Title:

Incremental costs and cost-effectiveness of intensive treatment in individuals with type 2 diabetes detected by screening in the ADDITION-UK trial: An update with empirical trial-based cost data

Running Title:

Cost-effectiveness of early intensive diabetes treatment

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Author contribution

ML, EW and SG designed the concept for the paper. ML performed the statistical analysis, interpreted the data and drafted the manuscript. SG and CB were involved in collecting the data. EW provided statistical support. All authors read and approved the final version of the manuscript.

Conflict of interest statement

None of the authors has competing interests.

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Highlights

What is already known about the topic?

- Previous work showed that early intensive treatment in patients with screen detected diabetes is probably not cost-effective in the long-term from the UK NHS perspective.
- However, this initial economic evaluation was based on conservative per protocol assumptions for the intervention costs and the incremental costs of the intervention actually delivered to patients might have been lower than expected.

What does the paper add to existing knowledge?

- By following an iterative approach to research and decision making this study firstly estimates the incremental costs of intensive treatment as delivered in the ADDITION trial using electronic primary care records of trial participants and secondly updates the long-term cost-effectiveness model according to a previously developed evaluation frame.

What insights does the paper provide for informing health care-related decision making?

- The updated cost-effectiveness analysis shows that from the UK NHS perspective intensive treatment in patients with screen detected diabetes is likely to be cost-effective over a time horizon of 20 years and more.

Abstract

Background:

There is uncertainty about the cost-effectiveness of early intensive treatment vs. routine care in individuals with type 2 diabetes detected by screening. The aim of this study is to derive a trial-informed estimate of the incremental costs of intensive treatment as delivered in the ADDITION trial and to revisit the long-term cost-effectiveness analysis from the perspective of the UK National Health Service (NHS).

Methods:

We analyzed the electronic primary care records of a subsample of the ADDITION-Cambridge trial cohort (n=173). Unit costs of utilized primary care services were taken from the published literature. Incremental annual costs of intensive treatment vs. routine care in years 1-5 after diagnosis were calculated using multilevel GLMs. We revisited the long-term cost-utility analyses for the ADDITION-UK trial cohort and report results for ADDITION-Cambridge using the UKPDS outcomes model and the trial-informed cost estimates according to a previously developed evaluation framework.

Results:

Incremental annual costs of intensive treatment over years 1-5 averaged £29.10 (SE=£33.00) for consultations with GPs and nurses, £54.60 (SE=£28.50) for metabolic and cardio-protective medication. For ADDITION-UK, over the 10-, 20-, and 30- year time horizon, adjusted incremental quality adjusted life years (QALYs) were 0.014, 0.043, and 0.048, and adjusted incremental costs were £1,021, £1,217, and £1,311 resulting in incremental cost-effectiveness ratios (ICERs) of £71,232/QALY, £28,444/QALY and £27,549/QALY, respectively. Respective ICERs for ADDITION-Cambridge were slightly higher.

Conclusion:

The incremental costs of intensive treatment as delivered in the ADDITION-Cambridge trial were lower than expected. Given UK willingness to pay thresholds in patients with screen detected diabetes intensive treatment is of borderline cost-effectiveness over a time horizon of 20 years and more.

Background

Diabetes mellitus is an increasing public health problem, associated with costly micro- and macrovascular complications, reduced quality of life, and premature death [1-4]. The direct and indirect societal costs of diabetes in the UK are expected to rise from £22bn in 2010 to £35bn in 2030, and a large share of this financial burden is attributable to the treatment of diabetic complications in patients with type 2 diabetes [5]. Cost-effective disease management strategies are therefore needed to diminish the burden of the disease on patients and health care systems.

Previous research has shown that intensive multifactorial treatment, including management of cardiovascular risk factors and glycemic control, reduces the risk of cardiovascular events and is an effective and cost-effective intervention for patients with longstanding diabetes [6-8]. There is also solid evidence that tight control of glucose and blood pressure in newly routinely diagnosed patients is an effective and cost-effective strategy [9-11]. Conversely, little is known about the cost-effectiveness of intensive treatment in individuals with type 2 diabetes detected by screening who, all else being equal, will typically be at an earlier stage in the disease.

The diagnosis of diabetes in routine care settings occurs on average a couple of years after physiological onset [12]. Owing to improvements in quality of care and ongoing considerations about population-based screening, this lead time is expected to decrease, resulting in a large number of patients who could potentially benefit from early intensive treatment.

The pragmatic cluster-randomized ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care–Europe) trial studied the effect of intensive multifactorial treatment compared with routine care on cardiovascular morbidity and mortality in individuals with type 2 diabetes detected by screening [13, 14]. The results showed a non-statistically significant relative risk reduction in the incidence of the composite cardiovascular endpoint over a time horizon of 5 years [15].

Of note, levels of cardiovascular risk factors improved modestly over the 5 years of the trial, and a modeling study using the United Kingdom Prospective Diabetes Study (UKPDS) risk equations indicated that the cardiovascular risk might be reduced in the long-term [15, 16]. Despite this, an initial cost-effectiveness analysis using the UKPDS outcomes model incorporating conservative protocol-driven intervention cost estimates showed that, over a time horizon of 30 years, the intervention was not cost-effective according to current UK willingness to pay (WTP) thresholds (ICER~£37,500/QALY vs WTP thresholds of £20,000 to £30,000),[17] albeit with substantial decision uncertainty (31% probability that the ICER is below £30,000). However, as we know from a previous study that the adherence of General Practitioners (GPs) to the trial protocol was not perfect, the incremental costs of the intervention

actually delivered might have been lower than expected [18]. Therefore, whilst our outcomes assessment would be valid we may have overestimated the incremental cost. Had the intensive treatment regimen been highly cost-effective or cost-ineffective and with a high degree of certainty, further exploration would have been of no value. However, given the proximity of the ICER to the (upper) threshold and the level of decision uncertainty, we felt further investigation into the intervention costs was justified.

The objective of this study is therefore to estimate the incremental costs of early intensive treatment as delivered in ADDITION using empirical data from electronic primary care records. We then use this new information to update our prior estimate of the long-term (10-30 years) cost-effectiveness analysis of the ADDITION intervention in the UK from an NHS perspective, in a manner consistent with an iterative approach to research and decision making [19-21].

Methods

Study design and study population

The ADDITION-UK (NCT00237549) study is part of the ADDITION-Europe study and consisted of two phases– a screening program and a pragmatic, cluster-randomized trial comparing the effect of early intensive treatment vs. routine care in individuals with type 2 diabetes detected by screening on a composite endpoint of cardiovascular morbidity and mortality [13, 14]. High risk individuals without known diabetes aged 40-69 years registered in 69 primary care surgeries within a range of 100 miles of the study centers in Cambridge and Leicester were invited to stepwise screening. Some 867 individuals (from 49 surgeries) from Cambridge and 159 individuals (from 20 surgeries) from Leicester with type 2 diabetes detected by screening participated in the primary care-based intervention study (ADDITION-UK). Two participants withdrew before year 5, leaving a total study size of 1024 participants. Details of the study protocol including assessment of primary endpoints and in- and exclusion criteria have been published elsewhere [15]. The study was approved by local ethics committees, and all participants provided informed consent.

Routine care vs. intensive treatment

Patients were treated according to the treatment allocation of their surgery. Patients in the routine care arm in Leicester and Cambridge received diabetes care through the UK National Health Service (NHS) based on contemporary UK treatment guidelines [22-24]. In the intensive treatment arm, additional features were added to routine care. Some of these intensive treatment features differed between the Leicester and Cambridge GP surgeries.

In Leicester, intensive treatment was delivered by a specialist team of doctors, nurses, and dieticians within peripatetic community clinics according to the Diabetes Education and Self-Management Programme (DESMOND). DESMOND

is a group education program delivered by two registered health care professionals in one 6-hour session [25]. The curriculum focuses on lifestyle changes and medication adherence using theories of efficient goal setting and self-efficacy. Additionally, in the first year after diagnosis, patients were offered bi-monthly appointments with a nurse or a GP in a community peripatetic clinic, and 4-monthly thereafter.

In Cambridge, primary care surgeries received funding for more frequent contacts between patients and practitioners. An initial practice-based academic detailing session conducted by a local diabetologist and an academic GP and interactive practice-based audit and feedback sessions were organized around 6 and 14 months after the initial education session and annually thereafter. Surgery staff received theory-based education materials to hand over to patients, and participants were encouraged to initiate lifestyle changes, to adhere to medication schemes, to self-monitor blood glucose levels if given a glucometer by their practice, and to attend annual health checks.

Additionally, in all intensive treatment arm surgeries (Leicester and Cambridge) GPs were advised to follow treatment algorithms for medication with glucose lowering, angiotensin converting enzyme (ACE) inhibiting, lipid lowering, and platelet inhibiting medication that were slightly tighter than those in contemporary UK treatment guidelines [13, 22-24]. According to the protocol, therapy with glucose lowering medication was indicated for patients with an HbA1c >6.5%, therapy with ACE inhibitors for patients with blood pressure >120/80 mmHg or prevalent CVD, statin therapy for patients with a cholesterol level>3.5 mmol/L, and aspirin therapy for all patients without specific contraindications [14].

Incremental costs of intensive treatment in ADDITION-Cambridge

Data source and operationalization

Due to the high cost of assessing and extracting data from electronic primary care records it was decided in the planning phase of the study that only the records of a subset of the study would be assessed. Records of each participant with a primary endpoint (i.e. CV event) plus the records of two random participants from the same GP surgery without a primary endpoint within the 5 year trial period were accessed. Consequently, the records of 30 participants with a primary endpoint and of 60 participants without a primary endpoint from the intensive treatment arm and the records of 33 participants with a primary endpoint and of 66 participants without a primary endpoint from the routine care arm were accessed.

These records comprised information on consultations with outpatient health care professionals, prescribed medications, and diagnostic tests from the date of diagnosis (between 2002 and 2005) until the end of the year 2010 (~ 80,000 observations in total). Costs associated with the utilization of these services were obtained by multiplying the number of consumed resources by their respective unit prices. Unit prices for consultations with GPs and nurses were

extracted from the Personal Social Services Research Unit (PSSRU) report on Unit costs of Health and Social Care [26]. Prices for all other consultations were taken from the National Schedule of Reference Costs 2009-10 for NHS Trusts [27]. The Prescription Cost Analysis (PCA) 2010 was used to assign unit prices for prescribed medications [28]. Owing to incomplete or ambiguous information from the free-text records, no unit costs could be assigned to around 1% of the recorded utilized resources. These services were therefore priced according to the mean unit price of utilized units for this person and year.

Based on the study protocol, we allocated cost items to the following categories:

(i) costs for consultations related to the trial protocol (contacts with GPs and nurses);

(ii) costs for medication related to the trial protocol (glucose lowering drugs, blood pressure lowering drugs, cholesterol lowering drugs, platelet inhibiting drugs);

(iii) costs for all other services (contacts with other primary health care professionals and outpatient specialists, other medications, and diagnostic tests).

