Archives of Cardiovascular Disease (2019) 112, 455—458

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SCIENTIFIC EDITORIAL

Proprotein convertase subtilisin/kexin type 9 inhibitors: New insights into cardiovascular atherosclerotic pathophysiology with therapeutic implications

Les inhibiteurs PCSK9 réceptions sur la pathophysiologie de l'athérosclérose: implications thérapeutiques

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Received 4 April 2019; received in revised form 25 June 2019; accepted 25 June 2019
Available online 5 September 2019

KEYWORDS
Familial hypercholesterolaemia;
Low-density lipoprotein cholesterol;
Low-density lipoprotein receptor;
Proprotein convertase subtilisin/kexin type 9;
PCSK9 inhibitors ;

MOTS CLÉS
Hypercholestérolémie familiale ;
Lipoprotéines de basse densité cholestérol ;
Lipoprotéines de basse densité récepteurs ;
PCSK9 inhibiteurs ;
Rétrécissement aortique

Background

Efforts towards winning the fight against coronary artery disease are ongoing. Although major advances have been made, as Angoulvant and Bejan—Angoulvant [1] have pointed out, ''the best is yet to come''.

Among the medical achievements, statin therapy—which results in marked reductions in total and low-density lipoprotein cholesterol (LDL-C), as per current recommendations—ranks high [2]. However, even with intensive statin treatment and the addition of ezetimibe [3], which is gaining ground but is still underutilized, we still 'cannot remove atherosclerotic plaques from coronary arteries' [1,4]. Moreover, only 23.6% of patients in the CORONOR study [4] with high plasma LDL-C achieved guideline-recommended levels of LDL-C [5] with

Abbreviations: LDL-C, Low-Density Lipoprotein Cholesterol; LDLR, Low-Density Lipoprotein Receptor; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9.

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https://doi.org/10.1016/j.acvd.2019.06.003

lipid-lowering therapy. In fact, Urban et al. [6] very pertinently mention that, in Europe and Canada, nearly 50% of hypercholesterolaemic patients do not reach desirable levels because of inadequate statin dosing due to adverse effects, statin resistance or insufficient adherence. Poor adherence can partially be explained by concerns and doubts still expressed in the lay literature despite the use of statins since 1986. Thus, many specialists suggest the addition of one of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on top of routine lipid-lowering treatment, or in patients with statin intolerance [7,8]. As well as LDL-C lowering, PCSK9 inhibitors may also exert pleiotropic effects — as will be further described — and PCSK9 could be a key molecule in the pathophysiology of atherosclerosis.

What is PCSK9? Association with clinical conditions

PCSK9 is a serine proprotein that was discovered in 2003. It is expressed in higher concentrations in the liver, kidney, brain and the small intestine [7,8]. Its main action is to reduce the concentration of low-density lipoprotein receptors (LDLR) in hepatocytes by directing them into the lysosome for degradation [9]. It has been found that circulating PCSK9 levels predict future risk of cardiovascular events independently of established risk factors [9]. PCSK9 level is considered to be a predictor of carotid atherosclerosis [10] and has been significantly correlated to plasma LDL-C levels [11]. Zhu et al. [12] have observed that body mass index, insulin, LDL-C and triglycerides are independent predictors of PCSK9 levels. In contrast, Arsenault et al. [13] did not find any association between plasma PCSK9 levels and body mass index or body fat distribution indices, but did identify a modest association with markers of insulin resistance. In the ATHEROREMO-IVUS study [14], PCSK9 levels were associated with an increased incidence of death and acute coronary syndromes independently of LDL-C levels or statin use.

In humans, single-point gain of function mutations in the PCSK9 gene are associated with autosomal dominant hypercholesterolaemia [7], while loss of function mutations are associated with low plasma LDL-C levels [15,16]. In intravascular coronary artery ultrasound studies, the main finding was that increased serum PCSK9 levels were linearly associated with an increased necrotic core fraction in the coronary arteries, independently of serum LDL-C levels [14].

PCSK9 and myocardial infarction

Interestingly, in male rats, plasma PCSK9 levels were increased from 12 to 96 hours and hepatic PCSK9 messenger ribonucleic acid expression was upregulated after an experimental myocardial infarction [17]. Similar results have been observed in humans [18]. Ding et al. [19] have reported that PCSK9 is upregulated in ischaemic myocardium — particularly in the zone bordering the infarct area — after an experimental infarction in murine hearts [19]. They also found that its inhibition reduced infarct size. Further, PCSK9 levels have been positively related to poorer outcomes in heart failure patients [20].

PCSK9 in aortic stenosis

Calcific aortic stenosis is the most common valvular disorder of the elderly. In a cross-sectional study of 40 patients, Wang et al. [21] found that plasma PCSK9 correlates with the presence of calcific aortic valve disease but not its severity. The authors postulated that PCSK9 inhibition may be more efficacious in this entity than statin therapy, which has — up to now — been disappointing.

Higher PCSK9 levels have also been found in patients with degeneration of aortic bioprostheses [22]. Further, Poggio et al. [23] have actually detected PCSK9 in stenotic aortic valves explanted at surgery.

