Editorial

The Effect of Drugs and Genetic Factors on the Development and Progression of the Atherosclerotic Process

Cardiovascular (CV) disease (*e.g*. Coronary Heart Disease (CHD) and stroke) is a leading cause of morbidity and mortality in both the developing and developed world [1].

Multiple risk factors are associated with an increased risk of CV events [1]. Besides traditional risk factors, such as dyslipidaemia, hypertension, Diabetes Mellitus (DM), obesity, abdominal obesity and smoking, several genetic and epigenetic factors are also involved [2, 3]. However, causality has only been shown for some of these risk factors [2, 3].

Regarding dyslipidaemia, the most extensively studied variable is Low-Density Lipoprotein Cholesterol (LDL-C) [2, 4-8]. Evidence for LDL-C causality is derived from genetic, epidemiologic and clinical intervention studies [2, 4-8].

Inherited disorders provide important evidence for LDL-C causality in CHD. In Familial Hypercholesterolaemia (FH), one of the most prevalent forms of inherited disorders of lipid metabolism, the extent of atherosclerosis and the risk of CV events, are proportional to both the absolute magnitude and the duration of exposure to elevated LDL-C levels [4]. Mendelian randomization studies have also consistently demonstrated that variants in over 50 genes coding for lower LDL-C levels are associated with a correspondingly lower risk of CHD [5, 6].

The Prospective Studies Collaboration [7], a large prospective epidemiologic study, reported a meta-analysis of 892,337 persons without CV disease at baseline who had been enrolled in 61 prospective cohort studies during which 33,744 CHD deaths accrued over nearly 12 million person-years of follow-up. This meta-analysis reported a strong, graded log-linear association between total plasma cholesterol and CHD mortality [7].

Probably the strongest evidence for causality derives from randomized clinical trials. In one of the largest meta-analysis of individual-participant data from 26 statin trials enrolling almost 170,000 individuals, treatment with a statin was associated with a log-linear 22% proportional reduction in the risk of major CV events per mmol/l reduction in LDL-C [8].

Undoubtedly, there is a need for a translation of genetic studies from the research field into every day clinical practice. In this context, the review by Peterlin, *et al*. [9] is focused on monogenic disorders associated with dyslipidaemia and atherosclerosis. The authors discuss the application of new genomic technologies as a potential effective screening tool for identifying individuals with a high risk of developing atherosclerosis.

One of the strongest predictors of CHD is DM [1]. The incidence of DM has been increasing in the last decades and this trend is expected to continue [10]. It is important to consider that patients with type 2 DM (T2DM) have a >10-fold risk of CV disease in their lifetime [11]. In T2DM, hyperglycaemia and insulin resistance progressively lead to both microvascular and macrovascular complications [10, 11]. Whereas the incidence of microvascular complications is closely related to tight glycaemic control, this does not apply to macrovascular complications [11, 12]. Hyperglycaemia influences many interweaving molecular pathways that lead to increased oxidative stress, increased inflammation and endothelial dysfunction [13].

Other risk factors, such as hypertension and dyslipidaemia, also play an important role in the progression of macrovascular complications. All these effects accumulate and lead to functional and structural arterial wall damage leading to major CV events [11]. The pathogenesis of atherosclerosis and macrovascular complications in DM were considered in the review by Lunder, Janić and Šabovič [13]. They covered different protective effects of current treatment approaches to prevent deleterious effects on the arterial wall. It seems that directly treating impaired arterial wall function (*e.g*. endothelial dysfunction and arterial stiffness), in addition to managing traditional risk CV factors, might be a more effective approach and could contribute to better prevention of macrovascular complications in diabetic patients [14, 15].

Genetic and epigenetic factors should not be neglected since on the basis of family and twin studies, the heritability of CHD was estimated to be between 40-60% [16]. Additional important data demonstrating the importance of genetics came from candidate gene studies and Genome-Wide Association Studies (GWAS) [3]. The largest contribution to the field so far was provided by the Cardiogram study involving 22,233 cases of CHD and 64,762 controls [5]. The vast majority of genes at loci that

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have been identified are novel, with no known connection to atherosclerosis [3]. The GWAS-identified polymorphisms are themselves rarely causal but rather in linkage disequilibrium with a neighbouring causal polymorphism. Moreover, the currently known gene loci explain only a small portion (<30%) of the genetic variability of atherosclerosis and its risk factors [3]. Of particular importance is the contribution of genetic variants to atherosclerosis in patients with DM (T1DM and T2DM). The importance of genetic variants (genetic markers) that contribute to the pathobiology of subclinical atherosclerosis in the setting of T2DM was covered in the review by Ramuš-Mankoč and Petrovič [17].

Despite the recent success of GWAS, close to 80% of the estimated heritability of CHD remains unknown [18]. Some of this missing heritability may be the result of gene environment interaction where the effect of a given genetic variant is only manifested in the presence of a modifier, such as obesity or cigarette smoking [18]. Interestingly, GWAS and candidate gene studies have identified an overlap between the genetics of T2DM and CVD, and the genetics of diabetic macrovascular complications [19].

Although traditional risk factors remain important, the application of genetic and epigenetic data and the use of a high-throughput methodology have demonstrated a significant role of genes and genetic pathways relevant to vessel wall biology [3]. Additionally, pharmacogenetics also has an emerging role in the evaluation of patients with CV diseases. Pharmacogenetics is the study of how the actions of and reactions to the drugs vary with the patient's genes. In their review, Machal and Hlinomaz [20] discussed the usefulness of pharmacogenomics for the optimal selection of P2Y12 inhibitors (clopidogrel, prasugrel and ticagrelor) for patients with acute coronary syndrome.

It is becoming clear that treatment should be aimed at improving arterial wall dysfunction [14, 15, 21]. Moreover, the findings of Mendelian randomization studies suggest that the causal effect of LDL-C on the risk of atherosclerotic CV disease is determined by both the absolute magnitude and the cumulative duration of exposure to LDL-C [22]. Because the effect of LDL-C on the risk of atherosclerotic CV disease appears to be cumulative over time, lowering the LDL-C level earlier may result in a greater reduction in the lifetime risk of atherosclerotic cardiovascular disease compared with that which is estimated in short-term trials [22]. In their review, Lunder, Janić and Šabovič [13] discussed why treatment should be focused directly on the arterial wall to prevent CV complications in patients with DM and why current therapeutic approaches may be insufficient.

In another review, Wang and Head [23] focused on the pathophysiology of stroke at a cellular level with special emphasis on the membrane protein caveolin-1 and its potential therapeutic role in recovery following stroke. Additionally, the role of novel anticoagulants in the treatment of atherosclerosis was reviewed by Fabjan and Bajrović [24].

To conclude, atherosclerosis and its clinical manifestations are complex disorders affected by external (environment, drugs) and internal (genetics, epigenetics) factors. Hopefully, a personalized approach using different "omic" technologies will optimize the efficacy of drug treatment, and pharmacogenetics are expected to play an important role in this regard.

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Mišo Šabovič
(*Guest Editor*)
Department of Vascular Diseases
Ljubljana University Medical Center
Zaloška cesta 7
SI-1000 Ljubljana
Slovenia
E-mail: miso.sabovic@kclj.si

Daniel Petrovič
(*Guest Editor*)
Institute of Histology and Embryology
Faculty of Medicine
University of Ljubljana,
Ljubljana
Slovenia
E-mail: daniel.petrovic@mf.uni-lj.si