a polypill could also lead to greater acceptance of this treatment approach and its use among stroke survivors, particularly as inadequate information and difficulties with new medications are associated with poor adherence.⁵⁸⁰ Further studies with a broader and larger sample of GPs can corroborate the findings reported here. Research on the efficacy of a polypill will also reassure practitioners whose concerns around inflexibility and the suitability of treatment are likely to influence the decision to prescribe a polypill to stroke/TIA survivors.

Conclusion

A growing body of evidence suggests that a fixed-dose combination pill may have a role to play in the prevention of cardiovascular disease. This study contributes to the growing literature on cardiovascular polypills, offers a unique insight into the field of stroke, and may inform future research and clinical practice on secondary prevention in the UK. A polypill may also have a role to play in improving adherence among stroke survivors. Addressing patients' and practitioners' concerns and intensifying efforts to increase the acceptability of this treatment approach is likely to determine future use of a cardiovascular polypill for the secondary prevention of stroke.

Chapter 8 – Discussion

In this chapter findings from the qualitative and quantitative investigations undertaken will be briefly summarised in the context of existing evidence. The strengths and limitations of the research will be discussed and the implications of the research findings for clinical practice and policy will be reported. The findings will then be discussed in the context of future research in the field of stroke and how they may inform the development of interventions to improve medication taking behaviour in this field.

The aim of undertaking this thesis was to identify strategies to inform interventions that could be used to improve the health outcomes of UK stroke survivors. To achieve this aim several key objectives were met. Barriers and facilitators of adherence to stroke medication were identified from two unique perspectives: semi-structured interviews in general practice and from an online stroke forum. These two approaches to data collection were compared to assess the appropriateness of an online forum as a valid source of qualitative data for researchers to understand barriers to secondary prevention medication among survivors of stroke.

An investigation was then undertaken to explore the help that stroke survivors receive in the community, to quantify their unmet medication needs and to identify potential factors that predict missing medicines and experiencing unmet needs. Finally, a novel approach to medication taking among stroke survivors was investigated, exploring attitudes towards a fixed-dose combination polypill for secondary prevention. The following summary briefly describes how these objectives were met.

8.1 Summary of findings from preceding chapters

Chapter 2 described a focused review of the qualitative literature to understand barriers and facilitators of medication adherence for the secondary prevention of stroke. The views of patients, caregivers and healthcare professionals on barriers to taking stroke medicines were explored. Multiple barriers were identified including medication side effects, burden of treatment, inadequate support, lack of information/knowledge and complexity of medication regimens. The review highlighted the need for further research across the stroke spectrum, demonstrated that survivors face considerable challenges to taking medicines and suggested that a multifactorial approach to improving medication taking behaviour among stroke survivors is needed.

Chapters 3 and 4 of the thesis describe qualitative investigations to explore barriers to medication adherence in stroke using two different methods: face to face interviews in the general practice setting and an online stroke forum. The interview approach identified multiple patient-level and medication-level barriers to adherence. Similar themes were reported within the forum as well as several new themes including the role of negative press attention on taking statins, concerns around GPs' prescribing practices and caregiver difficulty in acting as an advocate for the patient with the healthcare professional.

Chapter 5 provided a more in-depth investigation of two qualitative approaches, comparing semi-structured interviews (Chapter 3) and the online forum (Chapter 4) methodologies, to understand the potential of the forum as a viable source for collecting qualitative data in this patient group. This investigation showed that while interview and forum participants faced many similar barriers, new themes were identified within the forum, including concerns around prescribing practices, the role of negative statin publicity on medication taking behaviour and caregiver difficulties when acting as an advocate for the patient with healthcare professionals. Important characteristics differentiating the two data collection approaches were identified and differences reported. The forum offers a novel approach to data collection and has the potential to uncover interesting aspects of medication taking that traditional face-to-face interviews in the clinical setting may not capture by including harder to reach groups of stroke survivors and those who may not participate in traditional research methods such as interviews.

Chapter 6 reports the findings of a questionnaire study to evaluate the help that stroke survivors in the community receive to take their medicines and to estimate the proportions who miss medicines and have unmet needs. This investigation showed that over half of all those surveyed needed help with some aspect of medication taking and around one third reported missing medicines at some point. Missing medicines was associated with having unmet needs and being on a higher number of daily medicines, while getting help with medicines, taking more daily medications and being dependent for activities of daily living were associated with unmet needs.

Chapter 7 investigated attitudes towards a novel approach to taking medication for the prevention of secondary stroke- a fixed dose combination polypill. Benefits of a polypill that were highlighted included convenience and receiving correct treatment while concerns included suitability of a polypill strategy, side effects and the possibility of adjusting treatment. Acceptability of a polypill among survivors, caregivers and healthcare professionals is likely to determine implementation of a polypill approach in the future.

In summary, the findings reported in this thesis show that stroke survivors face considerable challenges to medication taking. Barriers and facilitators of medication adherence have been identified through different qualitative approaches and these can inform strategies to develop interventions designed to improve medication taking behaviour in stroke survivors. This thesis shows that the caregiver has an important role to play in the medication taking practices of stroke survivors and that survivors in the community need help to take their medication and have important unmet needs with respect to taking medicines. The polypill strategy represents is a novel approach to taking medication that, which may facilitate medication taking behaviour. Incorporating the caregiver role and adopting novel behavioural strategies have the potential to improve the medication taking behaviour among stroke survivors.

8.2 *Thesis findings in the context of existing literature*

A pervasive theme to emerge from this thesis is the role of the informal caregiver and their contribution to the medication taking practices of stroke survivors. Results demonstrated that the caregiver assists with many aspects of the medicine taking process including managing and administering medicines acting as an advocate for the survivor and involvement in practical aspects of medication taking such as collecting prescriptions, getting medicines out of the box and handling medicines. There is some evidence supporting caregiver involvement in the secondary prevention of stroke.^{264 404} This lack of emphasis placed on the caregiver in their role of facilitating adherence role was identified in a recent systematic review of interventions for adherence to antihypertensive medication in stroke, in which only two trials reported interventions that incorporated the caregiver role.⁴⁴³

Findings from the interview study indicate that caregivers often trivialised stroke, lacked knowledge on stroke care and were poorly informed about stroke and secondary prevention medicines. This suggests that unpaid caregivers such as family members who are largely responsible for supporting stroke survivors, may be relatively unprepared for the challenges they face.⁵⁸¹

Caregivers and patients in the interview study reported a lack of knowledge around stroke and medicine and felt that information provided around stroke was inadequate. Among patients and caregivers, unmet information needs associated with clinical aspects of stroke, prevention and treatment have been reported previously^{354 437} and information provided to patients and caregivers has been found to improve knowledge of stroke.^{420 582} Health professionals could play a role in providing suitable information and ensuring patients and caregivers have the appropriate knowledge of stroke and medication.²⁹⁷

Enhancing patients' and caregivers' knowledge of stroke may have a positive effect on medication taking behaviour, with research showing that being informed about side effects and having a greater understanding of why medication is prescribed were independent predictors of adherence and persistence at 1 year post stroke.²⁵⁵ Seeking information has been found to be associated with the caregiver's responsibility in managing and keeping track of medicines.⁵⁸³ This suggests that caregivers need to adapt to meet the challenges of their new role. Caregivers who are the key focus of support following a stroke event face considerable challenges in the early post stroke phase including a lack of information about stroke and their role in stroke prevention.⁵⁸⁴

With adherence to secondary prevention medication among survivors known to decrease in the first few years of stroke⁴⁰¹, patients and caregivers may benefit from advice and support in the immediate aftermath of an event, in hospital before discharge and in the early post stroke period. Initialising secondary prevention measures in stroke survivors prior to entering the community could help address some of the difficulties patients and caregivers face around the medication taking process once in the community, particularly as the initiation of pharmacotherapies in hospital is known to lead to higher rates of adherence¹⁵¹, while providing a prescription before hospital discharge supported better adherence in stroke survivors at one year and two year post discharge.⁵⁸⁵

An observation of the research completed on barriers to medication adherence in stroke was that older survivors in the interview study reported taking medicines because that was what the GP told them to do, whereas younger forum participants' behaviour was influenced more by information they obtained from the press. Interventions to improve medication taking behaviour in stroke may want to consider the information that different groups of stroke survivors and caregivers refer to and how this impacts on their beliefs about medication and subsequent adherence to secondary prevention medicines. Inadequate information provision is often highlighted by stroke survivors and their caregivers. Identifying information needs of stroke survivors and recognising the different approaches to information provision is important and can inform the development of interventions to improve information and knowledge among stroke survivors and caregivers.⁵⁸⁶

With around half of all adults who experience a stroke thought to be living with a long-term disability³⁵³, the role of the caregiver may have particular significance for this patient group, especially around taking medicines. In the survey study which included recruitment of disabled stroke survivors, organising medication prescriptions and collecting medicines were the areas where the informal caregiver provided the most help. A recent study involving disabled patients

reported involvement in instrumental activities for daily living and in medically related activities by the caregiver as being strongly associated with providing assistance with ordering medications.³⁴⁹

Support with getting medicines out of boxes, swallowing medicines and help with prescriptions and medication collection support findings reported in the qualitative studies where the caregiver played an active role in medication management and administration. Help provided by informal caregivers in medication taking activities includes such tasks as preparing pill boxes and organising and administering medicines.⁵⁸⁷ The benefit of medication management of stroke medications post discharge has also been identified by survivors and caregivers as potentially important in reducing preventable stroke readmissions to the hospital from the community.⁴³¹

Survey participants reported needing help from caregivers in reminding them when it was time to take medicines and with checking that medicine had been correctly taken. This finding supports the comments of interview participants who also needed to be reminded by the caregiver and reported forgetting to take night time medicines. However younger forum survivors did not identify this as a barrier, suggesting that forgetting medicines is more likely among older patients.

Cognitive impairment is known to reduce adherence to medication.⁵³⁹ Following a stroke event, cognitive impairment is common^{588 589}, manifesting itself in increased forgetfulness and difficulty in concentrating.⁵⁹⁰ Although the survey study explored the medication taking needs of stroke survivors with disability, recruitment did not focus on stroke survivors with cognitive impairment. With medication related difficulties likely to be even more pronounced among survivors with cognitive impairment, understanding the medication practices of these survivors and developing interventions that focus on their unique difficulties is important.

Elderly patients face difficulties taking medicines.⁵⁵⁸ In this group, poor medication knowledge, varied levels of nonadherence and taking more medicines are associated with greater nonadherence, while adherence aids such as pill organisers were considered to be potentially beneficial.⁵⁹¹ Swallowing difficulties, problems opening medication packaging, confusion around medication taking regimes and experiencing adverse side effects have all been identified as contributing to poor adherence among patients living in the community.⁵⁹² Stroke survivors in the qualitative studies reported here also describe swallowing, side effects and difficulties accessing packaged medicines as potential barriers to medication adherence.

Participants in the qualitative studies reported here identified adherence aids including pill boxes and blister packaged medicines as being important facilitators of medication adherence, but

difficulties with these devices were also identified. Nevertheless, the use of adherence aids for patient medication is considered beneficial in improving health outcomes.^{593 594}

A Cochrane review on the effectiveness of medication reminder packaging, such as pill boxes or blister packs, on medication taking behaviour, found that reminder packaging increased the proportion of people taking their medicines and it was also beneficial in improving clinical outcomes such as blood pressure.⁴⁷² However no significant improvement in adherence was reported for using these aids in a clinical trial of medication taking in patients with chronic conditions.⁵⁹⁵ The potential for electronic medication packaging devices in improving adherence has been reported ^{596 597}, including for cardiovascular medicines.⁵⁹⁸ In a qualitative investigation exploring attitudes of patients and healthcare professionals, multi-compartment medication taking devices were considered a potential benefit for those patients with cognitive impairment.⁵⁵⁶

Beliefs about medicines were important for stroke patients' decisions to take secondary prevention medications. Interviewed survivors reported doubts around needing medicines and questioned their effectiveness, while forum participants doubted the efficacy of statins and considered them detrimental to health. Research has shown that beliefs about medicines play an important role in the decision to take tablets for stroke in that patients who are non-adherent to medication were more likely to have lower positive beliefs (i.e. beliefs about the need for medication and the benefits the medicines provided) and higher negative beliefs (i.e. beliefs about medication concerns, overuse of medication and harm caused by medicines).⁴²⁸

Challenging patient beliefs by offering reassurance and emphasising the importance of medicines, as well as discouraging negative beliefs though addressing patients' concerns about side effects for example, could play an important role in improving medication taking behaviour and subsequent treatment adherence. In a meta-analytic review of the literature on understanding adherence-related beliefs about medicines, higher adherence was found to be associated with fewer concerns about treatment and stronger perceptions about the need for treatment.²⁷² GPs discussing the importance of medicines and addressing concerns such as side effects among stroke survivors, as well as employing caregivers to encourage tablet use and provide reassurance could help to alleviate patient concerns and challenge the negative beliefs that stroke survivors hold about their treatment, which in turn could contribute to improving medication adherence- particularly as stroke patients have been found to disregard the advice of GPs and stop secondary prevention medicines because of side effects.⁴²¹

Beliefs about stroke medicines identified in our studies could be used to inform the development of future interventions to improve adherence to medication in stroke survivors. Phillips and colleagues (2015) investigating the importance of psychological domains related to adherence to stroke prevention medications found that participants' affective treatment responses (i.e. fear responses defined as worries about having to take medicines, their long-term effect or becoming dependent) were strongly related to medication adherence both at baseline and follow up.⁵⁹⁹ This suggests that stroke survivors have greater concerns about the implications of taking secondary prevention medications than about the stroke itself, particularly as patients' beliefs related to their treatment are more predictive of adherence than beliefs related to their illness.³²⁵

Practical methods, including following routines, adopting habits or using environmental cues, were important facilitators of medication adherence that were identified by stroke survivors and caregivers. Previous research in elderly patients has shown that development of routines may be a potential solution to improve medication adherence.³⁴⁸ Medication routines frequently consist of placing tablets in a particular location in the home and associating medication taking with a particular action or environmental cue. Research has shown that, among older adults strategies such as using visual cues and adopting medication routines facilitate the medication management process⁶⁰⁰ while routines have been found to be an important facilitator of adherence in patients taking anticoagulant medication.⁴³³