Statistical analyses

In the long-term decision model costs for primary care and medication accrue until a person dies. As input parameters for this decision model one therefore needs an empirical estimate that describes the difference in average costs between a person alive in the intensive treatment arm and a person alive in the routine care arm. For this, we subdivided the 5-year analysis period into five annual intervals (year 1 to year 5 after diagnosis) and included the observation year in which a person died, but excluded subsequent years from the analysis. After exclusion of 16 participants for whom none or less than one year's data were available, 173 participants (from 34 surgeries, mean cluster size=5; min=2, max=17) provided 841 person years of data until death. Medication data were missing for 18 of the 173. These costs were imputed with Markov Chain Monte Carlo procedures using model covariates and available annual cost values for consultations, medications, and diagnostic tests. This yielded a final analysis sample of 173 participants with 841 complete observation years.

Here we firstly descriptively report the resource utilization of categories (i) and (ii) which has been described in detail elsewhere [18]. Secondly, we analyzed the annual incremental costs of intensive treatment for each resource utilization category separately using generalized linear models (GLMs). We tested a GLM with identity-link and Gaussian distribution (i.e. OLS-model), a GLM with log-link and gamma/Poisson distribution and a GLM with square root link and gamma/Poisson distribution (in models with a log-link all zero costs were set to a nominal £1)[29]. Results from these models were very similar; for overall costs we decided to use the OLS model which is the simplest and yielded the most conservative cost estimates [30]. Models accounted for observation years being clustered into

patients and patients being clustered into primary care surgeries (three-level random intercept model) and were adjusted for age, sex, and HbA1c at diagnosis. We also introduced an interaction term between the year after diagnosis and the treatment status to capture potential trends over time. In a second step, using the same statistical methods, we estimated the total annual incremental costs. To account for the non-random selection of the analyzed subsample, we introduced a general weighting factor, representing the inverse probability of being included in this analysis, based on the status of having a primary endpoint [31].

These models yielded mean estimates and SEs for the annual incremental costs of consultations ($\beta_{consultations\text{-}Cambridge}$; $SE_{consultations\text{-}Cambridge}$), medication ($\beta_{medication\text{-}Cambridge}$; $SE_{medication\text{-}Cambridge}$), and the intervention as a whole, including other primary care services ($\beta_{total\text{-}Cambridge}$; $SE_{total\text{-}Cambridge}$). Analyses were performed with SAS 9.3 using the GLIMMIX, MI, and MIANALYZE procedures (Cary, NC, USA).

Long-term cost-effectiveness of intensive treatment in ADDITION-UK/Cambridge

The long-term cost-effectiveness of ADDITION used the outputs from the UKPDS model as per the original model, with the updated short-term intervention costs from the electronic primary care records. The methods are briefly described below. The analysis is conducted from the perspective of the NHS. As we only have empirical data on the intervention costs from the Cambridge centers but not from the Leicester centers we firstly update the previous cost-effectiveness analyses for ADDITION UK (Leicester and Cambridge). In a second step we report a separate long-term cost-effectiveness analyses for ADDITION-Cambridge, only.

QALYs

The UKPDS outcomes model v1.3 was applied to simulate the individual accumulated QALYs of patients [17, 32]. The UKPDS outcomes model is a widely used individual-level state transition simulation model a micro-simulation model based on data from a UK population and applicable for the given evaluation context [33]. Its performance has been tested against the ADDITION 5-year outcomes in a previous study showing a moderate calibration and discrimination [34]. The model predicts future events (ischemic heart disease, myocardial infarction, heart failure, stroke, amputation, blindness, renal failure) and death as a function of several values at diagnosis of diabetes (e.g., sex, ethnicity, duration of diabetes) and based on values of risk factors at diagnosis and in subsequent years (e.g., smoking, body mass index (BMI), cholesterol, high-density lipoprotein (HDL), HbA1c, systolic BP). Results on risk factor changes and effects on micro and macrovascular events over the 5 year observation period have been reported previously and are summarized in **Appendix 1** [15-17, 35]. Utility decrements associated with the modeled events were obtained from the published literature, and the additive method was used for patients with multiple events (**Appendix 2**) [36-38].

Costs

We assumed that the costs for patients in the intensive treatment arm comprise the costs of treatment of complications plus the costs of the delivering the intervention itself, including costs for planning and implementation and for extra consultations and medication, whereas in the routine care arm, only the costs of the treatment of complications occur. All costs were calculated in British pounds (GBP) for the price year 2009/2010. The price year was chosen to maintain comparability with the previous economic analysis [17].

Treatment of events/complications: As for the effects, we used the UKPDS outcomes model v1.3 to estimate the per patient (pp) costs for treatment of events and complications [32]. Unit costs for the treatment of complications were obtained from the UKPDS study and other published literature (**Appendix 2** [37-39]. Again, the additive method was used to calculate costs in case of multiple complications or events.

Planning and implementation: The previously published internal accounting showed average pp costs of £375 in Cambridge and £71 in Leicester for the planning and implementation (teaching and feedback sessions) of the study [17]. Those values were also used in this analysis.

Extra consultations and medication: For Cambridge (total n=867), we used the empirically derived cost estimates ($\beta_{consultations\text{-}Cambridge}$, $SE_{consultations\text{-}Cambridge}$, $\beta_{medication\text{-}Cambridge}$, $SE_{medication\text{-}Cambridge}$). For Leicester (total n=159), no empirical cost data were available, and we used the cost estimates from the internal accounting[17], which were used for the protocol-based cost-effectiveness analysis [17]: $\beta_{consultations\text{-}Leicester}$ (annual pp costs for extra consultations in years 1-5)=£880/5=£176 and $\beta_{medication\text{-}Leicetser}$ (annual pp costs for extra medication in years 1-5 and thereafter)=£52.5. A detailed description of the protocol-based cost estimates is provided in **Table 1**.

Statistical analysis

For patients in both trial arms, the individual 10-, 20-, and 30-year accumulated QALYs and costs for the treatment of complications were projected by running simulations with 1,000 inner model loops and 100 bootstraps of the UKPDS outcomes model v.1.3 with a cycle length of one year [32]. Both costs and QALYs were discounted at a rate of 3.5% according to the guidelines of the National Institute for Health and Care Excellence (NICE) [40]. Some minor adjustments to the input data were performed before running the model: Patients with unknown or unclassifiable ethnicity were excluded from the analysis (n=25), and values of atrial fibrillation, peripheral vascular disease, ischemic heart disease, congestive heart failure, amputation, blindness, and renal failure, which were not collected in ADDITION, were set to zero. Further, missing values of input variables were imputed via MCMC procedures (n=5 imputations), and means and SEs were subsequently derived using Rubin's rules (supplementary information on the missing data is provided in **Appendix 3**).

As a base case scenario, we calculated the incremental cost-effectiveness for ADDITION-UK, including patients from Cambridge and Leicester. To the simulated costs for the treatment of complications which occur in both treatment arms, for patients in the intervention arm, we added the per patient (pp) mean costs for planning and implementation of the intervention, the discounted pp mean costs for extra consultations in years 1-5 $\left(\sum_{t=1}^{5} \frac{\beta_{consultations}(t)}{(1+0.35)^t}\right)$, and the discounted pp mean costs for medication until death $\left(\sum_{t=1}^{LE} \frac{\beta_{medication}(t)}{(1+0.035)^t}\right)$. Life expectancy (LE) for the 10-, 20-, and 30- year time horizons averaged ~9, ~15, and ~17 years. SEs of the different cost components were summed in an additive manner. In parallel to the method described by Tao et al. 2015, the resulting means and SEs of QALYs and costs at patient level were used to conduct a bootstrap analysis (n=500) adjusting for center, age at diagnosis, gender, and HbA1c at baseline [17].

We report the ICERs for the 10-, 20-, and 30-year time horizons and the probability of the intervention being cost-effective given a WTP threshold of £30,000. We also illustrate the decision uncertainty with a scatterplot in the cost-effectiveness plane and a cost-effectiveness acceptability curve. In additional analyses, we assumed that not only the costs of medication were incurred until death, but that the total incremental primary care costs, including costs of consultations and other primary care services, were incurred until death $\left(\sum_{t=1}^{LE} \frac{\beta_{total}(t)}{(1+0.035)^t}\right)$.

Analyses of modeled scenarios were conducted using the UKPDS outcomes v1.3 model and Microsoft Excel (Redmond, WA, USA). The manuscript was composed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [41].

Sensitivity analysis: We estimated an alternative model in which we incorporated total incremental primary care costs, including costs of consultations and other primary care services.

One-way sensitivity analyses were performed on the main model for ADDITION UK with varying treatment costs, utility decrements, and discount rates using the 30-year simulation data. The range for the discount rate (0%, 5%) was guided by NICE guidelines suggesting a discount rate of 3.5% as base case and 1.5% in sensitivity analyses [42]. The range for utility decrements and unit costs (-20%, +20%) was guided by the coefficient of variation of parameter estimates which averaged approximately 8-12% in the data sources from which the input parameters were taken [36, 39].

We also adjusted our models to most recently available prices as relative prices, particularly for medications, might have changed substantially since 2010. The PSSRU Unit Costs of Health and Social Care 2010 and 2015 [43, 44], the British National Formulary (BNF) for 2010 and 2016 [45], and the NHS trust reference cost schedules (NSRC) for

2009/2010 and 2015/2016 [46, 47] were used to retrieve relative price changes for GP and nurse contacts, for cardio-metabolic medications, and for hospitalizations of diabetes-related complications (compare **Appendix 4**).

Results

Study design and study population

Baseline characteristics of the total UK sample and of the weighted Cambridge subsample are presented in **Table 2**. The mean age of the UK sample was around 61.5 years. No substantial differences were observed between the UK sample (n=1024) and the weighted Cambridge subsample from which empirical cost data were available (n=173).

Incremental costs in ADDITION-Cambridge

The primary care cost components for patients in the intensive treatment and routine care arm are illustrated in **Figure 1**. Respective resource utilization for contact with health care professionals and medication related to the trial protocol is illustrated in **Appendix 5**. The majority of costs are attributable to contacts with GPs, metabolic and cardio-protective medication and other types of medications. The annual costs for contacts with GPs, nurses, and other health care professionals (HCP) and the annual costs for glucose lowering drugs, BP lowering drugs, lipid lowering drugs, aspirin, other medication, and diagnostic tests stayed constant or increased over the 5-year time horizon. Significant cost differences between the intensive treatment arm and the routine care arm were only observed for glucose lowering and lipid lowering drugs.

The mean incremental annual costs of intensive treatment are illustrated in **Table 3**. Total incremental annual costs pp over the 5-year time period averaged £92 ($\beta_{total\text{-}Cambridge}$=92.0, $SE_{total\text{-}Cambridge}$=115.4) using a GLM with a Gaussian distribution and an identity link. Incremental annual costs pp for GP/nurse consultations, and for metabolic/cardio-protective medication averaged £29 ($\beta_{consultation\text{-}Cambridges}$=29.1, $SE_{consultations\text{-}Cambridge}$=33.0) and £55 ($\beta_{medication\text{-}Cambridge}$= 54.6, $SE_{medication\text{-}Cambridge}$=28.5), respectively. The incremental costs for other services were £6 (β=5.7, SE=89.1). Around 5% of the variation in the total incremental costs was explained by the clustering of patients into surgeries (intra-class correlation coefficient (ICC)=0.036). A detailed analysis of the cost pattern over time showed that the cost difference varied considerably between the observation years (**Appendix 6**). Omitting the weighting factor or performing a complete case analysis (without imputed observation years) altered the results only marginally.