In vitro effects of PCSK9 — a direct influence? Do pleiotropic actions exist?

Lambert et al. [24] grew primary fibroblasts isolated from the forearm skin biopsy of four patients carrying LDLR molecular defects. Mevastatin treatment increased LDLR expression, which was significantly lowered after the addition of recombinant PCSK9 [24]. Walley et al. [25] also added recombinant human PCSK9 to immortalized human hepatocytes and observed that it can regulate removal of pathogen lipids such as lipopolysaccharide via LDLR. Kysenius et al. [26] found that PCSK9 knockdown reduced the death of potassium-deprived cerebellar granule neurons. These data suggest that PCSK9 could be added to cardiomyocyte or vascular tissue for evaluation of a direct action (apoptosis and vulnerability). Moreover, experiments with cultured aortic human vascular endothelial cells and smooth muscle cells have revealed a positive-feedback loop between lectin-like ox-LDL receptor-1 and PCSK9, such that induction of one will be stabilized by reciprocal induction of the other [27]. Thus, inhibition of PCSK9 reduces the expression of proinflammatory molecules, expression of membrane adhesive molecules and macrophage accumulation [28].

The discussion of the possible pleiotropic effects of PSCK9 inhibitors in addition to their LDL-C-lowering effects is parallel to that concerning statins some years ago. Thus, direct actions of PCSK9 inhibitors can affect inflammation (although they do not affect C-reactive protein), oxidation and vascular smooth muscle cell de-differentiation, migration and proliferation inhibition of autophagy as well as platelet reactivity [29].

Back in 2009, Davignon and Dubuc [30] underlined that PCSK9 levels increased with statins, with a further augmentation noted when ezetimibe was added. Interestingly, fenofibrate decreases serum PCSK9 together with very low-density lipoprotein particles in statin-treated patients with type 2 diabetes [31], although Troutt et al. [32] found that fenofibrate may increase these levels. These findings lead to the postulation that the addition of PCSK9 inhibitors to statins would be advantageous beyond further lowering LDL-C levels. Bandyopadhyay et al. [33] have given another possible explanation, namely that loss of function of PCSK9 results in further increases in surface LDLR, which increases

the LDLR activity induced by statins. This important mechanism is scarcely, if at all, noted in various reviews on PCSK9 inhibition. For example, in a 2019 clinical commentary, Banach and Penson [34], when discussing the encouraging results of the ODYSSEY and FOURIER trials, focus on the lipid-lowering effects of PCSK9 inhibitors without mentioning the importance of PCSK9 itself.

Walley et al. [25] have reported that PCSK9 inhibitors may improve septic shock outcomes. Conversely, inflammation (specifically lipopolysaccharide) increases PCSK9 levels [26]. Akram et al. [8] have offered the same hypothesis. Further, a recent position paper from the Working Group on Atherosclerosis and Vascular Biology of the European Society of Cardiology has suggested that PCSK9 inhibitors have anti-inflammatory effects [35].

Some concerns have been raised regarding possible deleterious effects of PCSK9 inhibitors, such as neurocognitive abnormalities and Alzheimer's disease, although these remain controversial. It should be remembered that PCSK9 inhibitors do not cross the blood — brain barrier. Also, that their effects on fatty liver disease and glucose tolerance are still under investigation [33].

Will PCSK9 inhibitors predominate in atherosclerosis prevention?

We think that it is too early to provide a definite answer to this question. Of note, PCSK9 inhibitors have been given in addition to statin and/or ezetimibe treatment in the majority of studies. Actually, in the ODYSSEY and FOURIER trials [34], high- or moderate/low-intensity statins were used 97.4% and 99.7% respectively. It should not be forgotten that PCSK9 inhibitors are the only class of drugs that have been reported to lower lipoprotein(a) levels [33]. The two currently used PCSK9 inhibitors—evolocumab and alirocumab—have similar LDL-C-lowering potency. It is not known whether they differ in their actions on internal and external pathways. However, as they are both monoclonal antibodies it would be surprising if their action differed, and they are both known to bind extracellular PCSK9. Other non-monoclonal antibody approaches might utilize alternative strategies to inhibit intracellular PCSK9.

Whether PCSK9 inhibitors may ever replace statins as a sole treatment is too premature to venture. It should be remembered that PCSK9 inhibitors have been used for a relatively short period of time compared with over 30 years of statin use. To date, several large trials have been conducted, but fewer patients have been enrolled in PCSK9 inhibitor trials than in statin trials. Obviously, more trials are needed. A shift is developing from using PCSK9 inhibitors only in familial hypercholesterolaemia towards its use in classes of patients with less severe clinical conditions. This is expected to provide more data and give more information on the roles of PCSK9 and its inhibitors beyond LDL-C lowering, which would shed further light on the possible importance of their pleiotropic effects.

There is, however, no doubt that PCSK9 inhibitors are a promising class of drugs for the prevention and treatment of atherosclerosis, and possibly also aortic stenosis. Importantly, they open new pathways of research for other modalities of anti-PCSK9 therapy.

Funding

The authors received no financial support for the research, authorship, or publication of this article.

Disclosure of interest

The authors declare that they have no competing interest.

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