Pill burden and having a complex drug regimen were recognised by survivors, caregivers and practitioners as having a negative influence on medication adherence. Simplifying drug regimens may therefore encourage more effective medication taking practices and medication of unnecessary medicines. Further exploration of the role of fixed-dose combination therapy for secondary prevention with the potential to reduce pill burden and improve adherence, is also warranted

The existence of multiple co-morbidities resulting in polypharmacy is not uncommon among stroke survivors²⁸⁶ and can contribute to treatment burden in this patient group. Multiple medications including anti-hypertensives and cholesterol lowering therapy for the prevention of stroke, as well as the need for anticoagulants or medicines to treat atrial fibrillation, further adds to the treatment burden in this patient group. Indeed research suggests that patient adherence to chronic disease medication may be affected by treatment regimen factors such as dosage frequency and regimen complexity.²⁹²

Results from a meta-analysis on the impact of medication frequency suggested that adherence to therapies for chronic disease may be improved by reducing medication dosing frequency.⁶⁰¹ With

medication complexity known to reduce adherence,²⁷³ a potential strategy to address this complexity of treatment in cardiovascular patients could be the polypill approach incorporating fixed-dose combination therapy. Research has been shown that a fixed dose combination pill for cardiovascular disease has the potential to reduce the risk of medication non-compliance³⁵⁹ and address the challenges of polypharmacy, through reducing medication complexity and pill burden.²⁸² With growing evidence for a polypill approach for secondary prevention of cardiovascular disease having the potential to improve medication adherence and control risk factors³⁷⁵, there are recent calls for this treatment to be considered as a strategy for cardiovascular disease.⁶⁰²

Although polypill research in stroke has been largely overlooked to date, there is nevertheless potential for this approach to treating secondary stroke in the community.⁶⁰³ Key benefits of this polypill approach reported here by stroke survivors included the convenience it offered by reducing pill burden, minimising the inconvenience of managing multiple medicines and making medication management less demanding for the caregiver. This support for a polypill in reducing pill burden is in line with findings of another study which showed a preference for a cardiovascular polypill strategy that reduced the number of tablets being taken.⁶⁰⁴ Important concerns about a polypill approach for stroke prevention included the inflexibility around treatment adjustment and suitability of pill components. Stroke survivors may therefore prioritise treatment that they feel is closely tailored to their needs. Indeed patients and practitioners participating in a recent polypill trial in primary care similarly asked whether this strategy provided therapy that was less tailored to individual patient's needs.¹⁸⁶

8.3 *Strengths of the findings*

The research conducted in this thesis has a number of strengths. First, the findings contribute to the growing body of evidence investigating medication taking behaviour and adherence to secondary prevention medication for stroke in the UK. Additionally, the results highlight potentially important strategies on which future interventions to improve medication taking may focus, including incorporating the caregiver role or exploring further the potential of a polypill strategy in stroke. Identifying barriers and facilitators of adherence can uncover strategies upon which future interventions designed to improve adherence can be focused.

Furthermore, the use of additional data collection techniques (i.e. the online forum) provides a broader examination of the challenges faced by stroke survivors than may be identified through traditional qualitative techniques. Such is the dearth of research on medication taking behaviour in the UK stroke population, these findings contribute to our understanding around stroke medication

practices and have the potential to shape clinical practice in this patient group. Using two different qualitative approaches to investigate the same topic provides a strong account of medicine taking concerns among two distinct groups of stroke survivors. The comparison of methodologies undertaken also represents the first meaningful attempt to understand the potential of using an online approach to understand patient behaviour in stroke.

A further strength is the identification of important facilitators of adherence, including the use of adherence aids, importance of medication routines, the caregiver role and provision of informational support and advice. Interventions that operationalise these strategies could be implemented with relative ease in the clinical practice setting. GPs are in a unique position to identify patients at greatest risk of nonadherence, including those who struggle to take tablets or have complex medication regimens.

Health care practitioners should seek to involve the unpaid family caregiver more closely, providing information and advice to the caregiver as well as the patient. Understanding how such strategies positively influence actual medication-taking practice among stroke survivors should be a key focus for future research in this field. Facilitating factors that are easily incorporated into stroke interventions including medication routines or the use of adherence aids, can become an established part of the stroke survivor's medication taking practices over the longer term.

This research highlighted the role of the unpaid caregiver, usually a family member, who was the main provider of support to the stroke survivor. Informal caregivers have been shown to play a key role in the medication-taking process, handling medicines, obtaining prescriptions, accessing tablets and assisting with everyday medication management, as well as addressing unmet medication needs and acting as an advocate for the stroke survivor. However, as a resource the contribution of the caregiver is often overlooked. This research emphasises the importance of the caregiver approach and the need to explore this role further. Furthermore, given caregivers' unique understanding of the stroke survivor's medication needs, health care professionals should seek to utilize this close relationship to better understand how this may positively influence medication taking behaviour.

The strong focus of the thesis on the use of qualitative methodology provides a rich source of data through which to investigate medication taking among stroke patients. Exploring survivors' and caregivers' attitudes towards a polypill highlights how this approach can help challenge difficulties with secondary prevention medication and inform interventions that may improve the medication taking ability of stroke survivors.

8.4 Limitations of the findings

However, several limitations of this research should be discussed. It is not clear to what extent the views and attitudes reported are representative of the UK wide stroke population. Cognitive impairment resulting in problems with memory and thinking is an important consequence of stroke with significant implications for medication adherence. However this group of stroke survivors was not a focus of the investigations conducted in this thesis. Patients who are cognitively impaired as a result of stroke may face their own unique set of difficulties with medication taking and may be in greater need of support from caregivers.

With the eligibility of stroke survivors assessed by a practice GP, it is possible that physical disability, inability to communicate (i.e. aphasia), poor cognitive functioning or other significant co-morbidities influenced the decision of the practitioner to consider the stroke patient ineligible for inclusion. Therefore, our findings may not be representative of UK stroke survivors with significant cognitive or physical impairment who are likely to be at greater risk of difficulties with medicine taking.

Survivors who participated in our studies may have self-selected and had a greater desire to participate with strong opinions around the topic being investigated. Increased efforts are needed to ensure that the views of hard-to-reach stroke survivors are heard and that survivors in greatest need of support are included in future research.

Also, patients from non- white ethnic groups, known to be at increased risk of cardiovascular disease including stroke, were largely underrepresented in our research, with only 3 % of interview participants and 21% of questionnaire participants being from ethnic minorities. As these participants may benefit considerably from the development of interventions designed to facilitate better medication adherence, understanding their medication needs and concerns around adherence is also important.

The response rate of 35% in our questionnaire study exploring help with medicines and unmet needs is low compared to a study examining the needs of young survivors in the UK which reported a 49% response rate⁵³¹ while an investigation of long-term unmet needs of stroke survivors in the UK reported a response rate of 60%.³⁵⁴ The low rate in our questionnaire study may have contributed to response bias. As we did not have any information on the characteristics of non-responders in this study, we could not directly compare this group with those who returned completed questionnaires to assess representativeness. Further work is therefore needed to understand these patient groups who

may be poorly represented and to develop effective recruitment strategies to ensure that hard-to-reach stroke survivors, such as those with cognitive difficulties or physical disabilities, as well as those less likely to participate in research, are included in future studies.

Sample size and response rates were important limitations of the studies included in this thesis. Time limitations and logistical restrictions contributed to difficulties recruiting participants in the general practice setting with maximum variation characteristics. For example, few stroke survivors with severe stroke were included. Future research should seek to corroborate the findings reported here, while also recruiting survivors and caregivers who are representative of the wider stroke population. In the interview studies, few GPs were recruited despite the significant role they have in prescribing secondary prevention medications for stroke survivors, providing information on side effects and offering support with adherence. Recruiting multiple practitioners from the same practice location may be one way of increasing sample sizes in future studies. In addition, recruitment of other health care professionals across the stroke pathway including stroke nurses and nurse practitioners as well as pharmacists who dispense secondary prevention medicines, can also provide additional perspectives on medication taking and adherence in stroke.

Survivors who had experienced a significant stroke were largely under-represented across studies, even though they may be in need of the most support with medication. Greater efforts are needed in future research to identify and recruit those survivors with significant impairment as a result of stroke, who may be at greatest risk of poor medication adherence. Studies in primary care could enlist the help of practitioners such as stroke nurses, to identify patients from across the stroke pathway including those with significant cognitive and physical difficulties who may be harder to reach and less likely to participate in face to face research.

Greater involvement of informal caregivers in the recruitment process may also contribute to improved response rates and larger sample sizes that are more representative of the stroke population. The response rate in the survey study was relatively low which could have been a source of bias. In particular, ethnic minorities were under-represented. Prioritising efforts to increase recruitment of ethnic minorities, who are known to be at increased risk of cardiovascular disease and stroke^{101 102 605} and have been associated with poorer adherence to medication^{280 606}, is needed. By recruiting a predominantly White sample of participants across these studies, an important section of the stroke population may have been overlooked. Further studies conducted within GP surgeries and across primary care could involve the use of interpreters to facilitate the participation of participants from ethnic minority backgrounds.

Wider involvement of informal caregivers across patient consultations, medication reviews and pharmacy visits, could also contribute to a more collaborative approach to secondary prevention, in which stroke survivors are more informed about their condition, about the risk factors, preventative medication needed and dealing with side effects and medication concerns. Caregivers can in turn become more informed about adherence to secondary prevention medicines and in representing the needs of patients can act as a 'go between', when dealing with healthcare professionals. Research should seek to increase recruitment and participation of informal caregivers in stroke studies. Interviewed caregivers only participated jointly with stroke survivors. However recruiting caregivers independently may have highlighted additional concerns and facilitators of medication adherence and enabled caregivers to communicate beyond the influence of the patient. Caregivers are usually recruited through the patient themselves, however, focusing on identifying caregivers directly through GP practice registers may contribute to improving caregiver sample sizes across studies.

Survivors and caregivers who volunteered may have had a specific interest in research on stroke and medication adherence which may represent another source of selection bias. Greater efforts are needed to identify and recruit those patients and their caregivers who do not traditionally participate in health research. Identifying survivors and determining their adherence levels such as through questionnaires, prior to recruitment, may further help to ensure recruitment of a more representative sample.

The online forum represents a potentially important medium for conducting qualitative research and a significant source of data through which the wider views of stroke survivors and caregivers may be better understood. Although participant forum data was explored retrospectively, forums provide an opportunity to recruit younger survivors and caregivers who may be more willing to communicate online rather than face to face. In addition, with a significant proportion of forum participants identified as caregivers, this may be an important source through which the perspectives of caregivers can be independently explored.

Survivors identified from the forum highlighted difficulties associated with prescribing, including concerns around incorrect medicine being prescribed, conflicting treatment advice and intentional overprescribing of medicines. Similar difficulties with prescribing in general practice have been reported previously.⁶⁰⁷ The findings reported here for stroke survivors suggest that greater efforts are needed on the part of general practitioners to ensure patient needs are addressed, that patients are reassured and that concerns around prescribing are minimised.

As a key point of focus in the delivery of secondary prevention, the GP has a unique understanding of patients' medication taking behaviour. While these qualitative investigations highlight GP views also, the perspectives of health care professionals are largely underreported. Greater emphasis is needed in recognising the role of others and tapping into the expertise and knowledge of health care professionals including pharmacists as well as nurses, all of whom can play an important role along the stroke care pathway.

8.5 *Implications for clinical practice.*

Findings from this thesis have important implications for clinical practice in informing the actions of primary care practitioners and other health care professionals towards improving medication taking practices and adherence to secondary prevention medicines among UK stroke survivors.

There are a number of ways in which practitioners could facilitate effective medication taking among stroke patients. Firstly, in the general practice setting, GPs could involve the caregiver more closely in consultations with the stroke survivor. These findings demonstrated that the caregiver had an important role to play in medication adherence. Therefore, making the caregiver a key part of the medication taking process, from the initial provision of information through prescribing medications and follow up consultations, the clinician can ensure that the stroke survivor is best placed to face difficult challenges around medication taking and that adequate secondary prevention resources are in place for stroke survivor on their return to the community setting.

Another way in which the practitioner could facilitate medication taking behaviour is through the provision of information on stroke, on secondary prevention and on the importance of being adherent to medication. GPs could focus on highlighting the importance of medication, while acknowledging patients' concerns about medicines and side effects, as well as providing reassurance about the benefits of the medication and increasing the confidence of stroke survivors in the medication taking process. Our investigations have identified inadequate information as a key barrier to medication adherence among stroke survivors. In fact, a review exploring stroke knowledge and awareness among the general public as well as stroke survivors themselves and caregivers found that, in general, knowledge on recognising stroke and preventing stroke was poor.⁶⁰⁸

Addressing patients' concerns about medication side effects is important to facilitate medication adherence among stroke patients. Research shows that GPs asking patients to rate their health including asking about management of illness, in GP appointments, is valuable.⁶⁰⁹ The

practitioner asking stroke survivors about their medication taking experiences, explaining the importance of medications being prescribed and addressing concerns around potential side effects can boost the survivor's confidence in using secondary prevention medication from the outset. Conversely, through understanding stroke survivors' reasons for not taking medication, practitioners may identify important barriers that contribute to poor adherence and develop strategies along with the patient to challenge inadequate medication taking practices. Using the consultation to provide information on medication, including potential problems, is important, particularly as patients in hospital are known to be dissatisfied with the information they receive on problems with medication, while inadequate information has the potential to result in poor adherence.⁶¹⁰ Given time constraints on the practitioner role in the primary care setting, other professionals including nurse practitioners and pharmacists can play a role in ensuring that patients are informed and aware of the importance of medication taking. The pharmacist is uniquely placed to discuss secondary prevention medication, advise on practical ways to manage tablets and provide effective packaging for stroke survivors, particularly the disabled or the very elderly who may experience physical difficulties accessing packaged medicines as a result of disability or poor manual dexterity. Potential opportunities for pharmacists providing secondary prevention care are known to exist, such as improving prescribing safety or providing medication reviews.⁶¹¹

Stroke survivors may therefore benefit from a collaborative approach to medication taking in primary care, with the practitioner ensuring that the survivor benefits from the inclusion of caregivers and other health care professionals in the management of secondary prevention.

