

# **Editorial**

## **From the Vulnerable Plaque to the Vulnerable Patient: Current Concepts in Atherosclerosis**

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Abbreviations: CAD – Coronary artery disease, CVD – cardiovascular disease, PCSK9 - Proprotein convertase subtilisin/kexin type 9, TCFA – Thin cap fibroatheroma, PET – Positron emission tomography, CT - Computed tomography, VSMC – vascular smooth muscle cells.

Cardiovascular disease affects a significant proportion of the population with global prevalence of 6081 per 100,000 (Virani et al., 2020). Most core risk factors are well characterized and can be controlled with interventions, also meaning it is possible to identify most people at increased risk of acute events, defined as a 10 year risk of events of >20% . However, the real world occurrence of events in this at risk population is relatively low suggesting there is still much to be learnt or identified in spotting the vulnerable patient harbouring vulnerable atherosclerotic plaque at the earliest possible time.

The development of atherosclerotic plaque spans people's lifetime. The risk of developing cardiovascular disease (CVD) can be estimated as a roughly equal balance of genetically inherited susceptibility and exposure to environmental risk factors. Increasingly, the complexity of coronary artery disease (CAD), as the archetypal CVD, is underlined by the fact that a large number of genes or gene sets comprising up to 14% of genes in the genome can be linked to functionally influencing CAD development (Nikpay, Soubeyrand, Tahmasbi & McPherson, 2020) through the association of genetic variants with CAD risk in large international cohorts. The majority of these variants play a small role (e.g. 2-5% effect size) (Howson et al., 2017) and so which novel gene products to target therapeutically remains a question that must be answered with future studies.

Atherosclerosis is almost universally present and is a long-standing pathology.

Fundamentally, plaque develops as a result of a maladaptive response of the artery wall and infiltrating immune cells to accumulation and modification of lipoprotein such as low density lipoprotein (LDL) and lipoprotein a (Lp(a)) (Lichtman, Binder, Tsimikas & Witztum, 2013). Well characterised risk factors in addition to the circulating LDL level are blood pressure, systemic inflammation, diabetes and obesity (Yusuf et al., 2004). Thus, the concept of vulnerable patients can be described as patients presenting with a combination of multiple risk factors and / or extremely high risk levels of one of these core risks (Naghavi et al., 2003). All these risk factors feed into the core interaction between LDL, vascular cells responding to the injurious accumulation and oxidative modification of LDL trapped in the sub-endothelial space, and invasion of myeloid cells and T cells that can either promote progression or resolution of plaque inflammation (reviewed in (Tabas & Lichtman, 2017)). In the last 30 years, a growing recognition that specific plaque characteristics making it prone to trigger thrombotic events are far more important clinically than absolute size or level of lumen occlusion (Finn, Nakano, Narula, Kolodgie & Virmani, 2010). For example, the majority of events in the SCOT-HEART study were not triggered by the presence of occlusive disease (Investigators et al., 2018). Thus, the concept of vulnerable plaques is the focus of endeavours in the field. This review series focuses on advances critical to the identification, mechanistic understanding and treatment of vulnerable patients and the vulnerable plaques that trigger adverse events. These articles were commissioned leading on from a British Atherosclerosis Society meeting entitled "From the vulnerable plaque to the vulnerable patient".

Vulnerable plaques are not all the same. Thin-cap fibroatheroma (TCFA), defined as a fibrous cap and evidence of macrophage infiltration, are prone to rupture. Another form of advanced plaque is prone rather to erosion. The increased use of statins has led to a shift from TCFA to plaque erosions over time (Libby & Pasterkamp, 2015). Originally defined by histology, defining vulnerable plaques in at risk (vulnerable) patients is now possible using a raft of imaging techniques including PET, CT, MRI and intravascular ultrasound. Characterising a patient's actual arteries is a powerful tool essential in formally quantifying the burden of disease. Now multiple modalities are available in the research setting and increasingly in routine clinical practice. Two complementary reviews from Sriranjana *et al* (Sriranjana, Tarkin, Evans, Le, Chowdhury & Rudd, 2019) and Daghm and Newby (Daghm

& Newby, 2019) review the use PET and CT in assessing vulnerable patients and defining vulnerable plaques.