Long-term cost-effectiveness in ADDITION-UK

Table 4 shows the crude accumulated QALYs and costs over the 10-, 20-, and 30-year time horizon for ADDITION-UK and ADDITION Cambridge. **Table 5** shows the adjusted incremental QALYs, costs and ICERs for ADDITION-UK and ADDITION-Cambridge. Due to larger cardiovascular risk factor reductions in Leicester [16, 35] incremental

QALYs in ADDITION-UK were higher than in ADDITION-Cambridge. However, due to higher implementation costs in Leicester ($\beta_{consultation}$), incremental costs in ADDITION-UK were higher than in ADDITION-Cambridge. Resulting ICER point estimates for the 10, 20 and 30 year time horizon were £71,232/QALY, £28,444/QALY and £27,549/QALY for ADDITION-UK, and £96,570/QALY, £36,115/QALY, £29,588/QALY for ADDITION-Cambridge.

Figure 2 shows the scatterplot of the 10-, 20-, and 30-year QALY and cost pairs of bootstrap replications in the cost-effectiveness plane and the cost-effectiveness acceptability curve. For all three time horizons, the majority of points lie in the north-east quadrant. For ADDITION-UK 0.7%, 53.5%, and 56.0% and for ADDITION-Cambridge 0.9%, 39.5% and 50.0%.are positioned below the £30,000/QALY WTP threshold.

Sensitivity analyses: Incorporating total incremental primary care costs, including costs of consultations and other primary care services yielded a 30-year ICER point estimate of £33k/QALY for ADDITION-UK and of £38k/QALY for ADDITION UK. The one-way sensitivity analysis with varying unit costs, discount rates, and utility decrement for ADDITON-UK is illustrated in the tornado diagram of **Figure 3**. It shows that for the specified ranges the ICER point estimate for ADDITION-UK lies close to or below the threshold of £30,000/QALY. Results from the sensitivity analysis for ADDITION-Cambridge are similar (not shown). Between 2010 and 2015/16, relative prices increased by 44% for GP and nurse contacts, by 15% for unit costs for treatment of diabetes complications, and decreased by 41% for relevant cardio-metabolic medications (**Appendix 4**). The price change adjusted models resulted in ICERs of £25k/QALY for ADDITION UK and £27k/QALY for ADDITION-Cambridge.

Discussion

Summary

There is uncertainty about the costs and the cost-effectiveness of early intensive multifactorial treatment as delivered in the ADDITION trial. Based on electronic primary care records of a subsample of the trial cohort, we analyzed the incremental costs of delivered intensive treatment in ADDITION-Cambridge. Following an iterative framework of decision making in health care, we used these empirical cost estimates to update the previously published cost-effectiveness analysis for ADDITION-UK and present estimates for ADDITION-Cambridge. The results show that the intervention was delivered at lower costs than previously assumed and that there is a moderate likelihood that the intervention will be cost-effective over a time horizon of 30 years.

Discussion of results

The difficulty of decision making in the context of chronic diseases is that potential positive effects of treatment, i.e., reduction in cardiovascular events and premature death, are likely to occur far from the time when interventions are delivered to patients. This issue is of particularly high relevance for interventions that target populations at a very early stage in disease progression, as in the case of treatment for individuals with type 2 diabetes detected by screening. As decisions in health care often need to be made promptly and cannot be postponed until evidence from long-term trials is available, models that simulate the natural course of the disease, and with it the expected effects (QALYs) and costs, have been established as helpful tools [48]. However, simulation models rely on a set of assumptions and input parameters that crucially determine the results of the simulation.

To assess the cost-effectiveness of the ADDITION intervention, we previously used the UKPDS outcomes model, which projects accumulated QALYs and costs over a 10-, 20-, and 30-year time horizon. This analysis showed that ICERs were only moderately sensitive to the used input parameters (unit costs for treatment of events, utility decrements for events, discount rate), but highly sensitive to the assumptions on the costs of the intervention itself [17]. The input parameter for the incremental treatment costs was solely estimated on the trial protocol assuming 100% protocol adherence. To receive an empirical, trial-informed estimate, we therefore analyzed the electronic primary care records of a subset of the ADDITION-Cambridge trial cohort and used this data to update the long-term cost-effectiveness model.

The results of the empirical analysis show that the incremental pp costs for actually delivered consultations were lower than expected (£145 empirical vs. £311 protocol-based for years 1-5), but that the assumption for extra medication was appropriate (£54.6 empirical vs. £52.5 protocol- based annually, compare **Table 1**). The former suggests that GPs did see their patients more often, but not to the extent for which they were reimbursed within the trial. The latter indicates that incremental costs for medication actually delivered were as high as the per-protocol estimated costs, which were based on the assumption of 100% protocol adherence with generic drug agents. This is surprising, as we know that the protocol adherence was not perfect [18]. A possible explanation for this finding is that the reduction of costs resulting from the suboptimal medication adherence has been cancelled out by an increase of costs resulting from the high usage of non-generic drugs observed in both treatment arms. In more detailed analyses, for example, we observed that after the year 2003 when simvastatin went off patent more than 35% of statin prescriptions were still for the much more expensive atorvastatin. Of note, costs for primary care services which were not directly related to the trial protocol were almost equal in both trial arms.

Revisiting the previously developed robust evaluation framework [17] with the empirical trial-informed cost estimates shows that the intervention has a moderate likelihood of being cost-effective over a time horizon of 30 years,

assuming the higher UK NICE WTP threshold of £30,000/QALY. Our sensitivity analyses also indicated that the intervention might be cost-effective with most recent prices.

This study also shows that empirical information on the incremental costs of the delivered intervention is invaluable for the economic evaluation of this trial. Unknown protocol adherence and the magnitude of generic drug usage can lead to a considerable over- or underestimation of incremental costs. Trialists should consider whether there could be value in measuring adherence to protocol when designing future pragmatic studies.

Comparison with the initial cost-effectiveness analysis

The cost-effectiveness analysis in this study is based on a previously developed modeling framework [17]. However, a few minor methodological adaptations have been made. Supported by the empirical data annual costs for extra consultations in ADDITION-Cambridge were assumed to occur until year 5 and not only until year 3. Further, the uncertainty of incremental costs was considered in the cost-effectiveness model by incorporating the standard errors of the empirically derived incremental cost estimates in an additive manner. In the initial long-term cost-effectiveness analysis we also erroneously presumed that the mean costs for additional medication would be incurred until the end of the 10-, 20-, and 30-year simulation time horizon independently of individual simulated deaths of participants [17]. In this study, we took the more plausible assumption that costs for extra medication will occur until a person dies or reaches the end of the simulated time horizon. Applying this assumption to the previous cost-effectiveness analyses would have led to ICER point estimates of around £83k/QALY, £32k/QALY, and £30k/QALY for a 10-, 20-, and 30-year simulation time horizon. The decrease of the ICER in our study can be explained by the lower frequency of extra consultations compared to the per-protocol assumed costs in the ADDITION-Cambridge sample **(**compare **Table 1)**.

Strengths and limitations

The main strength of this study is the use of empirical data from electronic primary care records from a subsample of the ADDITION-Cambridge trial sample. The use of these data provided a unique insight into the cost structure of intensive treatment as delivered in the ADDITION trial and allowed us to perform a detailed analysis of incremental cost components. This allowed us to revisit the cost-effectiveness analyses with the updated cost estimates using a previously developed robust evaluation framework and incorporated the uncertainty around the empirically derived cost estimates.

There are also some limitations that need to be taken into account. First and most importantly, the risk equations of the UKPDS outcomes model v1.3 were derived from an historical cohort followed from 1977 to 1997. As the general quality of diabetes care has improved since then, the model overestimates the absolute CVD risk in current populations. This finding was replicated in a previous validation study based on ADDITION data. However, this

validation study also showed that the model performed reasonably well in the prediction of incremental cardiovascular event rates in the ADDITION-UK sample [34]. Second, the input parameters for costs and utility decrements associated with the modeled events might be outdated und updating for inflation will not account for changes in relative prices. We therefore performed sensitivity analyses on these parameters, which showed that the results were only moderately sensitive towards variation in these parameters. Third, we only had empirical information on primary care costs for around 20% of the ADDITION-Cambridge trial cohort. We therefore kept the protocol-based assumptions for participants from Leicester in the analysis for ADDITION-UK, but performed separate analyses restricted to ADDITION-Cambridge participants. We further assigned mean cost estimates instead of individual-level costs to patients from Cambridge and Leicester. Fourth, owing to the relatively small sample size, the clustering of patients into GP practices, and the non-availability of information on resource utilization before randomization the uncertainty around the cost estimates remained relatively large. Fifth, we only had empirical information on primary care contacts. We therefore used the risk factor profile of participants together with the UKPDS Outcomes Model to predict complications and costs, (including hospital costs) associated with those complications. However, we do not know if the intervention provoked or prevented other unexpected care use that is not captured by the model and also not by our empirical primary care cost analyses. This shortcoming could have biased the cost estimates and ICERs in either direction. Sixth, we estimated incremental costs for medication based on prescriptions issued. However, we do not know how many of these were actually dispensed and we therefore probably overestimated the absolute (and incremental) costs for medications. Other limitations, such as the fact that the UKPDS outcomes model does not incorporate all diabetes-related complications and that the ADDITION-UK sample does not adequately represent UK ethnic diversity, limiting its external validity, have been discussed in detail by Tao et al. [17].

Conclusion

Revisiting and correcting the initial cost-effectiveness analyses with empirical trial-informed cost estimates suggests that money spent on intensive treatment in individuals with type 2 diabetes detected by screening might be borderline cost-effective according to conventional UK WTP thresholds. However, the results need to be interpreted with caution as the projection of trial data over a long time horizon is almost always associated with substantial uncertainty.

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Figures

Figure 1:

Title:

Adjusted means of annual primary care costs according to Intensive Treatment (gray) and Routine Care (black) in years 1-5 [#]

Legend:

generalized linear model (gamma distribution and log link) with a main effect for the intervention and for time since diagnosis and an interaction term between intervention and time; adjusted for sex and age of diagnosis and baseline HbA1c; accounted for patients being clustered in GP surgeries and observations clustered in patients; HCP health care professionals; Owing to the choice of the family distribution no SE is available for the cost difference.