8.6 *Implications for policy*

The findings from this thesis suggest that policy makers and health care commissioners should intensify efforts to address the difficulties around medication taking practices among stroke survivors in primary care. Implementing effective information strategies as part of secondary prevention policy could help alleviate patients' concerns around medication as well as inform stroke survivors on the need for effective prevention. Greater emphasis should also be placed on educating the wider population about stroke. Given the high level of stroke recurrence, advising patients about risk and the importance of secondary prevention is needed. Investing in the training of other health care professionals such as practice nurses and nurse practitioners to deliver advice to stroke survivors and their families should also be considered and could ease the workload on general practitioners.

The use of medication packaging and electronic adherence aids can also contribute to improved medicine taking, particularly for survivors disabled as a result of stroke who may be in

greatest need. Policy makers should consider the benefit adherence aids have in medicine taking practices and invest in the development of interventions delivered in the primary care setting that use these devices.

These findings also suggest that guidelines on secondary prevention should be adapted to take account of the growing influence of the unpaid caregiver and that this should be reflected in policy designed to inform practitioners in their efforts to facilitate good medication taking practices. Health care commissioners should also consider investing in multi-level interventions that target specific patient groups. For example, elderly stroke survivors who need help handling medicines may benefit from the use of dispensed pre-packed blistered medication while the pharmacist could also contribute by discussing in detail the medicines being dispensed, drawing on the advantages of stroke medication and highlighting medication difficulties stroke survivors may face. Other survivors such as those with aphasia who have difficulty remembering to take medication may benefit from the use of medication reminder devices.

There is some evidence for the use of electronic multi-compartment devices using reminder systems to improve adherence to medicines.⁵⁹⁷ Commissioning groups should consider funding studies that assess the feasibility of these devices for use in stroke prevention.

8.7 *Recommendations for future research in light of thesis findings*

A key focus of further work in light of the findings reported in this research should be in understanding medication concerns among stroke survivors and addressing the barriers patients face when taking secondary prevention medicines. To meet the challenge of nonadherence, researchers should seek to develop novel and uncomplicated interventions with the potential to deliver behaviour change in the primary care setting. The findings from this thesis highlight a number of important areas where future research in the field should be focused.

A key finding from this thesis was the caregiver as an important facilitator of medicine taking. Further research exploring the caregiver role is warranted. Future studies should focus on examining the potential for involving the caregiver in the patient-practitioner consultation and on improving the provision of information on stroke and medication to the caregiver, which in turn can inform the patient. Assessing the caregiver role in managing and administering medication in stroke should be explored further. Wider GP recognition of the caregiver's role in managing and administering medicine and as the 'link' between the patient and practitioner is needed. Greater understanding of the caregiver role in the context of stroke survivors with physical/ cognitive

impairment is also important given these stroke survivors may benefit most from caregiver support. Research could explore general practitioners perspectives around the caregiving role in secondary prevention more widely, including their understanding of the caregiver as an advocate of the stroke survivor. Given the complexity of medication adherence and the need for more effective medication taking practices, future research should seek to address the collaborative approach to medicine taking between the survivor, caregiver and healthcare professional.

A fixed-dose combination polypill represents a novel approach to stroke prevention with the potential to reduce pill burden and the complexity of the treatment regimen, thus contributing to improved medication taking behavior. As the first study to explore attitudes towards a preventative polypill for stroke in the UK, these findings add to the growing body of literature on secondary prevention polypills in general, while also highlighting a new approach to stroke prevention that has not been previously explored. Novel insights such as the importance of GPs endorsing and recommending a polypill strategy, perceived appropriateness and suitability of a polypill strategy and concerns around a lack of proven efficacy of polypills suggest there is still work to be done to convince both patients and practitioners of the benefits of a single pill approach to stroke prevention. A collaborative approach involving practitioners, patients and caregivers may help improve acceptability of this treatment approach. The role of the polypill in improving adherence was widely supported among survivors in my study, however, practitioners also needed to be reassured about its efficacy and the benefits of endorsing a polypill strategy in patients on established medication regimens. Nevertheless, this study provides a strong basis for further investigations on a polypill approach to secondary stroke prevention and identifies areas where a greater understanding of the polypill approach may be needed.

Exploring the growing potential of a fixed-dose combination polypill for secondary stroke prevention is warranted with further studies needed to corroborate the findings reported here. It would also be useful to understand polypill perspectives among different sub-groups of stroke patients who have difficulties taking their medicines including the physically disabled, patients known to be non-adherent and those on polypharmacy with a high treatment burden. Such stroke patients may be particularly suited to a single pill strategy. Patients need reassurance about the benefits of this treatment and for the healthcare professional to address any concerns of the polypill approach among stroke survivors. Given the caregiver role in medication management, exploring views around administering and handling a medication regimen including a polypill would be beneficial. A further recommendation for future research is in exploring the motivations of health

care professionals to prescribe polypill, in light of the concerns raised in the polypill study reported here.

8.8 Novel findings generated by this thesis

The findings reported in this thesis make an important contribution to the current literature on medication taking in stroke. Understanding barriers to medication adherence from the perspectives of the stroke survivor, caregiver and the GP can help in identifying important concerns around medication taking. Results showed that patients who had experienced a stroke or minor TIA faced similar difficulties with secondary prevention medication and these were often reinforced by the views of caregivers and health professionals. This study showed that patients often ignored the symptoms of a TIA and delayed visiting a healthcare professional or initiating secondary prevention therapies. With TIA known to precede recurrent stroke,^{49 612 613} those survivors who experience a mild TIA and who may overlook stroke symptoms should be the focus of increased attention by practitioners along the stroke care pathway.

An interesting finding was that survivors often trivialised TIA, and frequently reported ignoring the symptoms, which was also confirmed by GPs. This suggests patients may not be widely informed about stroke and the potential risk of a secondary event. TIA is an important risk factor for stroke and it has been shown that the risk of ischaemic stroke following a TIA is high for those patients diagnosed with a stroke compared to patients with no history of clinically diagnosed TIA.⁶¹⁴ Increasing patients' recognition of stroke and routinely advising about the risk factors and necessary preventative measures may be beneficial for those who are at heightened risk or who have experienced a TIA. A survey in the UK by the Stroke Association, exploring understanding of stroke within the general population, found that around 68% of people did not recognise the symptoms of a TIA, the same number had not heard of a TIA and around 40% did not know that a TIA was a significant warning sign for a further stroke.⁶¹⁵ It is known that around 1 in 10 patients who have had a TIA will go on to have a significant stroke within 7 days with the stroke risk from onset of first ever TIA 8.6% at seven days rising to 12% at 30 days.⁶¹⁶ GPs can play an important role in advising patients about medication and addressing concerns around side effects. In the interview study, GP s highlighted adherence concerns acknowledging that patients were often not fully adherent but accepting it was also important to respect the autonomy of the patient when deciding to take medications. A qualitative study with GP's examining barriers and facilitators of medication adherence found poor knowledge of illness and medication, as well as media as a source of information, to be potential barriers to good medication adherence among patients.⁶¹⁷ Adverse effects

of using medication, polypharmacy and complex regimens were also highlighted as therapy related barriers.⁶¹⁷

In recognising the importance of encouraging patient adherence, addressing concerns around pill burden and regimen complexity and acknowledging that patients underestimate the need for medication, this study has highlighted key areas in which resources to challenge medication taking difficulties could be focused in the clinical practice setting. Campaigns such as F.A.S.T.¹⁰⁴ have sought to increase knowledge and stroke awareness in the public domain, however these have not necessarily translated into a change in behaviour.⁶¹⁸ A multidisciplinary approach to challenging stroke along the care pathway has potential.⁶¹⁹ Involving the patient, their families and caregivers and encouraging participation in stroke care may help challenge barriers to medication adherence. In light of the importance of the multidisciplinary team in stroke prevention and rehabilitation,⁶²⁰ the collective perspectives of survivors, caregivers and healthcare professionals can inform the development of effective interventions to improve medication adherence in stroke.

The qualitative interview study reported in this thesis identified important beliefs about medication taking, including concerns around using statins and preferences for aspirin as a preventative therapy. Simple strategies delivered within clinical practice and the pharmacy setting including better understanding of side effects and highlighting the importance of adherence to preventative therapies have the potential to be beneficial in addressing concerns and improving medication taking. Exploring the potential of brief advice provided by the GP when prescribing medicines or the pharmacist addressing adherence and side effects when dispensing medicines, warrants further investigation.

The struggles that caregivers face in representing the needs of the patient also highlights difficulties in undertaking the caregiver role. As part of a multidisciplinary approach to stroke prevention, the role of the caregiver requires further attention. As well as recognising their unique position in understanding the stroke survivor, wider acknowledgment and support for the caregiver role may enable the caregiver to carry out this role more effectively. Health professionals and others along the stroke care pathway such as stroke nurses can look to the caregiver for important knowledge and understanding of the stroke survivor's medication taking behaviour including their concerns about secondary prevention. Practices to support the survivor in the use of medication management strategies and increasing patient knowledge about medication, should be explored further. The online forum investigation sheds light on 'new' concerns not identified through

traditional qualitative studies and may help in identifying areas of medicine taking where resources could be focused in the future.

Interestingly, forum users raised concerns about the negative press attention regarding statins on their decision to take medication. Survivors may therefore benefit from a collaborative approach to understanding medicine taking in which health professionals routinely address patients and caregivers concerns around statin treatment. For example, reassuring stroke survivors at the point of prescribing statins and providing the opportunity to change medications when reviewing treatment, should be considered. In addition, pharmacists can play an important role when dispensing medicines by addressing concerns raised as well as offering strategies for more effective medication management. With a rise in the 'expert patient' ⁶²¹ and the ability to access information online and through other information channels growing, there may be a greater onus on practitioners and professionals delivering stroke care to ensure that survivors are properly informed about secondary prevention medicines.

The appropriateness of a polypill for patients on an established medication regimen and the perceived inflexibility of a fixed-dose combination pill emerged as important concerns for both patients and practitioners. This suggests a collaborative approach to understanding this strategy for stroke prevention is needed. For stroke survivors using various combinations of statins, anti-hypertensives and anticoagulants or anti-platelets for secondary prevention, a 'one size fits all' polypill approach may be unrealistic. In response to concerns around the inflexibility of fixed-dose combination therapy, there has been significant progress in developing this treatment with polypills now available in over 30 countries.³⁹² To date, multiple polypills have been developed and studied in numerous trials which have demonstrated effectiveness of FDC pills in reducing cardiovascular risk.⁶²² In the current investigation stroke survivors on an established medication regimen were happy to continue with their current medication rather than change to a polypill regimen, highlighting the importance of the stability of their medication taking regimen and concerns around starting a new and largely untested treatment.

Results from the present study also corroborate previous findings on cardiovascular polypills and suggest that a FDC polypill approach may have potential for stroke survivors also. Support for a polypill reported here suggests that stroke survivors face difficulties with taking medicines and also highlights the need for a simple medication taking regimen. Stroke survivors often endure significant co-morbidities, such as hypertension, AF and diabetes, resulting in polypharmacy or the need for multiple prescribed medications. Therapeutic complexity including multiple prescribing and filling of

medication is known to be associated with low levels of adherence to cardiovascular medication.²⁷³ A polypill approach may therefore hold potential in reducing pill burden and simplifying complex medication taking practices among stroke survivors.

Patients and practitioners expressed concerns about switching to this approach from an established secondary prevention regimen. A recent investigation found that switching to a polypill strategy increased aspirin use and lowered cholesterol and systolic blood pressure when compared to continuing usual care in a high risk population. In fact, a polypill with component medicines that were moderately potent achieved outcomes that were similar to individual medicines that were more potent.⁶²³

Pharmacists may have a role to play in increasing understanding and awareness of the polypill approach and can help to address patients' concerns by offering reassurance on taking this medication. A study with pharmacists showed that despite inability to titrate dosage and tailor the treatment as well as difficulties in attributing side effects to a particular component of the polypill, most pharmacists viewed the polypill approach as a potential solution for improving medication adherence.³⁸⁹ Novel insights reported in the current study call for a more collaborative and multidisciplinary approach to understanding and implementing a polypill approach for stroke prevention. To date, uptake of the polypill has been slow.³⁹² However evidence has shown no significant safety concerns or that a polypill is any less well tolerated than when the medication is taken as individual components.⁶²⁴

This polypill study sheds light on a novel approach to secondary prevention not previously investigated among stroke survivors, but which could be of particular benefit to a patient group who are known to struggle with medication taking. Further research addressing the concerns of patients, caregivers and GPs is therefore needed if a FDC polypill is to become a realistic and accepted treatment for secondary stroke prevention.

In this thesis, the online forum represented a novel source of information providing rich data on barriers and facilitators of medication adherence faced by stroke survivors and their caregivers. As the first study to explore medication adherence in stroke through an online forum, these findings make an important contribution to the literature, furthering our understanding of medication taking within this patient group. Qualitative results from the forum study corroborate findings from the face to face interview study⁴⁴⁰, thus confirming that similar concerns are present among patients and caregivers from across the wider stroke population. A wide range of time elapsed since stroke and degrees of disability were represented across the stroke forum.⁴⁵⁶ In the present study users were a

younger stroke sample compared with their interviewed counterparts, thus offering the views of a patient group that may be less well understood and underrepresented in traditional research practice.

Caregivers were well represented and were predominantly children of stroke survivors. Their involvement further highlights the importance of representing the views of those survivors who may not be able to participate in traditional research and who may be unable to communicate effectively or manage their medication as a result of cognitive impairment or physical disability. Caregivers posting on the forum also identified the importance of a collaborative approach to medicine taking, recommending a role for the pharmacist in organising the survivor's medication and their own role in assuming control of family member's medication.

