PCSK9 in Haemostasis and Thrombosis: Possible Pleiotropic Effects of PCSK9 Inhibitors in Cardiovascular Prevention

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Abstract
Since increased cholesterol levels are crucial in determining the development of atheroma, their reduction represents a mainstay in primary and secondary cardiovascular prevention. The most recent spectacular advancement in cholesterol-lowering therapy is represented by proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors. Although their benefit over currently available treatments has been ascribed primarily to their strong low-density lipoprotein (LDL)-cholesterol reducing action, several clues suggest that PCSK9 inhibitors may also influence platelet function and blood coagulation. PCSK9 knockout mice develop less venous and arterial thrombosis and showed reduced in vivo platelet activation upon arterial injury. In patients with acute coronary syndromes (ACSs) treated with P2Y12 inhibitors, a direct association between PCSK9 serum levels and residual platelet reactivity was found. A direct correlation between urinary excretion of 11-dehydro-thromboxane-B2, a marker of in vivo platelet activation, and circulating PCSK9 levels was reported in patients with atrial fibrillation. Moreover, recombinant human PCSK9 added in vitro to human platelets potentiated activation induced by weak agonists. Finally, blood clotting factor VIII (FVIII), which is associated with stroke and ACS risk, is cleared from the circulation by members of the LDL receptor (LDLR) family. Given that PCSK9 degrades LDLR, it is conceivable that PCSK9 inhibitors by enhancing the expression of LDLR may slightly decrease circulating FVIII, in this way contributing to the prevention of cardiovascular events. This review aims to discuss the possible and hypothetical interactions between PCSK9 and the haemostatic system and to examine the possible pleiotropic effects of PCSK9 inhibitors in cardiovascular prevention.

Keywords
► atherothrombosis
► CD36
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► FVIII
► LOX-1

PCSK9, Lipid Metabolism and Cardiovascular Risk
Cholesterol is transported in the bloodstream by lipoprotein particles. The two major cholesterol-carrying lipoproteins are low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs). LDLs, whose main protein fraction is apolipoprotein B100, transport cholesterol from the liver to peripheral tissues, including the arterial walls.¹ LDLs are a major determinant of atherosclerosis, and both American and European guidelines recommend specific LDL threshold reductions to prevent cardiovascular events.² On the other hand, HDLs, whose main protein fraction is apolipoprotein A-I, transport cholesterol from peripheral tissues to the liver, facilitating its clearance.³ Circulating cholesterol levels are regulated by the balance between their biosynthesis and
clearance. The rate-limiting step in cholesterol biosynthesis is the conversion of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) into mevalonate catalyzed by HMG-CoA reductase, which represents the pharmacologic target of statins, the most widely used cholesterol-lowering agents. LDL clearance takes place via specific LDL receptors (LDLRs) in the liver which bind apolipoprotein B100 forming a complex which is internalized. The LDL component of the complex is then degraded by lysosomal enzymes, while LDLR are recycled to the cell membrane to bind other LDL particles. The expression of LDLR on the hepatocyte surface is regulated by intracellular cholesterol levels, with lower intracellular cholesterol levels leading to increased surface LDLR, and vice versa. LDLRs are also regulated by proprotein convertase subtilisin/kexin type-9 (PCSK9), originally called Narc-1, an enzyme which fosters their degradation. PCSK9 is mainly synthesized by the liver, but also by the brain, kidney, intestine, pancreas and steroideal tissue, and is found both in the intra- and extracellular space. Extracellularly, PCSK9 binds the first epidermal growth factor-like repeat of LDLR forming a tri-molecular complex (LDLR-LDL-PCSK9) which is then internalized. Once inside the hepatocyte, PCSK9 prevents LDLR from escaping lysosomal degradation, and therefore to recycle to the cell surface, thus reducing their expression. Intracellularly, PCSK9 binds nascent LDLR and targets them to lysosomes where they are degraded. The expression of LDLR on the hepatocyte surface is regulated by intracellular cholesterol levels, with lower intracellular cholesterol levels leading to increased surface LDLR, and vice versa. LDLRs are also regulated by proprotein convertase subtilisin/kexin type-9 (PCSK9), originally called Narc-1, an enzyme which fosters their degradation. PCSK9 is mainly synthesized by the liver, but also by the brain, kidney, intestine, pancreas and steroideal tissue, and is found both in the intra- and extracellular space. Extracellularly, PCSK9 binds the first epidermal growth factor-like repeat of LDLR forming a tri-molecular complex (LDLR-LDL-PCSK9) which is then internalized. Once inside the hepatocyte, PCSK9 prevents LDLR from escaping lysosomal degradation, and therefore to recycle to the cell surface, thus reducing their expression. Intracellularly, PCSK9 binds nascent LDLR and targets them to lysosomes where they are degraded. The expression of PCSK9 in mice caused a striking increase in plasma cholesterol. Since the discovery of the important role of PCSK9 in lipid metabolism, numerous approaches to its inhibition have been attempted, leading to the development of monoclonal antibodies (MoAbs) blocking its extracellular action, probably the most relevant for the regulation of circulating cholesterol levels. Several phase III trials with anti-PCSK9 MoAb have been performed in patients with hypercholesterolemia and high cardiovascular risk and, based on their positive results in terms of safety and efficacy, two fully humanized anti-PCSK9 MoAbs, alirocumab and evolocumab, have received Food and Drug Administration (FDA) and European Medicines Agency approval in 2015 as a second line treatment, in addition to diet and maximally tolerated statin therapy, to lower LDL-c in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease who require additional LDL-c lowering. Recently, based on the results of the landmark FOURIER trial, the FDA has approved evolocumab also to prevent heart attacks, strokes and coronary revascularization in adults with established cardiovascular disease. In this trial, including more than 27,000 high-risk patients with atherosclerotic cardiovascular disease with a LDL-c of ≥70 mg/dL who were receiving statin therapy, subjects randomized to evolocumab showed a significantly lower incidence of major adverse cardiovascular events compared with those randomized to placebo. Moreover, a meta-analysis of 24 phase II and phase III trials involving 10,159 adults with hyperchloesterolaemia, on statin treatment or not, has shown that anti-PCSK9 MoAbs significantly reduce all-cause mortality compared with no anti-PCSK9 treatment (odds ratio [OR], 0.45 [95% confidence interval Cl, 0.23–0.86], p = 0.015). Thus, PCSK9 inhibitors appear to be a very effective strategy to prevent cardiovascular events.