Figure 2:

Title:

Cost-effectiveness plane showing pairs of incremental costs and QALYs and cost-effectiveness acceptability curve showing the probability of intensive treatment being cost-effective

Legend:

Cost-effectiveness plane showing pairs of 10, 20, and 30 years incremental cost and QALYs from bootstrap samples; Cost-effectiveness acceptability curves which show the probability of intensive treatment being more cost-effective than routine care based on net benefit values from bootstrap samples over a time horizon of 10, 20, and 30 years

Figure 3:

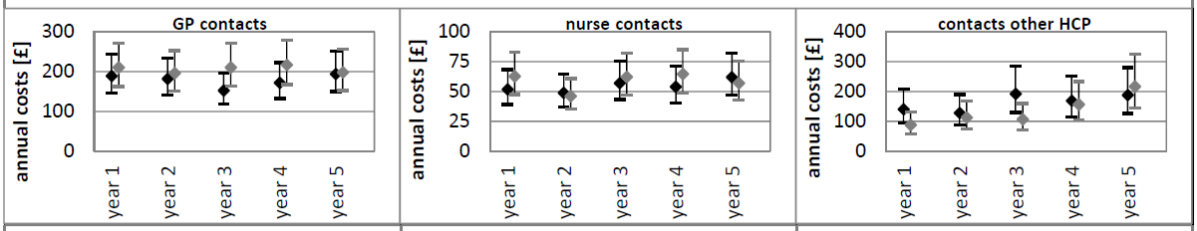
Title:

Tornado diagram showing the influence of changing different parameters

Legend:

Tornado diagram showing the influence of changing different parameters that contribute to the ICER in long-term cost-effectiveness modelling analysis. Choice of discount rate has the greatest impact on the ICER (higher discount rate, unit costs and lower utility decrements all associated with higher point estimate ICER).

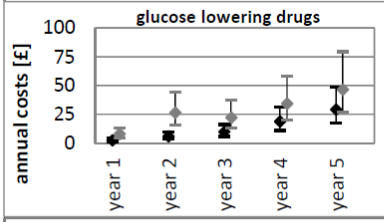
Figure 1: Adjusted means of annual primary care costs according to Intensive Treatment (gray) and Routine Care (black) in years 1-5 [#]



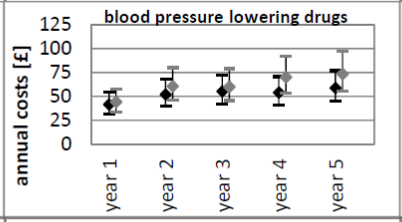
	adjusted mean (95% CI) [£]
IT	205.8 (167.1, 253.4)
RC	176.8 (143.1, 218.4)
IT vs. RC	29

	adjusted mean (95% CI) [£]
IT	58 (46, 73.1)
RC	54.4 (42.9, 69.1)
IT vs. RC	3.6

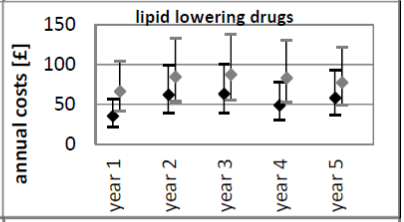
	adjusted mean (95% CI)
IT	128.9 (93.2, 178.2)
RC	161.2 (116.7, 222.7)
IT vs. RC	-32.3



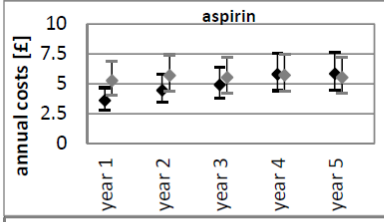
	adjusted mean (95% CI) [£]
IT	23.7 (16.1, 35)
RC	9.7 (6.7, 14.1)
IT vs. RC	14



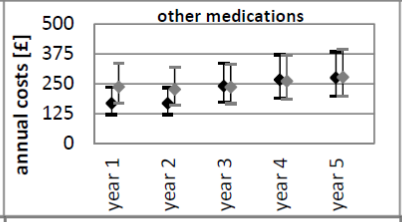
	adjusted mean (95% CI) [£]
IT	60.9 (48.1, 77.2)
RC	52.1 (41.3, 65.7)
IT vs. RC	8.8



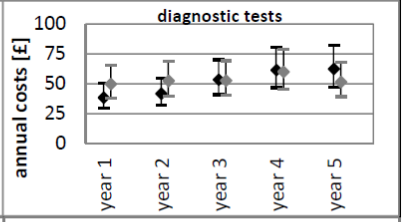
	adjusted mean (95% CI)
IT	79.5 (52.2, 121)
RC	52.5 (34, 81.1)
IT vs. RC	27



	adjusted mean (95% CI) [£]
IT	5.5 (4.4, 7)
RC	4.8 (3.8, 6.1)
IT vs. RC	0.7



	adjusted mean (95% CI) [£]
IT	247 (180.1, 338.7)
RC	218.6 (161.4, 295.9)
IT vs. RC	28.4



	adjusted mean (95% CI)
IT	53.2 (43.1, 65.7)
RC	50.5 (40.8, 62.5)
IT vs. RC	2.7

Figure 2: Cost-effectivness planes and cost-effectivness acceptability curves

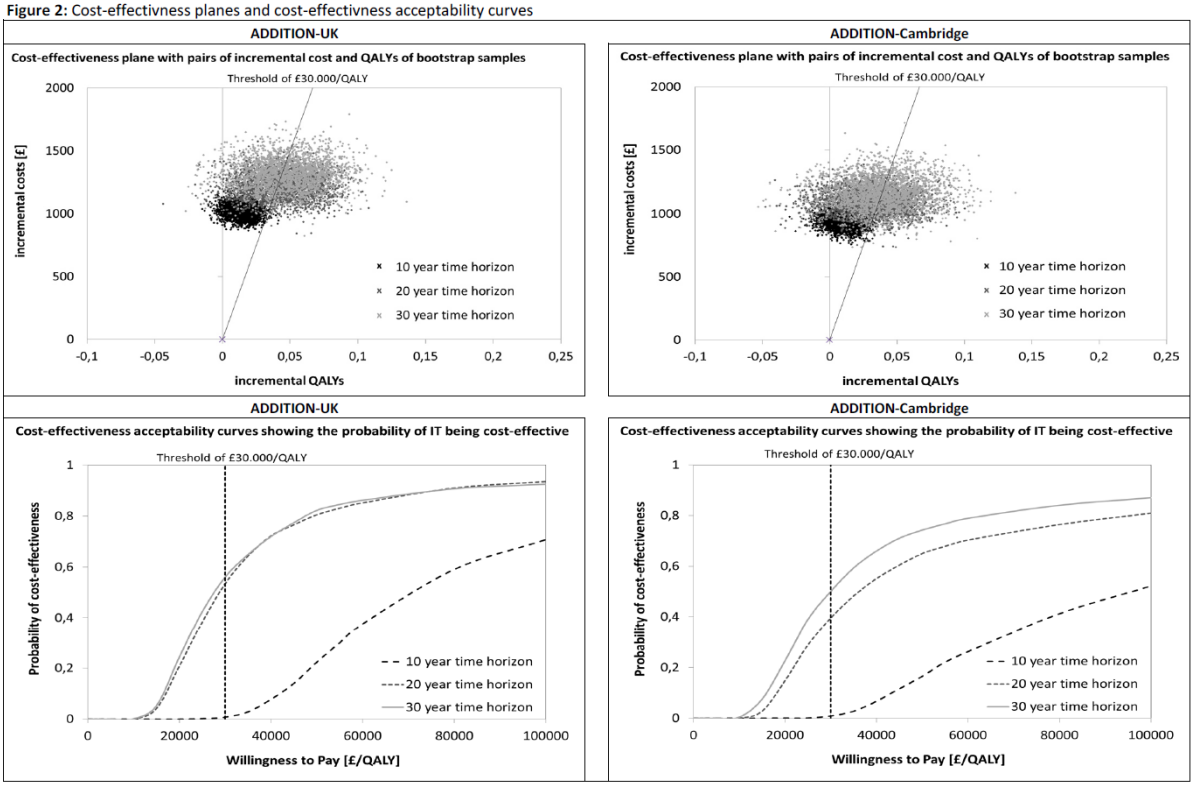
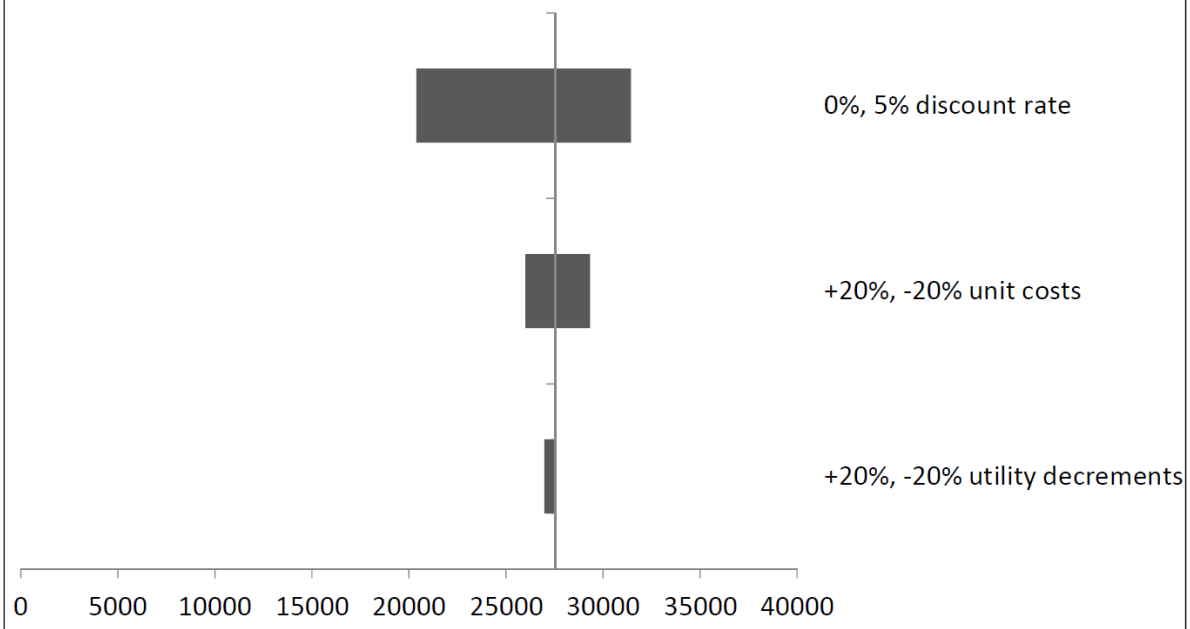


Figure 3: Tornado diagram showing the influence of changing different parameters for ADDITION-UK



Tables

Table 1: Protocol-based and empirical cost estimates used in the initial [17] and updated base-case cost-effectiveness analysis