The forum may also represent an important resource that healthcare practitioners and other stroke professionals can utilise to better understand the medication taking behaviour. In an investigation of care co-ordinators in the primary care setting, the online forum was considered a feasible and effective method to conduct qualitative research and an important source for sharing knowledge and networking among health care professionals.⁶²⁵ Younger forum users may be more influenced by the information around them, such as through the Internet, and more likely to question the medication they were taking, unlike some older survivors and caregivers who readily admitted to following the GP's advice without question.⁴⁴⁰ Interestingly, forum users also highlighted practical difficulties with taking medicines including using pill boxes or blister packaged medications, suggesting that those significantly affected by their condition relied on the caregiver, even though medication aids are known to have a beneficial effect on medication taking behaviour.⁵⁹⁷

Internet based web forums have the potential to provide a unique source of data through which to undertake qualitative research.⁶²⁶ Using the Internet to collect qualitative data offers the opportunity to tap a novel source of naturally occurring interactions.⁶²⁷ and rich data through which the accounts and experiences of individuals can be widely understood.⁶²⁸ In providing a voice to patients and caregivers who choose not to participate in face to face investigations, forum users can discuss topics at ease⁶²⁹ and researchers can explore conversations and sensitive information which may be difficult to obtain without otherwise influencing the discussions.⁶³⁰ As many conversation threads included conversations between caregivers, describing their own experiences and seeking reassurance or information on medication taking practices, the forum also enables the caregiver perspective to be examined and better understood. However limitations of this approach such as the inability to request clarification from participants⁴⁶⁷ and the absence of users' socio-demographic information, makes it difficult to verify information and the identity of those who provide it.⁶³⁰

Undertaking research using an online forum also raises some ethical considerations regarding the way this information should be used. Key established concepts of traditional research such as disclosure, anonymity, confidentiality of information and informed consent, are all associated with greater uncertainty when applied to research conducted online⁶²⁸ and represent important ethical challenges for the healthcare researcher.⁶³¹

Central to the discourse around using an online forum to undertake qualitative research is the understanding of what counts as ‘public’ and ‘private’ information, and how data collected from a novel platform such as a discussion forum should be used for research purposes. On one side it has been argued that messages posted to a publicly accessible forum are within the public domain and therefore not subject to the ethical principles of obtaining informed consent and seeking ethical approval, applied to traditional qualitative research.⁴⁶⁷ The ESRC Ethics Framework (2010) states that web forums on the Internet can be considered to be in the public domain and as a result, researchers would not be expected to obtain informed consent from users on the forum who have authored these posts.⁶³² On the other side of the argument is the view that using the text without first seeking the consent of forum contributors could be considered a violation of privacy.⁴⁶⁵ Messages posted to a forum may be perceived as being private and not intended for scrutiny for research purposes, while participants communicating in this environment may not expect their words to be read by people outside this virtual community.⁶³³ Few would also expect their words and postings to be the focus of research conducted retrospectively, raising issues around privacy and the degree to which potential participants are aware of this eventuality when they post the data online.⁶³⁴

The uncertainty around the role of ethical guidelines in Internet research has resulted in a lack of consensus among researchers on the way forward.^{635 636} As a result of issues identified around confidentiality and informed consent, it has been argued that the ethical decisions made in traditional qualitative research should equally be applied when conducting Internet research.⁶³⁷ while online research may need to consider the expectations of users ‘guided by consensus and contextual integrity’.⁶³⁸

New guidelines have been developed with the aim of addressing key ethical issues of confidentiality, informed consent and data privacy and ensuring research is conducted in a professional manner.^{527 638} Guidelines from the British Psychological Society (BPS) describing ethical practice when undertaking psychological online research, state that “participants may consider publicly accessible internet research as being ‘private’..., and where direct quotations are necessary to the research methodology, then the consent of those sampled should be sought”.⁵²⁷ In 2013, these guidelines were updated to acknowledge the different existing opinions regarding information that is easily accessible within the public domain reporting that “the researcher should consider the potential

for harm to the individual before such information is used without first obtaining participant consent". The BPS guidelines concluded that "Where it is reasonable to argue that there is likely no perception and/or expectation of privacy (or where scientific/social value and/ or research validity considerations are deemed to justify undisclosed observation), use of research data without gaining valid consent may be justifiable".⁵²⁷

Prior to undertaking the research reported here using data from an online forum, written informed consent was not sought from users and ethical approval was not obtained. Data was made available by the Charity running the forum, for the sole of purpose of undertaking research.

When the forum was active, it was open to the public and accessible to anyone with an Internet connection. Users needed to log into the forum to access threads and provide information, however, they could search the entire content of the forum and posts could be found and read openly through the current Internet search engine "Google", using relevant search terms. Given the ease of accessibility, it could therefore be argued that such information exists within the public domain and is not subject to the requirements placed upon researchers undertaking traditional research, such as the need to obtain informed consent beforehand.⁶³⁷ Although informed consent is central to traditional research, it can be more difficult to obtain within the Internet environment, particularly as populations in online research can be transient in nature and difficult to identify.⁶⁴⁰

This 'opportunistic' nature of this research raises ethical concerns around using material that was not originally developed for the purpose of conducting research.⁶³⁵ If online communication is not intended by the individual to be used for research purposes, it can be questioned whether researchers should be using it for this purpose, without the explicit permission of the individual who provided the information.⁶⁴¹

Although participants on a forum acknowledge that they are communicating in the public domain and their information is accessible to the wider population, they may not have a wider understanding of how their data is used by other parties, such as researchers. As a result it has been proposed that when conducting research using the Internet, the active participation of subjects should be sought and written informed consent should be obtained where possible.⁴⁶⁵ As suggested in the guidelines, ethical boundaries for online research are less easily defined which may have implications for consent procedures around protection of participants. With such guidelines open to interpretation on what defines 'public versus private space', the lack of clarity has resulted in differences in how online research is being conducted.⁶²⁹

The decision not to obtain consent from forum participants or seek ethical approval for the study described in this thesis was taken for mostly practical reasons. Firstly, data from the online forum was obtained retrospectively and as the forum was no longer operational there was no clear

way of tracing participants. Due to the significant amount of data accessed on the forum contacting all the online users who contributed to the forum threads would also have been virtually impossible. Furthermore, with no engagement between the researcher and forum users in this study, the potential for any intrusion was minimal. Nevertheless, in deciding to analyse data from the online forum in the absence of ethical approval, a number of other factors related to the confidentiality of participant information were considered. Given that respondents were participating in a public open forum it can be argued that they had no expectation of privacy and therefore using the data without first obtaining ethical approval is justifiable.⁵²⁷ In addition the potential risk of harm to the forum user⁶³⁹ of their words being used for research purposes was assessed and considered to be minimal. Direct efforts taken to maintain the confidentiality of participants and their information included paraphrasing the original data and forum users being identified through a unique ID number any subsequent publication.

Other potential challenges arising from undertaking this research that are acknowledged include traceability of quotes, pseudonymity, identity of research participants and the quality of data obtained.⁶⁴² Measures to ensure data provided in the forum could not be traced back to the individual attributed to the post included paraphrasing and not quoting participants verbatim. While this has the potential to provide an extra layer of anonymity to the forum participant, it may also involve an extra layer of ‘researcher interpretation’, thus reducing the ability of others to disagree with the researchers interpretation.⁶²⁹ Undertaking research using an online forum highlights the issues researchers face with regards to meeting the ethical requirements expected of conducting robust psychological research. Therefore, assessing issues around confidentiality and privacy on a case by case basis may be necessary, and researchers may need to employ commonsense principles that are applied to other qualitative methodologies when undertaking Internet based healthcare such as with an online forum.

The methods study reported here identified similar concerns among both groups of stroke patients (i.e older interview participants and younger forum participants) which could have important implications for medication taking across the wider stroke population. New themes reported in the forum, may further highlight under-reported difficulties experienced by younger groups of stroke survivors and caregivers who may be more likely to participate in online research.

This study offers support for the online forum as an appropriate data source for qualitative research and is unique in being the first to directly compare two separate investigations semi-structured interviews and an online forum, with an identical health focus (stroke), reporting the same outcomes (barriers to medication adherence) and using the same structured framework (PAPA). Mapping key features of both approaches onto theoretically derived attributes strengthens the role of

the online forum as an appropriate source of data for conducting qualitative healthcare research. Insights from this study can help inform other researchers on the best approach to take when undertaking qualitative research with a particular patient group, and to determine the appropriate source of qualitative data for the specific research questions being asked. New themes identified within the forum including concerns around the prescribing practices of general practitioners, the impact of negative press attention and caregivers' own experiences in acting as the survivor's advocate, were not uncovered in face to face interviews. This may suggest that forum participants who are younger than their offline interviewed counterparts are potentially engaged with their own health and in understanding the importance of medication. Further examination of this younger group of survivors and caregivers may uncover additional important knowledge around medication taking in stroke. Unlike the face to face interviews where caregivers and survivors were interviewed together, the forum enabled caregivers to communicate independently of stroke survivors and to discuss their own medication concerns with other caregivers and survivors, offering reassurance and advice and seeking support when needed. The ability to read and reply to themes throughout the forum also enabled users to explore the topic in depth, and make a significant contribution to the wider forum discussion on medication taking.

The nature of asynchronous communication, relative anonymity and the absence of researcher involvement, may have contributed to openness among forum users and a willingness to discuss sensitive issues and make more frank admissions regarding medication taking activities. Unlike the face to face interviews in the qualitative study where all caregivers were interviewed in the presence of stroke survivors, the 'independence' of the caregiver within the forum may also have reduced the likelihood of any self-censorship when communicating with others. The forum therefore offered a richness of data where threads could be contributed to and discussed over a long period of time, with the direction and content of discussion completely determined by users themselves and without any influence of researchers.

Limitations of the forum approach such as a lack of information on participant characteristics, absence of face to face interaction and inability to directly question participants, did not affect understanding and interpretation of the themes that were identified, indicating that even with a lack of knowledge of participants, the forum represents a potentially important source of qualitative data.

The important role of the caregiver in medication adherence identified within the qualitative studies in this thesis was examined in more detail in the survey study which investigated the unmet medication needs of stroke survivors. This study makes an important contribution to the stroke literature by providing an important account of the help survivors get with different aspects of medication taking in the community. Considerable practical unmet needs have been reported among

stroke survivors,³⁵⁴ however, there remains a dearth of research examining unmet medication needs. Understanding which practical aspects of medication taking activities stroke survivors need help with and identifying areas where they have unmet needs is important when implementing effective medication taking strategies. Stroke survivors who are dependent for ADLs represent an important patient group who can benefit from sustained caregiving support. Informal caregivers, primarily family members, who are best placed to understand patient's medication taking activities, have a key role to play in helping to address the unmet needs of stroke survivors, both medicine related and with activities of daily living.⁶⁴³

The survey study provides new knowledge on medication taking among survivors who are dependent for ADLs. This group may be particularly vulnerable to poor medication adherence and may therefore benefit from being the focus of future research. To date there is little evidence examining medication taking in stroke patients who are dependent on others, such as unpaid caregivers, with more work needed to fully understand their medication adherence practices.²⁶⁴ The findings can help practitioners along the stroke pathway to devise more effective strategies to address the challenges these patients face. With one in ten stroke survivors needing help with medicines this survey study demonstrates the importance of the informal caregiver in helping with medication management. Help with prescriptions and collecting medicines as well as being reminded to take tablets was where caregivers provided the most support. Survivors who suffer significant cognitive dysfunction as a result of stroke are more likely to struggle with remembering to take tablets and those with physical disability may struggle visiting the GP practice or pharmacy to collect their medicines, in the absence of caregiver support. Caregivers could therefore play an important role in ensuring medications are readily accessible through participating in GP consultations and pharmacy visits.

Interestingly, survey findings show that stroke survivors still needed help with handling medicines even though medication management devices and reminder packaging such as pill organisers are associated with better medication taking practice.⁴⁷⁰ Such devices may be effective for managing and organizing multiple medicines, for patients who are significantly disabled and who struggle with handling medications, however difficulties can remain without the help of a caregiver. Assessing the stroke survivor's needs on a case by case basis to determine their level of independence with medicine and the degree to which support is needed, may help to identify those survivors in greatest need of caregiver support.

With over half the sample reporting some kind of help, this study demonstrates the importance of informal caregiving in this patient group. In addition, it suggests that interventions to help with medication taking should be developed with the informal caregiver in mind. With around one third of

survey participants reporting missing medicines, adherence to medication in this group is problematic. Greater efforts are needed to maximize medication taking, particularly among survivors who are dependent for activities for daily living and who may often struggle with handling tablets and organising their medicines.

Being on a higher number of medicines was associated with having unmet needs and being more likely to miss taking medicines. Addressing pill burden by reducing the number of medications being taken by the stroke survivors may be one way of addressing these difficulties. Better management in prescribing as well addressing inappropriate prescribing of medicines at follow up consultations could reduce the overall pill burden on stroke survivors, and therefore contribute to better medication taking practices. The findings reported in this survey study suggest that stroke survivors who are disabled or take a large number of medicines could be at increased risk of future cardiovascular events as a result of missing important medication for the secondary prevention of stroke. Elderly patients with multiple co-morbidities may be at particular risk. Interventions that improve medication taking practice among stroke survivors who are dependent on caregivers and which address the unmet needs of these patients are urgently needed.

The research reported here identified important physical strategies that stroke survivors and caregivers adopted to facilitate everyday medication taking. Further research could explore the role of medication taking routines and environmental cues and how these influence everyday medication taking behavior. Researchers could benefit from examining the role of implementation intentions and if/when scenarios e.g. 'If I have a cup of tea I will take my medication' and the implications for medication taking activities. More research is needed to understand the use of medication adherence aids such as pill boxes and blister packed medication, particularly for those stroke survivors in greatest need and who could benefit most from their use (i.e. those who forget medicines/ are disabled/ have cognition difficulties).

Further research to improve interdisciplinary communication across the stroke care pathway would be beneficial. Strengthening the GP patient relationship within the clinical consultation and facilitating better patient-practitioner communication has the potential to improve patient trust, foster patient confidence and in turn encourage positive beliefs and patient motivation to take medications. Researchers should seek to better understand the patient practitioner consultation and the key facets of this interaction that could improve patient medication behavior. Further studies should also try to develop ways to improve communication between the consultant and GP, to address prescribing difficulties and ensure common agreement on the appropriate medication for the stroke patients

including continuity of the medication regimen from in patient to the community. The GP pharmacist relationship warrants further evaluation also, through increasing communication and co-operation with respect to patients who may benefit from packaged medications as part of secondary prevention regimens that are tailored to the stroke survivor's individual needs.