Positron emission tomography utilises radiotracers binding molecular targets to gain a detailed characterisation of body tissues non-invasively. It has most extensively been used in oncology but with the development of instrumentation and availability of novel radiolabelled probes is now used in other areas including prominently in cardiovascular disease patients. PET enables labelling of, for example, glucose incorporation and the presence of macrophages. In their review, Sriranjana et al (Sriranjana, Tarkin, Evans, Le, Chowdhury & Rudd, 2019) discuss the advances in PET usage for assessing vulnerable plaques and the results of trials using PET imaging. Fluorodeoxy-glucose has been used both in prognostic investigations and in interventional trials, particularly in those aiming to target inflammation directly. The range of PET ligands used to investigate plaque characteristics is growing, and the leading candidates such as 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid]-D-Phe1,Tyr3-octreotate (DOTATATE) are discussed further in their review.

Computed tomography is an X-ray based technique for fine detail discrimination of tissue morphology. Daghem and Newby (Daghem & Newby, 2019) review the importance of CT in cardiology. The detection of calcification and its use in quantifying plaque burden has been a major breakthrough achieved with non-invasive imaging. Despite limitations in this method as a means to quantify disease burden, there is yet to be a CT study adding better prognostic value. New innovations and trials are building on developing the prognostic potential of CT, and its use in combination with PET.

Smooth muscle cells are central players in atherosclerosis. During the development of the disease, these cells transition from a quiescent layer of cells encased in elastin fibres maintaining vessel function to proliferative, matrix-secreting cells that contribute to both adverse and beneficial plaque processes (Basatemur, Jorgensen, Clarke, Bennett & Mallat, 2019). Harman and Jorgensen (Harman & Jorgensen, 2019) review the many important contributions of SMCs to plaque vulnerability, new techniques to understand and modify SMC functions and future modalities that could target them therapeutically. SMCs are now recognised to play a prominent and diverse set of roles in plaque formation, with differentiation into macrophage-like cells, osteoblasts and foam cells, and in adventitial regions, lymphoid tissue organiser cells (Hu et al., 2015) all possible. In terms of the critical process of plaque vulnerability, VSMCs play a unique role in secretin extracellular matrix that maintains the integrity of the fibrous cap. However, in addition to macrophages, VSMCs also produced matrix-degrading cytokines that might trigger cap thinning. VSMCs are thought to be key to calcification, which also has important consequence for plaque vulnerability. Harman and Jorgensen (Harman & Jorgensen, 2019) also elucidate novel techniques now available to track in more detail the lineage of plaque SMC-derived cells and in identifying the heterogeneity of the culprit VSMCs that actually respond to the early injury responses triggering plaque formation.

Vulnerable patients may develop multiple plaques with vulnerable features compared to those without, and so need more aggressive treatment at an earlier disease stage. LDL has proven an effective targeting modality; statins reduce the risk of events in multiple large trials and although may have some pleiotropic effects, the absolute reduction in LDL is strongly linked to the reduction of risk. However, side effects and lack of efficacy in some patients preclude the universal use of statins, and highlights the need for competitive alternatives. The growing recognition of lipoprotein (a) as an additional risk factor has meant drugs that can also target this are required and under evaluation (Tsimikas, 2016). Familial hypercholesterolemia patients are among the most vulnerable, given the high lifetime burden

of exposure to LDL (FERENCE, Graham, Tokgozoglul & Catapano, 2018). PCSK9 regulates ldlr at the protein level and is now established as novel drug target to control atherogenic lipids. Nishikido and Ray (Nishikido & Ray, 2019) review the current state of the field of lipid lowering, how lipid targeting may be key in treating the vulnerable patient and the changes made possible with the discovery of PCSK9.

## **Conclusions**

Integration of imaging information on precursor lesions with systemic and genetic risk factors can help to build a more refined and personalized risk model for the vulnerable patient, and these innovative advances are coming online with increasing pace. However, studies suggest that event-triggering thrombosis following a plaque rupture may actually be relatively rare, and that many rupture events are clinically silent and lead to establishment of a more stable 'healed' plaque phenotype (Sriranjan, Tarkin, Evans, Le, Chowdhury & Rudd, 2019). We need more work to pinpoint the truly vulnerable plaque.

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