Cost component	Center	per protocol [1] accumulated mean	per protocol [1] accumulated SE	per protocol [1] annually mean	per protocol [1] annually SE	trial-based [2] accumulated mean	trial-based [2] accumulated SE	trial-based [2] annually mean	trial-based [2] annually SE
		upfront costs							
Costs 'planning and implementation'	Cambridge (n=452)	375.1	-	-	-	375.1	0.0	-	-
	Leicester (n=61)	*71.2*	-	-	-	*71.2*	*0.0*	-	-
		year 1-5 [ŀ]							
Costs 'Extra Consultations'	Cambridge (n=452)	311.3[#]	-	62.3[##]	-	145.5	161.5	29.1 [c]	32.3 [d]
	Leicester (n=61)	*880.1*[#]	-	*176.0*[##]	-	*880.1*	*976.9**	*176.0*	*195.4 **
Costs 'Extra Medication'	Cambridge (n=452)	262.5	-	52.5	-	273.0	142.5	54.6 [e]	28.5 [f]
	Leicester (n=61)	*262.5*	-	*52.5*	-	*262.5*	*137.0**	*52.5*	*27.4 **
		Year 6 until …							
		end of observation period				**death or end of observation period**			
Costs 'Extra Medication' (year 6-10)	Cambridge (n=452)	199.6 ¬	-	52.5	-	183.7 ⊣	95.9	54.6	28.5
	Leicester (n=61)	*199.6* ¬	-	*52.5*	-	203.4 ⊣	*106.2**	*52.5*	*27.4 **
Costs 'Extra Medication' (year 6-20)	Cambridge (n=452)	509.1 ¬	-	52.5	-	386.9 ⊣	201.9	54.6	28.5
	Leicester (n=61)	*509.1* ¬	-	*52.5*	-	434.9 ⊣	*227.0**	*52.5*	*27.4 **
Costs 'Extra Medication' (year 6-30)	Cambridge (n=452)	728.5 ¬	-	52.5	-	444.3 ⊣	231.9	54.6	28.5
	Leicester (n=61)	*728.5* ¬	-	*52.5*	-	520.3 ⊣	*271.6**	*52.5*	*27.4 **

1) protocol-based cost estimates according to the internal accounting of Tao et al. 2015 [17]

2) empirical cost estimates according to the analysis on a subsample of the ADDITION sample;
[c - f)] *ßs* and *SEs* extracted from Table 2;

[ŀ] accumulated costs described without discounting

* SE in Leicester were assumed to be proportional to the ones in patients from Cambridge;

[#] costs were assumed to occur from year 1-3

[##] annual costs if distributed over 5 years

¬ calculated through $\sum_{t=6}^{time\ horizon} \frac{\beta_{annual\ medication\ cost}(t)}{(1+0.035)^t}$

⊣ calculated through $\sum_{t=6}^{LE} \frac{\beta_{annual\ medication\ cost}(t)}{(1+0.035)^t}$,

Modeled life expectancy (LE) for the 10-, 20-, and 30- year time horizons averaged ~9.4, ~15.2, and ~17.0 years in Cambridge and ~9.6, ~16.3 and ~19.3 years in Leicester

Table 2: Baseline characteristics of the ADDITION population trial cohort

	ADDITION-UK (Cambridge + Leicester)		**ADDITION-Cambridge subsample (weighted*)**	
	IT	**RC**	**IT**	**RC**
N [#]	513	511	82	91
Primary outcome [%]	7.2	7.5	6.8	7.7
Female sex, [%]	36.6	40.7	40.8	39.4
Mean age (SD), [years]	61.1 (7.2)	60.1 (7.5)	61.8 (7.3)	61 (7.1)
Mean BMI (SD), [kg/m^2]	33.1 (5.6)	33.0(5.9)	33.4 (5.2)	34 (5.7)
Mean total cholesterol (SD), [mmol/L]	5.3 (1.1)	5.5 (1.2)	5.4 (1.1)	5.6 (1.2)
Mean HDL (SD), [mmol/L]	1.17 (0.4)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Mean systolic blood pressure (SD), [mmHg]	142.0 (20.1)	143.1(19.4)	141.6 (21)	142.5 (20.6)
Mean HbA1c (SD), [%]	7.3 (1.7)	7.3 (1.7)	7.7 (2.2)	7.4 (1.7)

SD, Standard Deviation; BMI, Body Mass Index; HDL, High Density Lipoprotein; HbA1c, glycated hemoglobin;

* weighting factor: inverse probability of being included in the study based on the status of having a primary endpoint

RC, routine care; IT, intensive treatment; [#] n=2 of the total sample (n=1026) withdrew from the study

Table 3: Adjusted means of annual primary care costs according to Intensive Treatment and Routine Care in the years 1-5 #

	Total		**Consultations (ADDITION)**		**Medication (ADDITION)**		**Other primary care services**	
	mean	**(SE)**	**mean**	**(SE)**	**mean**	**(SE)**	**mean**	**(SE)**
Generalized linear model with Gaussian distribution and identity link								
IT	906.3	(82.2)	266.4	(23.2)	182.1	(19.9)	454.1	(63.8)
RC	814.3	(81)	237.2	(23.5)	127.6	(20.4)	448.3	(62.3)
Difference	92[a]	(115.4)[b]	29.1[c]	(33)[d]	54.6[e]	(28.5)[f]	5.7	(89.1)

generalized linear regression models with a main effect for the intervention and for time since diagnosis and an interaction term between intervention and time; adjusted for sex and age of diagnosis and baseline HbA1c; accounted for patients being clustered in GP surgeries and observations clustered in patients, model based on 841 observation years from 173 patients

estimates used for long-term CE-model: [a] ß $_{total}$; [b] SE $_{total}$; [c] ß $_{consultation}$; [d] SE $_{consultation}$; [e] ß $_{medication}$; [f] SE $_{medication}$

Table 4: Crude Cumulative cost and QALYS according to Intensive Treatment (IT) and Routine Care (RC)

ADDITION-UK (Leicester & Cambridge)

	Routine Care					Intensive Treatment				
		crude costs		crude QALYs			crude costs		crude QALYs	
Time Horizon	**n**	**mean**	**(SE)**	**mean**	**(SE)**	**n**	**mean**	**(SE)**	**mean**	**(SE)**
10 years	501	6,157	(332)	6.45	(0.08)	498	7,256	(879)	6.40	(0.09)
20 years	501	11,175	(867)	9.32	(0.21)	498	12,392	(1,614)	9.16	(0.23)
30 years	501	13,181	(1,325)	10.08	(0.30)	498	14,308	(2,110)	9.82	(0.31)

ADDITION-Cambridge

	Routine Care					Intensive Treatment				
		crude costs		crude QALYs			crude costs		crude QALYs	
Time Horizon	**n**	**mean**	**(SE)**	**mean**	**(SE)**	**n**	**mean**	**SE**	**mean**	**(SE)**
10 years	501	6,228	(341)	6.42	(0.08)	498	7199	772,65	6.39	(0.09)
20 years	501	11,208	(885)	9.21	(0.22)	498	12291	1496,87	9.11	(0.23)
30 years	501	13,102	(1,324)	9.89	(0.31)	498	14170	1979,61	9.76	(0.31)

Table 5: Adjusted incremental costs and QALYs and incremental cost-effectiveness ratios (ICER) [#]

ADDITION-UK (Leicester & Cambridge)

Time Horizon	Adjusted incremental Cost (95% CIs)	Adjusted incremental QALYs (95% CIs)	ICER	P(ICER<£30,000/QALY)*
10 years	1,021 (920, 1,120)	0.0143 (-0.0015, 0.0294)	71,232	0.007
20 years	1,217 (1,029, 1,406)	0.0428 (0.0034, 0.0817)	28,444	0.535
30 years	1,311 (1,072, 1,559)	0.0476 (0.0011, 0.0932)	27,549	0.560

ADDITION-Cambridge

Time Horizon	Adjusted incremental Cost (95% CIs)	Adjusted incremental QALYs (95% CIs)	ICER	P(ICER<£30,000/QALY)*
10 years	927 (831, 1,017)	0.0096 (-0.0079, 0.0267)	96,570	0.009
20 years	1,086 (909, 1,268)	0.0301 (-0.0144, 0.0708)	36,115	0.395
30 years	1,157 (908, 1,414)	0.0391 (-0.0107, 0.0892)	29,588	0.500

means and SE of QALYs and costs at patient level were used to conduct a bootstrap analysis (n=500) adjusting for center, age at diagnosis, gender, and HbA1c at baseline

* probability that the ICER is below £30,000/QALY

Appendices

Appendix 1a: Baseline and five-year follow-up values for clinical variables for ADDITION-UK*

	Routine Care	Intensive treatment
	Adjusted difference* (SE) (follow up-baseline)	Adjusted difference* (SE) (follow up-baseline)
HbA_{1c} (%)	–0.25 (0.09)	–0.37 (0.09)
Total cholesterol (mmol/l)	–1.20 (0.07)	–1.30 (0.06)
Systolic blood pressure (mmHg)	–7.08 (1.13)	–7.32 (1.18)

* 85% of patients from are ADDITION UK belong to ADDITION Cambridge, compare Tao, L., et al. (2015). "Cost-effectiveness of intensive multifactorial treatment compared with routine care for individuals with screen-detected Type 2 diabetes: analysis of the ADDITION-UK cluster-randomized controlled trial." Diabet Med 6(10): 12711.

Appendix 1b: Hazard ratios for primary and secondary cardiovascular outcomes for ADDITION-UK*

	Routine Care	Intensive treatment
	HR (95%-CI)	
Myocardial infarction	ref	1.08 (0.40–2.94)
Stroke	ref	1.11 (0.52–2.35)
Revascularization	ref	0.68 (0.32–1.46)
CVD death	ref	0.45 (0.19–1.06)
All-cause death	ref	0.59 (0.35–0.98)
Composite cardiovascular events	ref	0.80 (0.55–1.17)

* 85% of patients from are ADDITION UK belong to ADDITION Cambridge, compare Griffin, S. J., et al. (2011). "Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial." Lancet 378(9786): 156-167.

Appendix 1c: Odds ratios for microvascular outcomes for ADDITION-Leicester and ADDITION-Cambridge*

	Routine Care	Intensive treatment
	OR (95%-CI)	
ADDITION-Leicester		
Any albuminuria	ref	0.49 (0.21-1.15)
Any retinopathy	ref	0.90 (0.45-1.81)
Neuropathy	ref	1.76 (0.91-3.44)
ADDITION Cambridge		
Any albuminuria	ref	1.06 (0.74–1.53)
Any retinopathy	ref	0.77 (0.45–1.32)
Neuropathy	ref	0.55 (0.27–1.12)

* compare Sandbaek, A., et al. (2014). "Effect of early multifactorial therapy compared with routine care on microvascular outcomes at 5 years in people with screen-detected diabetes: a randomized controlled trial: the ADDITION-Europe Study." Diabetes Care 37(7): 2015-2023.