8.9 *Potential interventions within the primary care setting that can improve medication taking behavior among stroke survivors.*

Findings from this thesis may also inform the development of interventions to improve medication taking behavior. There is growing potential for the use of emerging technology to improve medication taking behavior. Barriers and facilitators identified through the qualitative investigations reported here can inform content development in mobile phone text messaging interventions- including delivering tailored support messages to improve adherence in general practice- offering reminders to take medicines – providing reassurance when medicines have been missed – sending reminders about GP appointments, to attend medication reviews or change medicines if necessary.

Another potential intervention could be in providing brief information and advice to stroke survivors and their caregivers. Brief advice could be delivered by the GP during the patient practitioner consultation to boost the patient's confidence, address medication concerns, emphasise importance of taking stroke medicines, provide information on the importance of treatment post stroke, as well as the use of adherence aids. Advice provided by the pharmacist dispensing medicines could include information on potential side effects as well as addressing medication related concerns and offering reassurance.

Introduction of adherence aids into treatment regimens to facilitate medicine taking also has potential. Interventions are needed to compare the benefit of compliance aids including blister packaged medication and to determine which groups of stroke survivors may benefit most from their use - e.g. adherent/ nonadherent, higher dependence/lower dependence (on caregiver). The pharmacy liaising with the general practice can facilitate the introduction of blister packaged medicine for those survivors considered to be in greatest need.

Exploring a fixed-dose combination polypill approach to improve medication taking behavior has potential. A polypill approach to secondary stroke prevention may improve medication taking behaviour. Further work is needed to understand this approach and its acceptability among stroke survivors, caregivers and health care professionals, which has been explored in the field of

cardiovascular disease, but not in stroke. Further understanding of the perspectives of caregivers and healthcare professionals is needed as well as sub-groups of stroke survivors who may benefit most from this approach, such as those who are dependent (have difficulties handling medicines) or cognitively impaired (may be more likely to forget medication). A polypill approach could address barriers of treatment burden and regimen complexity. An intervention in primary care would compare a polypill approach with usual care for secondary prevention to test if taking a single pill can result in improved medication adherence among stroke survivors.

A growing body of research is now focusing on the use of electronic technology to improve patient adherence to medication. Mobile phones have emerged as an acceptable medium through which support and assistance can be provided to facilitate adherence to medication regimens among stroke patients.⁶⁴⁴ Furthermore, the use of SMS (short message service) technology has previously been studied in health behaviour interventions⁶⁴⁵, and messaging systems targeting preventative health behaviours have shown potential to deliver positive behaviour change.⁶⁴⁶ This technology has been used previously to provide reminders to patients to take medication⁶⁴⁷, to improve adherence to medication for the primary prevention of cardiovascular disease⁶⁴⁸ and to attend healthcare appointments.⁶⁴⁹

There is some evidence for the use of mobile technology to facilitate medication adherence in chronic disease,⁵⁶⁵ but the potential of this technology in encouraging medication adherence requires further exploration.⁶⁵⁰ One trial in this field found that a brief SMS text messaging intervention could improve medication adherence in stroke survivors with complex medication regimens.⁵⁶⁶ Future research could consider furthering the use of SMS technology to facilitate adherence through development of a reminder program incorporating tailored theory-based messages that address the barriers and concerns highlighted by patients in this research.

For example, a brief questionnaire could be administered during the patient practitioner consultation to collect data on medication habits, including precise timings of taking medicines, details on daily routines and information on side effects. This information could then be used to provide tailored support to the stroke survivor outlining personal medication taking habits, as well as providing reassurance and offering encouragement on the benefits of continuing medication as well as acknowledging concerns around side effects and strategies to manage these, including such as prompts to have medication reviewed or changed by the GP. Encouragement to follow a medication routine, adopting a simple plan or strategy, reminders to seek caregiver support and emphasising the

use of medication boxes to assist with taking tablets, are other areas the text messaging programme could explore.

Two-way functionality incorporated into a texting intervention could enable the stroke survivor to request additional support when struggling with side effects or seek advice if tablets have been missed as well as receiving reminders to collect repeat prescriptions or attend follow-up appointments. This support programme could also be adapted to incorporate a separate functionality whereby messages in which stroke survivors raised medication concerns could be relayed to a third party or caregiver who could provide additional encouragement and support to the stroke survivor.

Mobile phone apps ('applications') have also emerged as a potentially useful intervention to help patients take their medication.⁶⁵¹ Although the evidence for the use of mobile apps in facilitating adherence remains weak due to inadequate testing and basic levels of functionality, this technology represents a potential strategy for patients in the practice of taking everyday medication.⁶⁵²

Technology focussed interventions hold potential for enhancing cardiovascular medication adherence.⁶⁵³⁻⁶⁵⁵ This may offer survivors who may have limited cognition, mobility and communication, increased opportunity for better post stroke medication taking practices. Studies with cardiovascular patients including stroke survivors show that the use of technology including mobile phone and hand held computers (popularly called tablets) is acceptable and has the potential to have a positive influence on post stroke care and medication taking practices.^{566 656 657} Results from a Cochrane review of trials on the use of text messaging to improve adherence in secondary prevention of cardiovascular disease including stroke suggest that while there is promising support for the role of text messaging in improving adherence to medication taking, more high quality research is needed to further investigate the potential of this approach.⁶⁵⁸

Development of mobile phone apps as well as text messaging interventions to improve medication adherence can benefit from adopting behaviour change techniques to deliver robust and effective feedback to stroke survivors. An examination of behaviour change techniques within mobile apps for medication adherence has found their use to be inadequate.⁶⁵⁹

Future interventions aimed at improving medication adherence should also include strategies that facilitate medication taking such as the use of compliance aids. Survivors with disability or poor manual dexterity may struggle to use these devices. Efforts to understand the benefit of compliance aids on specific sub-groups of stroke survivors may be helpful. The general practitioner could help to identify stroke survivors at greatest risk of nonadherence and who may benefit most from pill boxes and other compliance aids that are relatively inexpensive and easily accessible.

To address a barrier to adherence the patient may have highlighted previously in the consultation, the practitioner could provide a brief intervention consisting of advice or a motivational message on the importance of taking stroke medicines, a suggestion to address nonadherence, or to encourage support from the caregiver.

Patient attendance at the pharmacy to collect medicines represents a further opportunity to deliver a brief intervention. This may be particularly important for patients who are prescribed new medications as research has shown these patients quickly become non-adherent.⁵⁸⁰ This also provides an opportunity to develop the patient- pharmacist relationship which could build trust in the patient, contributing to better medication taking practices later on. Brief advice provided by telephone by the pharmacist has been shown to be effective in improving medication adherence to diabetes and lipid medication⁶⁶⁰ and could be explored further among stroke survivors as a way of facilitating medication taking.

Another important facilitator of adherence includes the use of medication taking routines or following environmental cues. A simple intervention in which the patient follows a precise strategy to take medicine involves an approach called implementation intentions.⁶⁶¹ Here the individual makes a specific plan about how they will take their medication. For example, the patient may state 'If I am in the kitchen, having tea at breakfast, *then* I will take my medication.' Thus environmental cues to take medication become more pronounced and there is less emphasis on the patient having to think about the act itself. The benefit of having a plan for medication has already been demonstrated among stroke survivors.³⁴¹ Health care professionals could therefore encourage stroke survivors to make an if-then plan, reinforcing this message at subsequent follow-up appointments.

The online forum study highlighted the impact that negative press attention around statin side effects had on patients' subsequent medication taking behaviour. In an investigation on the impact of negative related statin news stories on persistence with statin medication, odds ratios (OR) for early statin discontinuation versus continued use were 1.09 (95% confidence interval, 1.06-1.12) for negative statin-related news stories, as well as 1.04 (1.02-1.06) per increasing defined daily dose of statin, and 1.05 (1.03-1.06) for male sex.⁴⁶⁹ Discontinuation of statin medicine therefore increased with being male, with increased negative press attention and with increasing statin dose, while the opposite was true for positive statin related news stories.⁴⁶⁹ Concerns around the use of statins suggests that a wider discussion is needed between stroke survivors, caregivers and health care professionals around the role of side effects on medication taking behaviour and a collaborative shared decision making approach may help to address patient concerns about statins and ensure

continued adherence to this medication. With two- year adherence rates for statins for secondary prevention falling to around 76%,²⁴³ addressing patients' concerns around statin medication should be a focus of future research aimed at improving adherence to medication in stroke survivors. A 2018 systematic review of qualitative studies of factors influencing patients' attitudes towards taking statins identified debilitating side effects, fear of dependence, uncertainties around pharmacological mechanisms and scepticism around overprescribing as just some of the key themes associated with not taking statins.⁶⁶²

Research has shown that press coverage on the side effects of statins has the potential to increase discontinuation of statin medication amongst users,⁶⁶³ while an investigation of data from the UK Clinical Practice research data link study reported that intense media coverage around the side effects of statins may have contributed to the occurrence of over 2000 cardiovascular events, with up to 200,000 people stopping taking statins as a result.⁶⁶⁴ Highlighting benefits and addressing concerns or misplaced beliefs about statin side effects may help to mitigate the impact of negative publicity on subsequent patient behaviour. Delivering educational programs could counter the influence of negative press on medicine taking and ease stroke survivors' anxieties and concerns around side effects, particularly if negative medication experiences lead survivors to refuse medication completely.

A significant finding of the research reported in this thesis is the importance of the role of the caregiver in the medication taking activities of stroke survivors. The caregiver helped facilitate the organisation and management of stroke medicines, acted on behalf of the stroke survivors when dealing with the healthcare professional, assisted with prescriptions and obtaining medications as well as reminding patients when medicines should be taken. Results demonstrate the importance of the caregiver in medication activities and reinforce the importance of the caregiver role for patients who are dependent on others due to cognitive or physical difficulties. Caregivers of stroke survivors can therefore play an important role in informing the development of interventions aimed at improving adherence in stroke. It is known that a significant number of people, usually family members, play an important role in helping others with a long- term illness⁶⁶⁵ with approximately 10% of the population of both England and Wales identifying themselves as a caregiver to another individual.^{666 667} Other issues highlighted by caregivers in this research included a lack of knowledge and information provision around stroke and secondary prevention medication, the importance of taking medicine to reduce the risk of a further cardiovascular event, highlighting the consequences of nonadherence, struggling in the face of negative information about medications, concerns around GPs' prescribing medication practices, and recognising the importance of the patient in following the

GP's advice. These findings suggest that caregiver involvement should be at the core of any strategy designed to improve medication taking among stroke survivors. Despite evidence that involvement of the caregiver in medication taking behaviour among stroke survivors improved adherence,⁴⁰⁴ there are a lack of interventions that consider the caregiver role.⁴⁴³ Future interventions to improve medication adherence among survivors of stroke or TIA should be developed with the caregiver role in mind.

Despite their increasing role, caregivers reported difficulties acting as an advocate of the stroke survivor with the healthcare professional, suggesting that the importance of their role may not yet be fully recognised. Caregivers are likely to become more vocal in representing the needs of the stroke survivor, and establishing their role as a patient advocate may take time.

Findings of the polypill investigation provide only a snapshot of the views of GPs on using FDC therapy, but this warrants further investigation. With little research to date on a polypill for stroke prevention, there is a growing need for a broader understanding of the potential of this treatment approach.

Addressing the concerns of general practitioners regarding the effectiveness of a combination pill, the level of patient risk and limitations associated with treatment inflexibility, will be the key to ensuring acceptability of a polypill in the future. From the patient perspective a fixed dose combination pill has the potential to reduce overall pill burden and the complexity of drug regimens and may therefore benefit stroke survivors who struggle with complicated medicines taking procedures. A better understanding of those sub-groups of stroke survivors who would benefit most from a polypill approach is needed. Further work confirming attitudes towards a polypill reported here, could in turn inform the development of effective interventions for secondary prevention.

A key benefit of the polypill approach is the potential to improve medication adherence. With clinical trials reporting strong support for better adherence in patients using a polypill compared with usual care for the prevention of CVD, further research is needed to confirm whether a polypill would have a similar role for stroke prevention. However, studies have not yet been designed to detect a difference in clinical outcomes with a polypill, suggesting that more work is needed to understand the true efficacy of a preventative polypill.⁶²² Developing interventions to compare a polypill approach with usual care for secondary stroke prevention in the primary care setting can help to address questions around the acceptability, feasibility and efficacy of this treatment approach.

Finally, future research exploring medication adherence in stroke and the barriers stroke survivors face should also focus on examining the distinction between intentional and unintentional nonadherence, both of which contribute to poor adherence. An investigation of unintentional nonadherence found that forgetting followed by running out of medicines were the two most important reasons for unintentional nonadherence while predictors of unintentional adherence included medication beliefs, disease type and patient demographics.⁶⁶⁸ Efforts to address unintentional nonadherence such as forgetting to take medication, could incorporate the caregiver role and encourage the stroke survivor to establish medication routines.

9.0 Concluding remarks

There is a paucity of evidence examining adherence to medication among survivors of stroke or TIA. Further examination of barriers and facilitators of medication adherence is needed to understand the reasons why survivors of stroke do not take medication as prescribed. Further investigation of medicine taking in this patient group is warranted. Exploring the beliefs and perspectives of stroke patients who take medications and practitioners who administer medicines can help to identify strategies that may be used to inform the development of effective interventions to improve adherence to stroke medication. Caregivers have also emerged as having the potential to play an important role in contributing to effective medication taking practices. This thesis set out to identify important strategies that could inform interventions to improve medication taking behaviour among stroke survivors. The research reported here has demonstrated that stroke patients face considerable barriers to medication adherence and that they need help to take their medicines. However, important strategies also exist that can facilitate medication taking in stroke. Identifying the challenges stroke survivors face when taking medication and the facilitators that contribute to effective medication taking practices, is an important step towards understanding strategies that can underpin effective interventions to improve medication taking behaviour among stroke and TIA survivors.

Traditionally, qualitative data collection techniques such as semi-structured interviews have been used to examine attitudes to medication adherence, however, novel methods of data collection such as the use of online forums have the potential to offer a new approach to understanding medication taking behaviour and nonadherence among stroke survivors. By facilitating communication without restriction of time or place, the online forum enables participation from across a wide geographical area with the potential to reach those who may not participate in traditional research.

Interventions strategies should be informed by different data collection techniques, and guided by patient and caregiver experience and the expertise of healthcare professionals. The participation of key players within stroke care including caregivers, survivors, and practitioners will be important along with the ability of health professionals including general practitioners and pharmacists to effectively deliver these interventions within routine clinical care.

Different interventions targeting different subgroups of stroke survivors are needed with low cost interventions that can be easily implemented in clinical practice likely to be the most beneficial.

It is hoped that this thesis has shed light on the different strategies that could be used to inform interventions to improve the medication taking behaviour of survivors of stroke and transient ischaemic attack in primary care.

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Appendices

Chapter 2

Appendix 1: Search strategy used to identify articles included in the review.

Cinahl

{prevention (ab)} AND {stroke (ab) or transient ischaemic attack (ab)} AND {barriers (ab) or facilitators (ab)} (n=49)

Embase

{prevention (af)} AND {stroke (af) or transient ischaemic attack (af)} AND {barriers (af) or facilitators (af)} (n=421)

PsychInfo

{prevention} AND {stroke or transient ischaemic attack} AND {barriers or facilitators} (n=106)

Pubmed

{prevention} AND {stroke or transient ischaemic attack} AND {barriers or facilitators} (n=242)

(ab) = abstract*; (af) refers = all fields*

Chapter 2

Appendix 2: Characteristics of participants in semi structured interviews.

ID number	Age	Gender	Time since stroke/TIA (yrs)	Stroke Classification	Diabetic status	Smoking status
Pt01	71	Female	18	Stroke	Not diabetic	Non-smoker
Pt02	65	Male	3	Stroke	Diabetic	Smoker
Pt03	86	Male	5	Stroke	Not diabetic	Non-smoker
Pt04	80	Male	2	TIA	Not diabetic	Ex-smoker
Pt05	64	Male	10	TIA	Not diabetic	Non-smoker
Pt06	61	Male	7 months	TIA	Diabetic	Smoker
Pt07	67	Male	4.5	Stroke	Not diabetic	Non-smoker
Pt08	87	Male	2	TIA	Diabetic	Non-smoker
Pt09	68	Male	3	TIA	Not diabetic	Ex-smoker
Pt10	66	Male	3	TIA	Not diabetic	Ex-smoker
Pt11	73	Male	13	Stroke	Not diabetic	Ex-smoker
Pt12	67	Male	2	Stroke	Diabetic	Ex-smoker
Pt13	70	Male	10	TIA	Diabetic	Ex-smoker
Pt14	66	Female	6	Stroke	Not diabetic	Non-smoker
Pt15	67	Male	6 months	Stroke	Not diabetic	Ex-smoker
Pt16	82	Female	4 months	TIA	Diabetic	Non-smoker
Pt17	79	Male	10	TIA	Not diabetic	Non-smoker
Pt18	88	Male	12	Stroke	Diabetic	Non-smoker
Pt19	93	Male	10	TIA	Not diabetic	Non-smoker
Pt20	89	Male	2	TIA	Not diabetic	Non-smoker
Pt21	68	Female	3.5	Stroke	Not diabetic	Ex-smoker
Pt22	71	Female	9	TIA	Not diabetic	Non-smoker
Pt23	74	Female	5	TIA	Not diabetic	Non-smoker
Pt24	75	Male	2	Stroke	Not diabetic	Non-smoker
Pt25	76	Male	9 months	Stroke	Diabetic	Ex-smoker
Pt26	72	Male	17	TIA	Diabetic	Non-smoker
Pt27	73	Male	2	Stroke	Not diabetic	Ex-smoker
Pt28	74	Female	4	Stroke	Not diabetic	Ex-smoker

Appendix 3: Key categories/themes identified from interview data

Patient related barriers

Key Category: Knowledge and attitude to stroke & health

Sub-themes

- Lack of knowledge of stroke.
- Beliefs about stroke e.g. reason for stroke, issues with diagnosis, stroke recognition, acting quickly,
- Attitude and reaction to stroke occurring : e.g. stroke trivialised, attitude to 2nd event occurring, feeling lucky, determined to overcome, accepting of stroke
- Survivors attitude to recovery- determination, motivation to self-care
- Poor stroke recognition
- Obtaining/ seeking out information (post stroke)
- Information provided: insufficient & too much, issues around diagnosis.
- Beliefs about importance of medication.

Key Category: Relationships and support

Sub-themes

- GP- patient relationship
- GP- patient communication.
- Role of caregiver e.g. support/managing medication
- Role of GP: Faith in GP, follow advice, seeing the same GP.
- Social Support from others e.g. carer/pharmacy/ family/ practice.

Key category: Secondary prevention care

Sub-themes

- Patient experience of secondary prevention treatment/care
- Role of Self-monitoring
- Medication refusal
- Inability to follow recommendations
- Beliefs about the need for medication
- Patient choice/decision not to take meds
- Patient refusal to take medication- lack of motivation

Medication related barriers

Key category: Beliefs about medication, effectiveness and role

Sub-themes

- Patient negative beliefs around the need for medication and its importance
- Results of medication- patient recognise medication works
- Attitudes towards taking medication- difficulties

- Health misconceptions- patients feel invincible

Key Category: Medication taking behaviour

Sub-themes

- Strategies for taking / managing medication e.g. routines/regimen/habit, storage, organisation of medication devices (e.g. nomad, pill box).
- Factors affecting medication taking e.g. medication being changed, difficulties swallowing, side effects, costs, identification of medication, accessing blisters etc.
- Burden of medication & polypharmacy
- Role of co-morbidities- prioritising medications & importance of other conditions
- Organising medication (running out)
- Burden of taking medication (too many)
- Difficulties around taking medication (swallowing, handling etc...)
- Changing medications (side effects, identification).

Key Category: Attitudes to Polypill

Sub-themes

- Stroke survivors, carers, GPs beliefs and views about Polypill
- Acceptability of prescribing Polypill - GP
- Queries/ concerns around using Polypill – GPs carers, survivors

Key Category: Compliance with medication

Sub-themes

- Reasons for non-compliance e.g. out of routine, outside the home, on holiday,
- Factors facilitating compliance e.g. carer, pill box, blister pack, medication organisers
- Following medication routines.
- GPs checking compliance e.g. home visit, electronic prescriptions, asking survivors
- Difficulties in following secondary prevention treatment e.g. deprivation, physical ability, age
- Medication side effects

Clinical related barriers

Key Category: GP Medication role

Sub-themes

- Factors affecting decision to prescribe e.g. following guidelines, costs of medication, prescribing difficulties.
- GP role e.g., accessibility to GP, GP beliefs about care
- Accessibility to patients e.g. house bound patients
- Tailoring care to the individual/ no 1 size fits all

Key Category: Delivery of care

Sub-themes

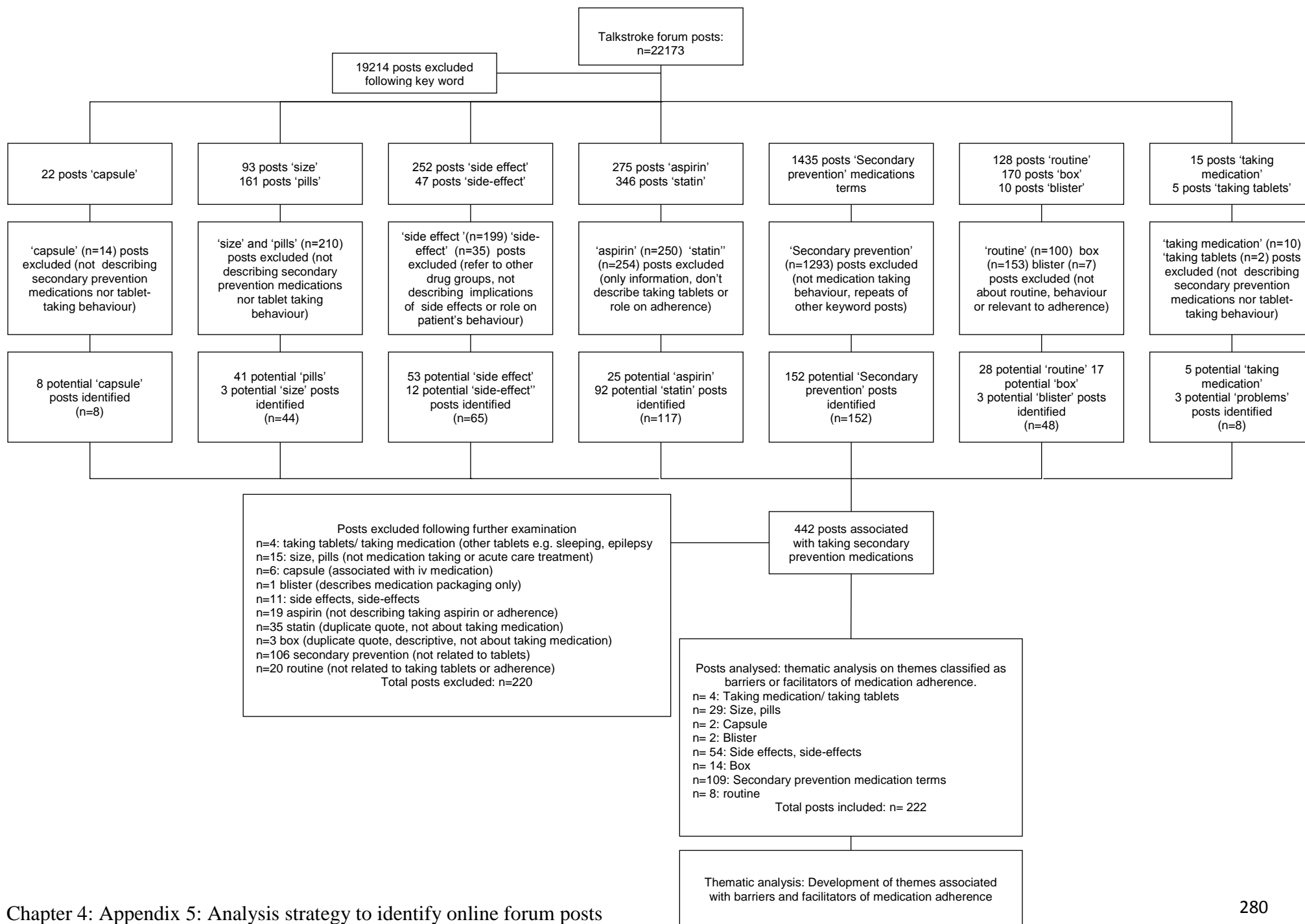
- GP practice experience e.g. obtaining GP appointments, communication.
- Obtaining medications.

Chapter 3

Appendix 4: Example themes identified from semi-structured interviews

Participant	Interview quote	Theme	Barrier/Facilitator
2	Well she erm...you take erm and give me blood pressure pills and that but I didn't take them. I felt alright. I erm...You know if I stopped for a day or two I erm ...it felt...so I didn't bother. Pity really.	Noncompliance: consequence	Barrier
3	I was (lucky) but I know lots of people who have had TIAs that it's, it's erm yeah it doesn't always have to be a big one. It depends really how erm how bad the clot was and how much of it goes.	Feels lucky post stroke	Facilitator
4	They tried to change that (statin) the other day erm well a few weeks ago and I was getting all sorts of muscle pain so they went back to this one again	Changing medication	Barrier
6	But it's like when you open them, when you pop 'em open if one flies on the floor I think nah leave it, leave that, sweep it up later on	Noncompliance	Barrier
8	I do depend on Beryl to you know just le- you know she puts my pills in the little...long box and every morning at breakfast time	Dependence on caregiver	Facilitator
9	I probably don't think it would burden you- a burden, I probably sometimes think oh here we go again, gotta take them but no it's something that's not really in my mind thinking like that no.	Burden of medication	Barrier
10	Erm it's just remembering to do it basically its erm so them being in a box in a pill box...isn't really going to make a great deal of difference depending on where I put it	Pillbox: use makes no difference	Facilitator
11	They didn't tell me nothing. Me doctor said a few things [clears throat] I wish they had told you more because it would've settled you down, you're panicking inside.	Lack of information on stroke	Barrier
13	If we just decide to pop down the pub for a meal or something yeah, I'll get home and then perhaps at 9 o'clock I'll think oh I ain't took them it's too late rally and they told me not to take them on an empty stomach	Noncompliance	Barrier
14	No I just take, well, he puts them on here altogether and then I sort them out into the order I'm gonna take them	Medication taking routine	Facilitator
15	You know I might be watching television and feel a bit tired, oh I've got to go to bed, get into bed, oh I forgot me tablet ah bugger it can't be bothered	Intentional nonadherence	Barrier

19	I've read a lot about statins and I'm afraid I feel I wouldn't want to take them well from what I've read. Because the side-effects and everything	Beliefs about medication: Statins	Barrier
20	you get a very funny feeling, erm...it's as though everything is going haywire...most peculiar erm and then erm...my wife wanted to send for the paramedics, I didn't really want to	Experience of stroke occurring	
21	Oh no, no, no they're all in the one place so I know exactly where they are, hmmm. Go in the kitchen at night, switch- before I switch the lights off, take me medication with water, switch the lights off and up I go	Medication taking routine	Facilitator
22	I look at the packets on...every...Saturday and I look and think oh god I've only got erm I've just got two weeks now in my packet so I think right, they'll have to I'll have to put me re- repeat prescription in	Obtaining medications	Facilitator
23	I've got aspirin up beside me and pop it in the water and then just throw the packet on the floor and if I'm down here I pop the aspirin in the water and put the packet back on the cupboard so that I know I've taken it so I am quite good like that yeah	Following a medication routine	Facilitator
24	I don't think I've got what I call high blood pressure as such. When he checked me out he said oh just slightly above well sometimes its normal but he still gives me them and I think to meself you know do I have to?	Beliefs about needing medicines	Barrier
25	I thought it was gonna be but it's not no, it's not because it's like getting up in the morning you know, cleaning your teeth, you know erm all them sort of things it becomes a habit that you just get into. I thought it would be a burden but	Medicine taking not a burden: a habit	Facilitator
26	My Dr says if I want to keep alive, I want to stay alive, you've got to take the medicine	Necessity of medicine-GP	Facilitator
27	Erm I wouldn't think it was a burden really to be quite honest I don't mind taking it do you know what I mean as I say I have a routine up in the morning	Burden of medication	Barrier



Chapter 4

Appendix 6: Key themes highlighting survivors' and caregivers' barriers and facilitators of adherence to secondary prevention medications classified according to PAPA.