Appendix 2: Unit cost (£, 2009/10 UK national level) and utility decrement for diabetes and diabetic complications modelled by the UKPDS outcomes model

	Year of event	Subsequent years				
	Fatal	**Non-fatal**		**Ref.**	**Utility decrement**	**Ref.**
Type 2 diabetes	-	494.5	494.5	[32]	-0.22	[31]
IHD	-	3558.4	1175.2	[32]	-0.09	[29]
MI	2295.6	6861.8	1129.8	[32]	-0.055	[29]
Heart failure	3968.4	3968.4	1391.1	[32]	-0.108	[29]
Stroke	5786.8	4196.9	793.4	[32]	-0.164	[29]
Re-vascular	-	4943.1	316.3	[30]	-0.059	[30]
Amputation	13664.2	13664.2	788.7	[32]	-0.28	[29]
Blindness	-	1791.7	758.9	[32]	-0.074	[29]
Renal failure	30599.2	30599.2	30599.2	[31]	-0.263	[29]
CVD death	3724.3	-	-	[30]	-	-

Costs extracted from the UKPDS study were based on participant hospital records and survey of 3488 UKPDS participants in 1996-97, from which inpatient and out-patient costs were predicted and updated to 2009/10 price year; compare Tao et al. [17]

Appendix 3: Exploration of missing data

810 out of 31968 (32 variables x 999 observations) data were missing (2.5%). Missing data at follow-up was 10.9% (546 of 4995 data, 5 variables x 999 observations). Fifteen out of 32 baseline and follow-up variables had one or more observations missing. Missing data did not differ between treatment groups for 10 of the 15 variables. However, there was a statistically significant difference in the proportion of missing data between groups for baseline height (p=0.002), and follow-up measurements of total cholesterol (p=0.012), HDL (p<0.001), systolic blood pressure (p<0.001) and HbA1c (p=0.002). (Missingness in these follow-up parameters will be very highly correlated as they were intended to be collected at the same study visit).

Parameters associated with missing follow-up data on total and HDL cholesterol, SBP and HbA1c included gender, age, smoking status and HbA1c at diagnosis, ethnicity, although overall there is a mixed picture, with some likely spurious findings without any clinically plausible causation (e.g. a significant association between height and probability of HDL measurement being missing).

Based on the above, it may be reasonable to conclude that the data are not MCAR, but may be MAR. However, it is not (ever) possible to rule out MNAR. Given the low overall proportion of missing data (2.5% overall, 10.9% at follow-up), we conclude that MI is a reasonable approach to imputing missing data, allowing use of data that would otherwise be discarded in a complete case analysis.

STATA output log follows.

```
-------------------------------------------------------------------------------
      name:  <unnamed>
       log:  ExplorationofMissingness.smcl
  log type:  smcl
 opened on:  21 Feb 2017, 09:38:57

. import delimited "Unimputed_data.csv"
(33 vars, 999 obs)

.
. * change categorical to numeric
. gen male =0

. replace male = 1 if gender=="M"
(612 real changes made)

. drop gender

.
. gen diag_af = 0

. replace diag_af = 1 if diagnosisatrialfib == "Y"
(0 real changes made)

. drop diagnosisatrialfib

.
. gen diag_pvd = 0

. replace diag_pvd = 1 if diagnosispvd == "Y"
(0 real changes made)

. drop diagnosispvd

.
. misstable summ, gen(M_)
                                                      Obs<.
                                            +------------------------------
                |                           | Unique
     Variable   |     Obs=.     Obs>.     Obs<. | values        Min         Max
  --------------+-------------------------------+------------------------------
        weight  |         7                 992 |    397       44.9       169.4
        height  |       125                 874 |    317      1.414        1.92
  diagnosisc~l  |        19                 980 |     65        2.2         9.2
  diagnosishdl  |        23                 976 |    154        .52         3.8
  diagnosiss~p  |         3                 996 |    254   90.33334         228
  diagnosis~1c  |        21                 978 |     90        4.1        15.3
   currentchol  |        19                 980 |     65        2.2         9.2
    currenthdl  |        23                 976 |    154        .52         3.8
  currentsysbp  |         3                 996 |    254   90.33334         228
```

```
  currenthba1c |        21                978  |     90        4.1        15.3
     fusmoking |        51                948  |      3          0           2
     futotchol |       109                890  |     53        2.1         8.8
         fuhdl |       138                861  |    152         .4         3.9
         fusbp |       124                875  |    214         93         220
       fuhba1c |       124                875  |     63        3.8        13.4
  ------------------------------------------------------------------------------

.
. * descriptive analysis of missing data
. * by trial group
. tabulate group M_weight, chi2

           |      (weight>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       497          4 |       501
         2 |       495          3 |       498
-----------+----------------------+----------
     Total |       992          7 |       999

          Pearson chi2(1) =   0.1379   Pr = 0.710

. tabulate group M_height, chi2

           |      (height>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       422         79 |       501
         2 |       452         46 |       498
-----------+----------------------+----------
     Total |       874        125 |       999

          Pearson chi2(1) =   9.7328   Pr = 0.002

. tabulate group M_diagnosischol, chi2

           |  (diagnosischol>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       488         13 |       501
         2 |       492          6 |       498
-----------+----------------------+----------
     Total |       980         19 |       999

          Pearson chi2(1) =   2.5863   Pr = 0.108

. tabulate group M_diagnosishdl, chi2

           |   (diagnosishdl>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       486         15 |       501
         2 |       490          8 |       498
-----------+----------------------+----------
     Total |       976         23 |       999

          Pearson chi2(1) =   2.1378   Pr = 0.144

. tabulate group M_diagnosissysbp, chi2

           |  (diagnosissysbp>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       499          2 |       501
         2 |       497          1 |       498
-----------+----------------------+----------
     Total |       996          3 |       999

          Pearson chi2(1) =   0.3283   Pr = 0.567

. tabulate group M_diagnosishba1c, chi2

           |  (diagnosishba1c>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       489         12 |       501
         2 |       489          9 |       498
-----------+----------------------+----------
     Total |       978         21 |       999

          Pearson chi2(1) =   0.4196   Pr = 0.517

. tabulate group M_currentchol, chi2
```

```
           |   (currentchol>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       488         13 |       501
         2 |       492          6 |       498
-----------+----------------------+----------
     Total |       980         19 |       999

           Pearson chi2(1) =   2.5863   Pr = 0.108

. tabulate group M_currenthdl, chi2

           |    (currenthdl>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       486         15 |       501
         2 |       490          8 |       498
-----------+----------------------+----------
     Total |       976         23 |       999

           Pearson chi2(1) =   2.1378   Pr = 0.144

. tabulate group M_currentsysbp, chi2

           |   (currentsysbp>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       499          2 |       501
         2 |       497          1 |       498
-----------+----------------------+----------
     Total |       996          3 |       999

           Pearson chi2(1) =   0.3283   Pr = 0.567

. tabulate group M_currenthba1c, chi2

           |   (currenthba1c>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       489         12 |       501
         2 |       489          9 |       498
-----------+----------------------+----------
     Total |       978         21 |       999

           Pearson chi2(1) =   0.4196   Pr = 0.517

. tabulate group M_fusmoking, chi2

           |    (fusmoking>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       470         31 |       501
         2 |       478         20 |       498
-----------+----------------------+----------
     Total |       948         51 |       999

           Pearson chi2(1) =   2.4311   Pr = 0.119

. tabulate group M_futotchol, chi2

           |    (futotchol>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       434         67 |       501
         2 |       456         42 |       498
-----------+----------------------+----------
     Total |       890        109 |       999

           Pearson chi2(1) =   6.2688   Pr = 0.012

. tabulate group M_fuhdl, chi2

           |      (fuhdl>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       409         92 |       501
         2 |       452         46 |       498
-----------+----------------------+----------
     Total |       861        138 |       999

           Pearson chi2(1) =  17.4720   Pr = 0.000

. tabulate group M_fusbp, chi2
```

```
           |      (fusbp>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       417         84 |       501
         2 |       458         40 |       498
-----------+----------------------+----------
     Total |       875        124 |       999

          Pearson chi2(1) =  17.5252   Pr = 0.000

. tabulate group M_fuhba1c, chi2

           |     (fuhba1c>=.)
     Group |         0          1 |     Total
-----------+----------------------+----------
         1 |       423         78 |       501
         2 |       452         46 |       498
-----------+----------------------+----------
     Total |       875        124 |       999

          Pearson chi2(1) =   9.2103   Pr = 0.002

.
. * association between missingness and baseline variables & observed outcomes
. logit M_fusmoking i.group i.ethnicity i.male age durationofdiabetes weight height i.dia
> g_af i.diag_pvd i.diagnosissmoking diagnosischol diagnosishdl diagnosissysbp diagnosish
> ba1c i.currentsmoking currentchol currenthdl currentsysbp currenthba1c preexistingihd p
> reexistingchf preexistingamp preexistingblind preexistingrenal preexistingstroke preexi
> stingmi

note: 1.ethnicity != 1 predicts failure perfectly
      1.ethnicity dropped and 75 obs not used

note: preexistingstroke != 0 predicts failure perfectly
      preexistingstroke dropped and 18 obs not used

note: preexistingmi != 0 predicts failure perfectly
      preexistingmi dropped and 43 obs not used

note: 2.ethnicity omitted because of collinearity
note: 3.ethnicity omitted because of collinearity
note: durationofdiabetes omitted because of collinearity
note: 0.diag_af omitted because of collinearity
note: 0.diag_pvd omitted because of collinearity
note: 1.currentsmoking omitted because of collinearity
note: 2.currentsmoking omitted because of collinearity
note: currentchol omitted because of collinearity
note: currenthdl omitted because of collinearity
note: currentsysbp omitted because of collinearity
note: currenthba1c omitted because of collinearity
note: preexistingihd omitted because of collinearity
note: preexistingchf omitted because of collinearity
note: preexistingamp omitted because of collinearity
note: preexistingblind omitted because of collinearity
note: preexistingrenal omitted because of collinearity
Iteration 0:   log likelihood = -104.67557
Iteration 1:   log likelihood = -100.22295
Iteration 2:   log likelihood = -99.016378
Iteration 3:   log likelihood = -99.012197
Iteration 4:   log likelihood = -99.012196

Logistic regression                               Number of obs   =        704
                                                  LR chi2(11)     =      11.33
                                                  Prob > chi2     =     0.4163
Log likelihood = -99.012196                       Pseudo R2       =     0.0541

------------------------------------------------------------------------------
       M_fusmoking |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
           2.group |  -.4369343    .426696    -1.02   0.306    -1.273243    .3993744
                   |
         ethnicity |
                2  |          0  (empty)
                3  |          0  (empty)
                   |
            1.male |   .5959359   .6852547     0.87   0.384    -.7471386     1.93901
               age |   .0068199   .0327479     0.21   0.835    -.0573648    .0710047
durationofdiabetes |          0  (omitted)
            weight |   .0054153   .0146481     0.37   0.712    -.0232945    .0341252
            height |  -.6735042   3.406297    -0.20   0.843    -7.349724    6.002716
         0.diag_af |          0  (omitted)
        0.diag_pvd |          0  (omitted)
                   |
```

```
  diagnosissmoking |
                1  |  -.1189077   .5426201    -0.22   0.827    -1.182424    .9446082
                2  |   .9886518   .5306364     1.86   0.062    -.0513765     2.02868
                   |
     diagnosischol |  -.2643285   .1965389    -1.34   0.179    -.6495377    .1208807
      diagnosishdl |  -.4479791   .7774532    -0.58   0.564    -1.971759    1.075801
    diagnosissysbp |   .0037443   .0112236     0.33   0.739    -.0182535    .0257422
    diagnosishba1c |   .0145227   .1199981     0.12   0.904    -.2206692    .2497145
                   |
    currentsmoking |
                1  |          0  (omitted)
                2  |          0  (omitted)
                   |
       currentchol |          0  (omitted)
        currenthdl |          0  (omitted)
      currentsysbp |          0  (omitted)
      currenthba1c |          0  (omitted)
    preexistingihd |          0  (omitted)
    preexistingchf |          0  (omitted)
    preexistingamp |          0  (omitted)
  preexistingblind |          0  (omitted)
  preexistingrenal |          0  (omitted)
preexistingstroke |          0  (omitted)
     preexistingmi |          0  (omitted)
             _cons |  -2.245222   6.202811    -0.36   0.717    -14.40251    9.912064
------------------------------------------------------------------------------

. logit M_futotchol i.group i.ethnicity i.male age durationofdiabetes weight height i.dia
> g_af i.diag_pvd i.diagnosissmoking diagnosischol diagnosishdl diagnosissysbp diagnosish
> ba1c i.currentsmoking currentchol currenthdl currentsysbp currenthba1c preexistingihd p
> reexistingchf preexistingamp preexistingblind preexistingrenal preexistingstroke preexi
> stingmi

note: 2.ethnicity != 0 predicts failure perfectly
      2.ethnicity dropped and 11 obs not used

note: durationofdiabetes omitted because of collinearity
note: 0.diag_af omitted because of collinearity
note: 0.diag_pvd omitted because of collinearity
note: 1.currentsmoking omitted because of collinearity
note: 2.currentsmoking omitted because of collinearity
note: currentchol omitted because of collinearity
note: currenthdl omitted because of collinearity
note: currentsysbp omitted because of collinearity
note: currenthba1c omitted because of collinearity
note: preexistingihd omitted because of collinearity
note: preexistingchf omitted because of collinearity
note: preexistingamp omitted because of collinearity
note: preexistingblind omitted because of collinearity
note: preexistingrenal omitted because of collinearity
Iteration 0:   log likelihood = -86.740425
Iteration 1:   log likelihood = -78.864431
Iteration 2:   log likelihood = -74.632087
Iteration 3:   log likelihood = -74.577762
Iteration 4:   log likelihood = -74.577679
Iteration 5:   log likelihood = -74.577679

Logistic regression                               Number of obs   =        829
                                                  LR chi2(14)     =      24.33
                                                  Prob > chi2     =     0.0418
Log likelihood = -74.577679                       Pseudo R2       =     0.1402

------------------------------------------------------------------------------
       M_futotchol |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
           2.group |   .6055944   .5283212     1.15   0.252    -.4298962    1.641085
                   |
         ethnicity |
                2  |          0  (empty)
                3  |   1.855084   1.214619     1.53   0.127    -.5255253    4.235694
                   |
            1.male |  -1.774157   .7614911    -2.33   0.020    -3.266652   -.2816621
               age |   .1278512   .0527805     2.42   0.015     .0244033    .2312991
durationofdiabetes |          0  (omitted)
            weight |   .0145182   .0170165     0.85   0.394    -.0188336      .04787
            height |   4.867089   3.936642     1.24   0.216    -2.848587    12.58277
         0.diag_af |          0  (omitted)
        0.diag_pvd |          0  (omitted)
                   |
  diagnosissmoking |
                1  |   1.023356    .681976     1.50   0.133    -.3132925    2.360004
                2  |   1.884861   .7276166     2.59   0.010     .4587584    3.310963
                   |
     diagnosischol |   .1628792   .2125308     0.77   0.443    -.2536736     .579432
```