Perceptions	
Barriers	Facilitators
<p>Necessity beliefs</p> <p>Lack of perceived benefits of medication</p> <ul style="list-style-type: none"> • Questioning the effectiveness of secondary prevention medications in preventing stroke recurrence. • Considering statins detrimental to health and not effective. • <i>Valuing adherence but recognising that is the choice of the patient to take tablets.</i> • <i>Realising that stroke could still occur despite taking secondary prevention medications.</i> <p>Concerns</p> <p>Management of medication side effects*</p> <ul style="list-style-type: none"> • Experiencing statins side effects and considering they have potential to worsen quality of life. • Changing diet/lifestyle as alternative to taking medication to reduce side effects.* • Healthcare professionals recommending diet and exercise to reduce cholesterol instead of taking statins.* • <i>Struggling to raise issues about side effects of statins with healthcare professionals and obtaining changes in treatment when patients find it unsuitable.</i> 	<p>Necessity beliefs</p> <p>Attributing importance to medications</p> <ul style="list-style-type: none"> • Recognising taking tablets as important to prevent stroke recurrence. • Feeling reassured by taking secondary prevention medications. • Experiencing consequences of nonadherence (a further stroke) as driver of necessity beliefs. • <i>Feeling secondary prevention medications are important and should only be stopped in consultation with the GP.</i> • <i>Holding strong beliefs about the need for secondary prevention medications.</i> <p>Concerns</p> <p>Management of medication side effects*</p> <ul style="list-style-type: none"> • Awareness that not all patients are affected by side effects. • Healthcare professionals changing medications to counteract side effects • Modifying medications to achieve optimal treatment • <i>Obtaining changes in treatment from healthcare professionals until side effects are manageable</i> <p>Trusting healthcare professionals</p>

<p>Impact of negative press attention on statins</p> <ul style="list-style-type: none"> • Being extra-cautious about commencing statins for fear of side effects • <i>Struggling to ensure patients' adherence to statins in face of negative press attention</i> <p>Questioning prescribing practices</p> <ul style="list-style-type: none"> • Being disappointed as medications considered ineffective were not changed by GPs. • Having concerns around incorrect medications being prescribed. • Receiving conflicting information about medications. • <i>Worrying about medications being prescribed for financial reasons or guidelines over clinical judgement</i> • <i>Experiencing difficulties with asking GPs to prescribe alternative tablets as current ones considered unsuitable.</i> • <i>Feeling the role of GPs is limited to advising about secondary prevention medications</i> • <i>Intentionally missing medications to manage side effects</i> 	<ul style="list-style-type: none"> • Perceiving medications to be beneficial as secondary healthcare professional also taking it.
Practicalities	
Barriers	Practicalities
<p>Problems associated with taking tablets</p> <ul style="list-style-type: none"> • Swallowing medication capsules, especially big size ones. • Experiencing difficulties with handling medications due to size and stroke related physical impairments. • <i>Experiencing frustration with burden of multiple medications and episodic patients' refusal of medications.</i> • <i>Experiencing frustration at patient refusal to take statins and attend routine medication appointment.</i> • <i>Experiencing difficulties when helping patients with aphasia taking tablets in the context of changes in treatment.</i> 	<p>Storage devices for managing medication</p> <ul style="list-style-type: none"> • Using pill box: helping seeing the correct medication was taken and when prescription needed to be renewed. • <i>Using pill-boxes to provide written instruction to patients or keeping a note of tablets taken.</i> • <i>Advice from pharmacist on taking medication correctly.</i>

<ul style="list-style-type: none"> • <i>Experiencing frustration at patients failing to keep up with refilling prescriptions.</i> <p>Cost of medications</p> <ul style="list-style-type: none"> • Struggling to meet the costs of secondary prevention medications. 	<p>Good medication taking routines</p> <ul style="list-style-type: none"> • Linking tablet use to an everyday activity to facilitate medication taking behaviour. • <i>Assuming control of medication when patients have problems with short term memory and reminding when tablets have to be taken.</i>
<p>Legend: Statements in italics refer to caregivers' themes.</p> <p>* Because of missing details of the underlying clinical scenario, these themes could act both as barriers or facilitators to adherence to secondary prevention medications, therefore have been reported under both headings.</p>	

Chapter 5: Appendix 7: Comparison of themes from interviews and the online forum

Perceptions				
Key themes identified (interviews)	Interview quote^	Interview participant (Age, gender)	Forum quote*	Forum participant ♦ (Age, gender)
	Treatment necessity		Treatment necessity	
1. Knowledge of stroke and medications	The importance of taking this exactly on time is trivial. I would probably survive for a week, if I didn't take the. For a month I'd probably survive. It would not make any difference in two days.	Male, 86 yrs, N.03, ischaemic stroke	A female survivor commented that it was better to take a few extra tablets from the GP than to experience a stroke. Tablets were provided to prevent a further stroke, and she stressed that they shouldn't be stopped except on professional advice	Female, age 51, age at stroke 51, N.17
	Whenever I've got a new pill or anything I'd read the instructions only because they've made a mistake before now, like for instance they gave me one which I'm allergic to... So I keep check of what I'm taking now.	Male, 80 yrs N. 04, TIA	A stroke survivor recalled being on 75mg of aspirin as well as beta blockers, however, his nephew who was a consultant surgeon, suggested that had he been taking warfarin instead of the aspirin he may not have suffered a second stroke	Male, age 67, age at stroke 55, N.82
			<i>(Negative press influences attitudes to medicines)</i> A female survivor read about the hype around statins and stated she still didn't have confidence in them. She had read a research paper on statins suggesting they only added an extra 9 months of life. Her mum had been taking statins for 14 years and this still	Female, age 56, age at stroke 56, N.66

			<p><i>didn't prevent her arteries from clogging up</i></p> <p><i>(Negative press influences attitudes to medicines)</i> <i>A survivor who had suffered 2 mini-strokes and been prescribed aspirin and cholesterol lowering statin but was refusing to take them because she had read in the press about bad side effects that they caused</i></p>	<p><i>Female, age unknown, age at stroke unknown, N.74</i></p>
<p>2. Doubts about medicines</p>	<p>I think aspirins are good for you. That's the one I fancy. Well it thins the blood and the blood it flows and that stops any clots so I do like to take it. I just don't see why I'm taking the other medication. I'm not fat or anything like that. I don't get very high blood pressure and well cholesterol, what is cholesterol..?</p>	<p>Male, 75yrs, N.24, ischaemic stroke</p>	<p>A survivor acknowledged statins were used to control cholesterol, but questioned whether high cholesterol was actually a problem. He believed strokes occurred frequently, regardless of cholesterol levels. He talked about the 'Cholesterol Myth' having researched the topic on the Internet. He said he was feeling confused about the value of statins and taking these when in reality they weren't needed</p>	<p>Male, age 67, age at stroke 55, N.70</p>
<p>3. Realisation of the importance of medicines</p>	<p>At one time I wouldn't take a pill, I wouldn't even take an aspirin. Now I take it because I understand it keeps me alive. I just think it's fate, that's the way I look at it. If I stop taking medication I might as well lie down in the fast lane.</p>	<p>Male, 67yrs, N.12, ischaemic stroke</p>	<p>A male survivor already suffered 2 strokes and said it was impossible to ever fully recover from the experience. He said after his first stroke he was prescribed tablets he didn't take and he realizes this was a big mistake.</p>	<p>Male, age 67, age at stroke 55, N.82</p>
<p><i>Differing attitudes to</i></p>	<p>Well I don't know what I'd be without taking them put it that</p>	<p>Male, 73 yrs, N.11</p>	<p>A female survivor felt it was better to take tablets from the GP than to experience another stroke.</p>	<p>Female, age 51, age at stroke 51, N.17</p>

<i>medicines</i>	way...because I've had a stroke and I've been fortunate. They keep me going, keep me on the straight and narrow.	ischaemic stroke	Tablets were provided to prevent another stroke and shouldn't be stopped except on professional advice	
	I refused it and I said well it's not because its rat poison. If you tell me I've got warfarin, I must be ill but if I take aspirin I can't be that ill.	Female, 71yrs, N.22 TIA	Another survivor remarked that, although being on pills was an inconvenience and she had stopped some medication, she continued to take aspirin and statin which she considered important	Female, age 52, age at stroke 52, N.76
	The only thing I like, I think aspirin's good for you, that's the only one I fancy. Well it thins the blood, and well thinning the blood makes it flow better and that stops any clots so I do like, like to take it	Male, 75 yrs N.25, ischaemic stroke	A survivor had suffered 2 strokes in the previous year, but none since commencing warfarin. She felt reassured by taking warfarin and worried about coming off the medication	Female, age 42, age at stroke 42, N.35
	I just take them because the hospital prescribed them. If the doctor prescribed them I probably wouldn't bother. I'd probably say forget about it. He's a consultant so he should know what he's talking about	Male, 67 yrs N.15 ischaemic stroke	<p>A survivor described how he trusted his vascular surgeon who had changed his medication from warfarin to aspirin and statin. The survivor was happy to take aspirin and felt it would be good to continue as the surgeon also took it regularly, concluding it must be beneficial and would enable him to live longer.</p> <p><i>A female survivor decided to reduce cholesterol using diet instead, because of side effects from medication. She felt that once the symptoms completely disappeared she wouldn't take a statin again. She said she would start taking olive oil and follow a healthy diet to keep her cholesterol balanced naturally. She said she would continue aspirin as it didn't seem to cause any side effects</i></p>	<p>Male, age 35, age at stroke 34, N.71</p> <p><i>Female, age 52, age at stroke 52, N.76</i></p>

	Treatment Concerns		Treatment Concerns	
4. How seriously people take medicines for secondary prevention of stroke	<p>I wouldn't take them because I still, to me, blood pressure and cholesterol tablets to me I don't see what they're doing for me</p> <p>Well she gave me blood pressure pills and that but I didn't take them. I felt so, i didn't bother, pity really. But never mind. I do now. I'm religious about that. I'll have another stroke if I don't. Didn't want to put the family through that again.</p>	<p>Male, 75 yrs, N.24, ischaemic stroke</p> <p>Male, 65 yrs, N.02 ischaemic stroke</p>	<p>A female survivor who had read bad reports about statins reported being nervous about them. She didn't want to jeopardise feeling good by taking medication that she wasn't convinced she needed</p> <p>A survivor refused statins after her first stroke because of side effects. However, after suffering a second one she was now worried enough to take them.</p>	<p>Female, age 54, age at stroke 54, N.37</p> <p>Survivor, female, age 68, age at stroke 67, N.14</p>
5. Taking medications <i>Nonadherence to medicine</i> <i>Trust in GP</i>	<p>Well now and again I forget the cholesterol because that's the one at night and it's the only one I take at night</p> <p>So if the doctor says take ten pills a day, I'll, I'll do it....he makes the decision and erm he, he's the boss man as you might say, who knows what he's up to</p> <p>I do exactly as the Dr tells me. He's the Dr isn't he? He should know better than what I do. I don't push</p>	<p>Male, 67yrs, N.15, ischaemic stroke</p> <p>Male, 87yrs, N.8, TIA</p> <p>Male, 80 yrs N.04, TIA</p>	<p>A male survivor said he was on 2 tablets for blood pressure and that he continued to take one every day. But the other was a diuretic and having got fed up frequently running to the toilet, he decided to check his blood pressure every day and would skip the diuretic if it was fine.</p> <p><i>A male survivor agreed with his doctor to stop taking a blood pressure tablet because of intolerable side effects, and his wife being a nurse made it easier. He felt strongly that doctors are there to advise not instruct.</i></p> <p><i>(Collaborating with GP/ patient)</i> <i>A caregiver said that her husband ceased taking</i></p>	<p>Male, age unknown, age at stroke unknown, N.63</p> <p><i>Male, age unknown, age at stroke unknown, N.63</i></p> <p><i>Male, age 54, age at</i></p>

	them anymore and say well you know I don't like taking this		<p><i>medications except aspirin, because of side effects. He made this decision, together with the GP and stressed the importance of doing this before stopping tablets</i></p> <p><i>(Prescribing concerns)</i> <i>A caregiver (sister) suggested that GPs shouldn't be paid for prescribing statins with the decision based on clinical judgement alone. The involvement of money could lead to medication being over prescribed for financial reasons</i></p> <p><i>(Prescribing concerns)</i> <i>A survivor described taking 9 pills a day for stroke and its side effects and felt that the GP should understand which were necessary. Following another appointment her consultant was furious about the medications she had been prescribed.</i></p>	<p><i>stroke 52, N.68</i></p> <p><i>Gender and age unknown, age at stroke unknown, N.78</i></p> <p><i>Female, age 37, age at stroke 36, N.81</i></p>
Practicalities				
	Capability/ resources		Capability/ resources	
6. Ability to self-care	My wife sorts it out and that's why I don't know so much about it you see she [taps].She puts them there, I take them and that's it	Male, 80 yrs, N.04, TIA	<p>A caregiver stated that she was providing the stroke survivor with all of his medication due to his poor memory as a result of the stroke. She was now in complete control of his medication which she was happy about but it was difficult as he was a loved one and something she had no training for.</p> <p><i>(Caregiver as an advocate for the stroke survivor)</i> <i>A female caregiver described consistently trying to have her husband's 40mg statin dosage reduced by</i></p>	<p><i>Female, Age 46, age at stroke 40, N.5</i></p> <p><i>Male, age 54, age at stroke 52, N.68</i></p>

			<p><i>his GP. As a result of the high dosage he was chronically tired, so he stopped taking statins</i></p> <p><i>(Caregiver as an advocate for the stroke survivor)</i> <i>A caregiver recommended being firm with GPs about being prescribed atorvastatin if simvastatin was not tolerated, as atorvastatin was a bit more expensive but recommended by NICE guidelines as an alternative</i></p>	<p><i>Gender and age unknown, age at stroke unknown, N.18</i></p>
<p>7. Taking medication</p> <p><i>Problems swallowing</i></p> <p><i>Accessing packaged medicines</i></p>	<p>The big ones, I, do actually feel I have to swallow two or three times to get them down</p> <p>Some of the, the pills are a hell of a trouble, you know the bubble wrap, flipping them out especially with my hands not as strong as they should be</p> <p>I'd have to rely on the wife to...cause I can't get them out the packet, just can't get your hands in</p>	<p>Male, 66yrs, N.10, TIA</p> <p>Male, 87yrs, N.08, TIA</p> <p>Male, 65yrs, N.02, Ischaemic stroke</p>	<p>A male survivor described 'swallow panic', i.e. fear of choking when trying to take Dipyridamole capsules. The user said it took around 3 months before he got over that.</p> <p>A caregiver (son in law) mentioned that despite the use of a nomad tray, tablets were still being taken from the wrong day with several days tablets being taken in a single day. The stroke survivor often didn't take the time to work out the days or to look at the calendar.</p> <p>A survivor agreed with another user about the problem with the size of dipyridamole tablets, which were getting stuck in the pill box organizer.</p>	<p>Male, age unknown, age at stroke unknown, N.85</p> <p>Male, age unknown, age at stroke unknown, n.27</p> <p>Female, age 46, age at stroke 45, N.30</p>
<p>8. Medication routines</p>	<p>I only remember to take the others if I take them out of the cupboard the night before and leave them on the top. If I didn't I would probably forget... because it isn't the first thing that I think of</p>	<p>Male, 66yrs, N.10, TIA</p>	<p>A female survivor described keeping the pill box in a specific location in the house, such as by the kettle, which then acted as a reminder to check the medication box</p>	<p>Female, age 60, age at stroke 60, N.52</p>

	I usually take it around 5 o'clock which strangely enough is about the time that we feed the dog and normally speaking I take the medication then I get his dinner	Male, 68 yrs N.09, TIA	A survivor suggested using a white board and having method in place helped. She remembered taking her own medications through repetition or linking tablet use to another everyday activity	Female, age 54, age at stroke 46, N.19
9. Changing medications	They changed his medication to cheaper cholesterol and Dean was physically ill. He couldn't cope on it at all so he went back and the doctor said 'oh well it was just to try and they put him back on the others	Female, caregiver, N.24, age unknown	A survivor described being on 80 mg of simvastatin which they were happy with but that upon leaving hospital the dose was halved by the consultant which had very bad consequences, resulting in daily angina turns for a week. In the end he had to go back to his GP and be put back on the 80mg dose.	Female, age 53, age at stroke 50, N.62
	She gave me an extra pill and I had a horrific night. She made an apology and said I'm sorry it took so long to get it right, but the fine tuning takes a bit of doing.	Male, 80 yrs N.04, TIA	A male survivor said he was taking up to 7 different blood pressure tablets and that it was unusual to only need a few tablets. He recommended going back to the GP as necessary to keep changing tablets until the correct combination was found.	Male, age 52, age at stroke 52, N.64
10. Regimen complexity and burden of treatment	I have to take 10 a day now altogether but I went up there (to the practice) to say can I get off some of these tablets, and I come back and I was on an extra one so I've not been up since	Male, 70yrs, N.13, TIA	A caregiver (son) was asking advice on how to encourage medication taking. His mother was originally taking multiple tablets up to 4 times a day but now she was refusing to take them all and he was upset by this. Persuading her to continue taking the most important tablets had taken hours to do.	Female, age 77, age at stroke 77, N.8
	I've got yards of them. I don't know half the names I'm just told when to take them. That's one thing I'd like to do away with	Male, 73 yrs, N.11, Ischaemic stroke	A caregiver (wife) described how her husband was adamant he was not prepared to take statins because he didn't have the time to keep going back to the GP for checkups. The caregiver said she was feeling helpless and wasn't sure what she could do about it (Burden of side effects on stroke survivor)	Male, age 55, age at stroke 55, N.14] Female, age 34yrs,

			A survivor described similar side effects from 3 different statins despite varying the medication dosage. She said tests confirmed this and she concluded long term use could result in problems that had a negative effect on her quality of life.	age at stroke 32, N.36
<p>*Quote not transcribed - described to protect user confidentiality.</p> <p>^Quote transcribed</p> <p>◆ Demographic characteristics relate to the stroke survivors only (either talking in first person or talked about by a caregiver). Quotes in italics refer to additional themes identified in the online forum only</p>				

Appendix 8: Survey study- Patient questionnaire



QUESTIONNAIRE – PATIENT

Many people with stroke need help with taking their medicines. We would like to ask you few questions about the help you might need with taking your medicines.

How many different type of medicines do you take in one day?

Write the number or an approximation. Please count all medications including eye drops, injections etc.

How old are you?

How long ago was your stroke

years

What is your sex?

☐ M☐ F

For each question below, please tick the box that best describes how you have taken your medicines in the last month:

1. Is somebody helping with prescriptions and collection of your medicines?

all the time

often

sometimes

rarely

never

<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>

Do you feel you need more help with prescriptions and collection of your medicines?

Yes

☐

No

☐

2. Is somebody helping you getting the medicines out of the box, bottle or blister pack?

all the time

often

sometimes

rarely

never

Do you feel you need more help with getting the medicines out of the box, bottle or blister pack?

Yes

☐

No

☐

3. Is somebody helping with reminding you when is the time to take your medicine?

all the time

often

sometimes

rarely

never

Do you feel you need more help with reminding when is the time to take your medicine?

Yes

☐

No

☐

4. Is somebody helping you with swallowing your medicine? For example by giving you a drink

all the time

often

sometimes

rarely

never

Do you feel you need more help with swallowing your medicine?

Yes ☐

No ☐

5. Is somebody helping you with checking that you have taken your medicines?

all the time	<input type="checkbox"/>
often	<input type="checkbox"/>
sometimes	<input type="checkbox"/>
rarely	<input type="checkbox"/>
never	<input type="checkbox"/>

Do you feel you need more help with checking that you have taken your medicine?

Yes ☐

No ☐

Missing medicines

Thinking of the last 30 days, how often did you miss taking your regular medicines?

all the time	<input type="checkbox"/>
often	<input type="checkbox"/>
sometimes	<input type="checkbox"/>
rarely	<input type="checkbox"/>
never	<input type="checkbox"/>

Remember - tick one box only

Barthel Questionnaire

These are some questions about your ability to look after yourself.

They may not seem to apply to you.

Please answer them all.

Tick one box in each section.

Bathing

In the bath or shower do you:

manage on your own?

need help getting in and out?

Remember - tick one box only

need other help?

never have a bath or shower?

need to be washed in bed?

Stairs

Do you climb stairs at home:

without any help?

with someone carrying your frame?

Remember - tick one box only

with someone encouraging you?

with physical help?

not at all?

don't have stairs?

Dressing

Do you get dressed:

without any help?

just with help with buttons?

Remember - tick one box only

with someone helping you most of the time?

Mobility

Do you walk indoors:

without any help apart from a frame?

--

Remember - tick one box only

with one person watching over you?

with one person helping you?

with more than one person helping?

not at all?

Or do you use a wheelchair independently?
(e.g. round corners)

Transfer

Do you move from bed to chair: on your own?

with a little help from one person?

Remember - tick one box only

with a lot of help from one or more people?

not at all?

Feeding

Do you eat food: without any help?

with help cutting food or spreading butter?

Remember - tick one box only

with more help?

Toilet use

Do you use a toilet or commode: without any help?

with some help but can do something?

Remember - tick one box only

with quite a lot of help?

Grooming

Do you brush your hair and teeth without help?

Wash your face and shave: with help?

Remember - tick one box only

Bladder

Are you incontinent of urine?

never

less than once a week

Remember - tick one box only

less than once a day

more often

Or do you have a catheter managed for you

Bowels

Do you soil yourself?

never

Occasional accident

Remember - tick one box only

all the time

or do you need someone to give you an enema?

Appendix 9: Survey study- Caregiver questionnaire



Help with taking tablets after stroke
FAMILY MEMBER/FRIEND OR PRIVATE CARER COPY

Many people with stroke need help with taking their medicines. We would like to ask you few questions about the help you might be offering to your family member/friend/ patient with stroke with taking medicines.

Relation with your family member/friend with stroke

Are you:

partner

son or daughter

friend

carer from an agency

other

if other, please specify

Remember - tick one box only

How many different types of medicines does your family member/friend/patient with stroke take in one day?

--

Write the number or an approximation. Please count all medications including eye drops, injections etc.

--

How old is your family member/friend/patient with stroke? (years)

--

How many years ago was your family member/friend/patient's stroke?

What is your family member/friend/patient with stroke sex?

M

F

For each question below, please tick the box that best describes the help needed by your family member/friend/patient with stroke with taking medicines in the last month.

- 1. Is somebody helping your family member/friend/patient with stroke with prescriptions and collection of his/her medicines?**

all the time

often

sometimes

rarely

never

Do you feel your family member/friend/patient with stroke needs more help with prescriptions and collection of his/her medicines?

Yes

☐

No

☐

- 2. Is somebody helping your family member/friend/patient with stroke getting the medicines out of the box, bottle or blister pack?**

all the time

often

sometimes

rarely

never

Do you feel your family member/friend/patient with stroke needs more help with getting the medicines out of the box, bottle, or blister pack?

Yes

☐

No

☐

3. **Is somebody helping your family member/friend/patient with stroke with reminding when is time to take his/her medicine?**

all the time
often
sometimes
rarely
never

Do you feel your family member/friend/patient with stroke needs more help with reminding when is time to take his/her medicine?

Yes

☐

No

☐

4. **Is somebody helping your family member/friend/patient with stroke with swallowing his/her medicine?
For example by giving a drink.**

all the time
often
sometimes
rarely
never

Do you feel you your family member/friend/patient with stroke need more help with swallowing his/her medicine?

Yes

☐

No

☐

5. **Is somebody helping your family member/friend/patient with stroke with checking that he/she has taken his/her medicines?**

all the time
often
sometimes
rarely
never

Do you feel your family member/friend/patient with stroke needs more help with checking that he/she has taken his/her medicine?

Yes

☐

No

☐

Missing medicines

Thinking of the last 30 days, how often did your family member/friend/patient

with stroke miss taking his/her regular medicines?

all the time

often

sometimes

rarely

never

Remember - tick one box only

Barthel Questionnaire

These are some questions about the ability of your family member/friend/patient with stroke to look after him/herself.

Please answer them all.

Please fill this questionnaire even if you are not regularly caring for your family member/friend/patient with stroke, trying to answer questions in the way you think most accurately describes the disability of your family member/friend/patient with stroke.

Tick one box in each section.

Bathing

In the bath or shower do you:

manage on your own?

need help getting in and out?

Remember - tick one box only

need other help?

never have a bath or shower?

need to be washed in bed?

Stairs

Do you climb stairs at home:

without any help?

with someone carrying your frame?

Remember - tick one box only

with someone encouraging you?

with physical help?

not at all?

don't have stairs?

Dressing

Do you get dressed:

without any help?

just with help with buttons?

Remember - tick one box only

with someone helping you most of the time?

Mobility

Do you walk indoors:

without any help apart from a frame?

with one person watching over you?

Remember - tick one box only

with one person helping you?

with more than one person helping?

not at all?

Or do you use a wheelchair independently?

(e.g. round corners)

Transfer

Do you move from bed to chair:

on your own?

with a little help from one person?

Remember - tick one box only

with a lot of help from one or more people?

not at all?

Feeding

Do you eat food:

without any help?

with help cutting food or spreading butter?

Remember - tick one box only

with more help?

Toilet use

Do you use a toilet or commode:

without any help?

with some help but can do something?

Remember - tick one box only

with quite a lot of help?

Grooming

Do you brush your hair and teeth

without help?

☐

Wash your face and shave:

with help?

☐

Remember - tick one box only

Bladder

Are you incontinent of urine?

never

☐

less than once a week

☐

Remember - tick one box only

less than once a day

☐

more often

☐

Or do you have a catheter managed for you

☐**Bowels**

Do you soil yourself?

never

☐

Occasional accident

☐

Remember - tick one box only

all the time

☐

or do you need someone to give you an enema?

☐

Chapter 7

Appendix 10: Polypill themes identified from semi-structured interviews

Participant	Participant quote	Polypill Theme
2	Because it means that you, you know, if you've taken that one you've taken them all. Whereas sometimes if you run short, you think oh I'll just take that and forget about the other one until you go the doctors and get the refill.	Polypill ensures all medications have been taken
3	Well if you're going for the idea of polypill, it, it seems to me ultimately that is very good sense because it, once you had a person's medication...fixed... or personalised then you could easily provide a pill or two pills or three pills which would contain	Polypill offers fixed treatment
5	Well the only thing, would it disturb the dosage? If it, as I say, my only concern would be, would it not erm would the statin content of the tablet would it be reduced and would it not do the job my statin's doing	Concerns around a polypill effecting dosage?
8	It's no different if I'd missed me polypill I'd have missed me four pills there so you're in a routine basically so instead of taking four just one polypill	Polypill no additional benefit if routine already established
9	A combination drug no problem as long as I know that it is those two things combined on those strengths yeah fine, no problem. And it's one pill less you know take one instead of two or three	Importance of same treatment.
14	Probably, it would be having less pills to pop out basically but apart from that I don't see as its gonna be any different. It's still got to be done every day	Convenience but not necessarily better than current practice
19	Well it sounds alright yes, but I wouldn't take it, I wouldn't let him take it willy nilly, he'd have to have another episode	Careful attitude to taking a polypill
21	It would have to be a pill that would incorporate all three but then...maybe six months down the line my blood pressure's because I've lost weight blah blah, has eased down and maybe my blood pressure can be reduced what would that do with the polypill?	Concerns about changing polypill components
25	Whereas now if I forget to take one pill that's not disastrous because I've got the other three to take whereas if erm if erm i- lost one, dropped one, that's all four pills	Noncompliance of polypill would lose the benefits of all pills
27	If it, if it's going to be the exact same you know I mean it would definitely benefit people who find it hard and who miss their tablets it would definitely be of great benefit to them	Polypill providing same treatment