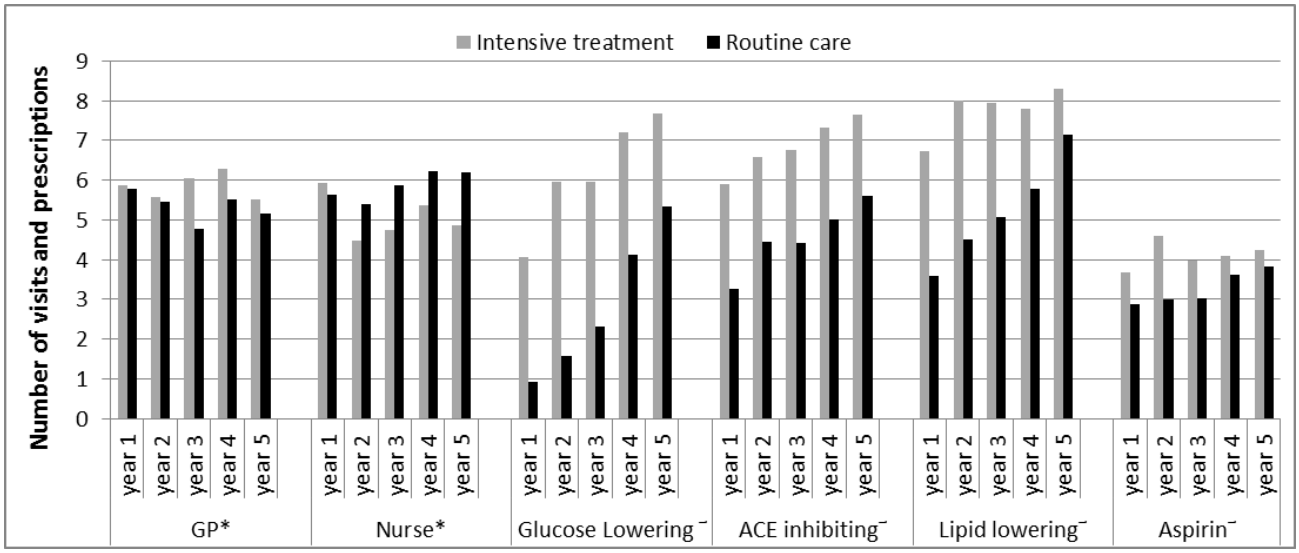
```
      diagnosishdl |   .4883364   .6982475     0.70   0.484    -.8802036    1.856876
    diagnosissysbp |   .0143141    .011474     1.25   0.212    -.0081745    .0368027
    diagnosishba1c |   .1743563   .1285212     1.36   0.175    -.0775407    .4262532
                   |
    currentsmoking |
                1  |          0  (omitted)
                2  |          0  (omitted)
                   |
       currentchol |          0  (omitted)
        currenthdl |          0  (omitted)
      currentsysbp |          0  (omitted)
      currenthba1c |          0  (omitted)
    preexistingihd |          0  (omitted)
    preexistingchf |          0  (omitted)
    preexistingamp |          0  (omitted)
  preexistingblind |          0  (omitted)
  preexistingrenal |          0  (omitted)
 preexistingstroke |   .0475647   .1322037     0.36   0.719    -.2115498    .3066792
     preexistingmi |   .0004308   .0812079     0.01   0.996    -.1587337    .1595952
             _cons |  -26.72693   8.207629    -3.26   0.001    -42.81359   -10.64027
------------------------------------------------------------------------------

. logit M_fuhdl i.group i.ethnicity i.male age durationofdiabetes weight height i.diag_af
>  i.diag_pvd i.diagnosissmoking diagnosischol diagnosishdl diagnosissysbp diagnosishba1c
>  i.currentsmoking currentchol currenthdl currentsysbp currenthba1c preexistingihd preex
> istingchf preexistingamp preexistingblind preexistingrenal preexistingstroke preexistin
> gmi

note: 2.ethnicity != 0 predicts failure perfectly
      2.ethnicity dropped and 11 obs not used

note: durationofdiabetes omitted because of collinearity
note: 0.diag_af omitted because of collinearity
note: 0.diag_pvd omitted because of collinearity
note: 1.currentsmoking omitted because of collinearity
note: 2.currentsmoking omitted because of collinearity
note: currentchol omitted because of collinearity
note: currenthdl omitted because of collinearity
note: currentsysbp omitted because of collinearity
note: currenthba1c omitted because of collinearity
note: preexistingihd omitted because of collinearity
note: preexistingchf omitted because of collinearity
note: preexistingamp omitted because of collinearity
note: preexistingblind omitted because of collinearity
note: preexistingrenal omitted because of collinearity
Iteration 0:   log likelihood = -145.02106
Iteration 1:   log likelihood = -137.00905
Iteration 2:   log likelihood =  -135.5593
Iteration 3:   log likelihood = -135.55551
Iteration 4:   log likelihood =  -135.5555

Logistic regression                               Number of obs   =        829
                                                  LR chi2(14)     =      18.93
                                                  Prob > chi2     =     0.1676
Log likelihood =  -135.5555                       Pseudo R2       =     0.0653

------------------------------------------------------------------------------
           M_fuhdl |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
           2.group |  -.5516725   .3616837    -1.53   0.127     -1.26056    .1572144
                   |
         ethnicity |
                2  |          0  (empty)
                3  |  -.3972339   1.093944    -0.36   0.717    -2.541325    1.746857
                   |
            1.male |  -1.301736   .5508324    -2.36   0.018    -2.381348   -.2221248
               age |   .0173194   .0294563     0.59   0.557    -.0404139    .0750528
durationofdiabetes |          0  (omitted)
            weight |   .0046728   .0120955     0.39   0.699     -.019034    .0283795
            height |   5.619519   2.861427     1.96   0.050     .0112243    11.22781
         0.diag_af |          0  (omitted)
        0.diag_pvd |          0  (omitted)
                   |
  diagnosissmoking |
                1  |   .5523239   .4510155     1.22   0.221    -.3316503    1.436298
                2  |   1.140725   .4933152     2.31   0.021     .1738448    2.107605
                   |
     diagnosischol |    -.16806    .160809    -1.05   0.296    -.4832399    .1471199
      diagnosishdl |   .5487335   .5323884     1.03   0.303    -.4947285    1.592196
    diagnosissysbp |   .0105278   .0088739     1.19   0.235    -.0068648    .0279203
    diagnosishba1c |   .0532259   .1014626     0.52   0.600    -.1456373     .252089
                   |
    currentsmoking |
                1  |          0  (omitted)
```

```
               2  |          0  (omitted)
                  |
       currentchol |          0  (omitted)
        currenthdl |          0  (omitted)
      currentsysbp |          0  (omitted)
      currenthba1c |          0  (omitted)
    preexistingihd |          0  (omitted)
    preexistingchf |          0  (omitted)
    preexistingamp |          0  (omitted)
  preexistingblind |          0  (omitted)
  preexistingrenal |          0  (omitted)
 preexistingstroke |  -.0110728   .1450093    -0.08   0.939    -.2952859    .2731402
     preexistingmi |  -.0362379   .0844939    -0.43   0.668    -.2018428    .1293671
             _cons |  -15.20218   5.366486    -2.83   0.005     -25.7203    -4.68406
------------------------------------------------------------------------------

. logit M_fusbp i.group i.ethnicity i.male age durationofdiabetes weight height i.diag_af
>  i.diag_pvd i.diagnosissmoking diagnosischol diagnosishdl diagnosissysbp diagnosishba1c
>  i.currentsmoking currentchol currenthdl currentsysbp currenthba1c preexistingihd preex
> istingchf preexistingamp preexistingblind preexistingrenal preexistingstroke preexistin
> gmi

note: 2.ethnicity != 0 predicts failure perfectly
      2.ethnicity dropped and 11 obs not used

note: preexistingstroke != 0 predicts failure perfectly
      preexistingstroke dropped and 18 obs not used

note: preexistingmi != 0 predicts failure perfectly
      preexistingmi dropped and 44 obs not used

note: durationofdiabetes omitted because of collinearity
note: 0.diag_af omitted because of collinearity
note: 0.diag_pvd omitted because of collinearity
note: 1.currentsmoking omitted because of collinearity
note: 2.currentsmoking omitted because of collinearity
note: currentchol omitted because of collinearity
note: currenthdl omitted because of collinearity
note: currentsysbp omitted because of collinearity
note: currenthba1c omitted because of collinearity
note: preexistingihd omitted because of collinearity
note: preexistingchf omitted because of collinearity
note: preexistingamp omitted because of collinearity
note: preexistingblind omitted because of collinearity
note: preexistingrenal omitted because of collinearity
Iteration 0:   log likelihood = -81.567845
Iteration 1:   log likelihood = -68.508296
Iteration 2:   log likelihood = -60.419285
Iteration 3:   log likelihood = -60.035641
Iteration 4:   log likelihood = -60.032374
Iteration 5:   log likelihood = -60.032374

Logistic regression                               Number of obs   =        767
                                                  LR chi2(12)     =      43.07
                                                  Prob > chi2     =     0.0000
Log likelihood = -60.032374                       Pseudo R2       =     0.2640

------------------------------------------------------------------------------
           M_fusbp |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
           2.group |  -.9131446    .605406    -1.51   0.131    -2.099719    .2734295
                   |
         ethnicity |
                2  |          0  (empty)
                3  |   4.315916   .9033088     4.78   0.000     2.545463    6.086368
                   |
            1.male |  -.8184545   .7601726    -1.08   0.282    -2.308365    .6714565
               age |   .0980135   .0456757     2.15   0.032     .0084907    .1875362
durationofdiabetes |          0  (omitted)
            weight |  -.0030261    .017827    -0.17   0.865    -.0379664    .0319142
            height |   1.316118   4.518181     0.29   0.771    -7.539354    10.17159
         0.diag_af |          0  (omitted)
        0.diag_pvd |          0  (omitted)
                   |
  diagnosissmoking |
                1  |    .352746   .8390663     0.42   0.674    -1.291794    1.997286
                2  |   1.800109   .7406252     2.43   0.015       .34851    3.251707
                   |
     diagnosischol |    .143628   .2561239     0.56   0.575    -.3583656    .6456216
      diagnosishdl |   1.000652    .861717     1.16   0.246    -.6882825    2.689586
    diagnosissysbp |   -.010975   .0163859    -0.67   0.503    -.0430907    .0211407
    diagnosishba1c |   .3939303   .1562118     2.52   0.012     .0877608    .7000999
                   |
    currentsmoking |
```

```
               1  |          0  (omitted)
               2  |          0  (omitted)
                  |
      currentchol |          0  (omitted)
       currenthdl |          0  (omitted)
     currentsysbp |          0  (omitted)
     currenthba1c |          0  (omitted)
   preexistingihd |          0  (omitted)
   preexistingchf |          0  (omitted)
   preexistingamp |          0  (omitted)
 preexistingblind |          0  (omitted)
 preexistingrenal |          0  (omitted)
preexistingstroke |          0  (omitted)
    preexistingmi |          0  (omitted)
            _cons |  -16.07387   8.862739    -1.81   0.070    -33.44452    1.296782
------------------------------------------------------------------------------

. logit M_fuhba1c i.group i.ethnicity i.male age durationofdiabetes weight height i.diag_
> af i.diag_pvd i.diagnosissmoking diagnosischol diagnosishdl diagnosissysbp diagnosishba
> 1c i.currentsmoking currentchol currenthdl currentsysbp currenthba1c preexistingihd pre
> existingchf preexistingamp preexistingblind preexistingrenal preexistingstroke preexist
> ingmi

note: 2.ethnicity != 0 predicts failure perfectly
      2.ethnicity dropped and 11 obs not used

note: preexistingmi != 0 predicts failure perfectly
      preexistingmi dropped and 47 obs not used

note: durationofdiabetes omitted because of collinearity
note: 0.diag_af omitted because of collinearity
note: 0.diag_pvd omitted because of collinearity
note: 1.currentsmoking omitted because of collinearity
note: 2.currentsmoking omitted because of collinearity
note: currentchol omitted because of collinearity
note: currenthdl omitted because of collinearity
note: currentsysbp omitted because of collinearity
note: currenthba1c omitted because of collinearity
note: preexistingihd omitted because of collinearity
note: preexistingchf omitted because of collinearity
note: preexistingamp omitted because of collinearity
note: preexistingblind omitted because of collinearity
note: preexistingrenal omitted because of collinearity
Iteration 0:   log likelihood = -136.75016
Iteration 1:   log likelihood = -133.02949
Iteration 2:   log likelihood = -118.99277
Iteration 3:   log likelihood = -118.70479
Iteration 4:   log likelihood = -118.70386
Iteration 5:   log likelihood = -118.70386

Logistic regression                             Number of obs   =        782
                                                LR chi2(13)     =      36.09
                                                Prob > chi2     =     0.0006
Log likelihood = -118.70386                     Pseudo R2       =     0.1320

------------------------------------------------------------------------------
         M_fuhba1c |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
           2.group |  -.0584053   .3870503    -0.15   0.880    -.8170098    .7001993
                   |
         ethnicity |
                2  |          0  (empty)
                3  |   3.242644   .6263551     5.18   0.000     2.015011    4.470277
                   |
            1.male |  -1.271986   .5590786    -2.28   0.023     -2.36776   -.1762125
               age |   .0834566   .0327163     2.55   0.011     .0193338    .1475794
durationofdiabetes |          0  (omitted)
            weight |   .0091622   .0123752     0.74   0.459    -.0150929    .0334172
            height |    4.75904   3.074451     1.55   0.122    -1.266772    10.78485
         0.diag_af |          0  (omitted)
        0.diag_pvd |          0  (omitted)
                   |
  diagnosissmoking |
                1  |   .4008047   .5096235     0.79   0.432    -.5980389    1.399648
                2  |   1.386312   .5194204     2.67   0.008     .3682664    2.404357
                   |
     diagnosischol |   .0333093   .1715088     0.19   0.846    -.3028419    .3694604
      diagnosishdl |   .5690557   .5785333     0.98   0.325    -.5648486     1.70296
    diagnosissysbp |   .0113376   .0096713     1.17   0.241    -.0076177     .030293
    diagnosishba1c |   .1466052   .1065584     1.38   0.169    -.0622454    .3554557
                   |
    currentsmoking |
                1  |          0  (omitted)
                2  |          0  (omitted)
```

```
                  |
       currentchol |          0  (omitted)
        currenthdl |          0  (omitted)
      currentsysbp |          0  (omitted)
      currenthba1c |          0  (omitted)
    preexistingihd |          0  (omitted)
    preexistingchf |          0  (omitted)
    preexistingamp |          0  (omitted)
  preexistingblind |          0  (omitted)
  preexistingrenal |          0  (omitted)
preexistingstroke |   .0277705   .1338047     0.21   0.836    -.2344818    .2900228
    preexistingmi |          0  (omitted)
            _cons |  -20.91242   6.064717    -3.45   0.001    -32.79905   -9.025794
------------------------------------------------------------------------------

.
. log close
      name:  <unnamed>
       log:  ExplorationofMissingness.smcl
  log type:  smcl
 closed on:  21 Feb 2017, 09:38:58
```

Appendix 5: Resource utilization according to intensive treatment (IT) and routine care (RC)



* number of annual contacts; ¬ number of annual prescriptions

Appendix 6: Adjusted means of annual primary costs according to Intensive Treatment and Routine Care in the years 1-5 #

		year 1		**year 2**		**year 3**		**year 4**		**year 5**		**overall**	
		mean	**(SE)**	**mean**	**(SE)**	**mean**	**(SE)**	**mean**	**(SE)**	**mean**	**(SE)**	**mean**	**(SE)**
Total *	IT	809.9	(92.1)	836.9	(92)	886.7	(91.9)	992.8	(92)	1005.1	(92.6)	906.3	(82.2)
	RC	688.0	(90.2)	706.9	(90.4)	847.0	(90.3)	871.2	(90.8)	958.3	(91.1)	814.3	(81)
	dif.	**122.0**	**(128.6)**	**130.0**	**(128.7)**	**39.7**	**(128.9)**	**121.5**	**(129.3)**	**46.8**	**(129.9)**	**92.0[a]**	**(115.4)[b]**
Total **	IT	794.2	(81.1)	822.7	(83.9)	867.2	(88.4)	972.8	(99.2)	1001.0	(102.8)	887.9	(80.7)
	RC	693.6	(69.3)	703.8	(70.5)	846.7	(84.7)	869.4	(87.5)	952.1	(96.1)	806.9	(72.3)
	dif.	**100.6**	**-**	**118.9**	**-**	**20.5**	**-**	**103.4**	**-**	**48.9**	**-**	**80.9**	**-**
Consultations (ADDITION) *	IT	273.1	(28.6)	241.3	(28.6)	275.1	(28.5)	285.0	(28.6)	257.3	(28.9)	266.4	(23.2)
	RC	241.5	(28.4)	232.4	(28.5)	216.6	(28.4)	231.3	(28.7)	264.5	(28.8)	237.2	(23.5)
	dif.	31.6	(40.1)	8.9	(40.2)	58.6	(40.3)	53.7	(40.5)	-7.1	(40.8)	29.1[c]	(33.0)[d]
Medication (ADDITION) *	IT	134.1	(21.3)	180.3	(21.3)	191.3	(21.3)	200.9	(21.3)	204.1	(21.4)	182.1	(19.9)
	RC	92.8	(21.6)	124.5	(21.6)	133.1	(21.6)	133.9	(21.7)	153.6	(21.7)	127.6	(20.4)
	dif.	41.3	(30.3)	55.7	(30.3)	58.2	(30.3)	67.0	(30.4)	50.5	(30.5)	54.6[e]	(28.5)[f]
Other primary care services*	IT	398.9	(71)	412.0	(70.9)	416.7	(70.9)	503.4	(71)	539.3	(71.4)	454.1	(63.8)
	RC	352.2	(69)	348.6	(69.1)	495.8	(69.1)	505.5	(69.4)	539.7	(69.6)	448.3	(62.3)
	dif.	46.7	(98.7)	63.4	(98.9)	-79.0	(99)	-2.1	(99.3)	-0.3	(99.8)	5.7	(89.1)

generalized linear regression models with a main effect for the intervention and for time since diagnosis and an interaction term between intervention and time; adjusted for sex and age of diagnosis and baseline HbA1c; accounted for patients being clustered in GP surgeries and observations clustered in patients

* GLM with Gaussian distribution and identity link; ** GLM Gamma distribution and log-link

Estimates used for long-term CE-model: *[a] ß total ; [b] SE total ; [c] ß consultation ; [d] SE consultation ; [e] ß medication ; [f] SE medication*

General note: due to the complex 3-level structure of the model estimates on single dimensions do not exactly sum up to the total cost ;