**Pleiotropic Effects of Lipid-Lowering Interventions**

Since the detrimental effect of LDL-c on the cardiovascular system is concentration-dependent, the reduction of ischemic cardiovascular events produced by PCSK9 inhibitors when added to statins has been ascribed primarily to their further, strong LDL-c-lowering action.

However, statins may exert cardiovascular protective actions independent from LDL-c lowering which have been called pleiotropic effects. The reduction of cardiovascular events attained with statins in some clinical trials, like the JUPITER trial, has been indeed greater than that expected solely from LDL-c reduction. In fact, cholesterol-independent beneficial effects of statins on the cardiovascular system, such as the stabilization of atherosclerotic plaques, reversal of endothelial dysfunction, blunting of inflammation, enhancement of fibrinolysis and inhibition of platelet activation and blood coagulation, have been well documented.

On the other hand, in a recent meta-analysis of trials with lipid-lowering interventions including more than 300,000 patients, the relative risk reduction of major vascular events associated with PCSK9 inhibitors use was higher, even if not significantly, than that observed with statins for the same LDL-c reduction (OR, 0.49 [95% CI, 0.34–0.71] vs. 0.61 [95% CI, 0.58–0.65]). Reasons advocated for this observation are the raising activity on anti-atherogenic HDL and the ability to reduce lipoprotein (a) [Lp(a)] of PCSK9 inhibitors. However, pleiotropic effects of PCSK9 inhibitors independent from lipid metabolism can also be considered.

Indeed, many pre-clinical and clinical data support the hypothesis that the cardiovascular protective effect of PCSK9 inhibitors may be more complex, involving mechanisms which go beyond their lipid-lowering action, several of which may affect the haemostatic system.

**Hints for Pleiotropic Effects of PCSK9 on Haemostasis and Thrombosis**

Haemostasis begins at a vascular injury site with platelet adhesion and aggregation (primary haemostasis), followed by the activation cascade of clotting factors (secondary haemostasis). Thrombosis, which can be considered an excessive extension of a haemostatic reaction, occurs in the arterial and venous vascular beds by mechanisms which differ in relation to the anatomical and rheological characteristics of these two systems. In arteries, thrombosis originates from the rupture of atherosclerotic lesions and is mainly generated by platelet
activation,\textsuperscript{28} while in veins, thrombi are mainly the consequence of clotting activation favoured by stasis, hypercoagulability and endothelial damage.\textsuperscript{29} However, several recent observations suggest that these two pathways contribute to both arterial and venous thrombosis. In fact, risk factors for ischaemic cardiovascular disease, among which hyperlipidaemia, induce endothelial dysfunction in both the arterial and venous vascular beds, leading to the development of either arterial or venous thrombosis depending on the concomitant inciting conditions.\textsuperscript{30,31}

**Studies in Animals**

The discovery of the central role played by PCSK9 in lipid metabolism has also been grounded on studies performed in gene-modified mice. The adenovirus-induced over-expression of PCSK9 in mice resulted in decreased hepatic LDLR expression with associated hypercholesterolaemia, whereas the deletion of the PCSK9 gene increased hepatic LDLR expression and reduced LDL-c circulation,\textsuperscript{11} recapitulating the phenotypes of gain- or loss-of-function PCSK9 variants in humans.

Interestingly, PCSK9\textsuperscript{-/-} mice showed a reduction of FeCl\textsubscript{3} injury-induced carotid artery thrombosis, with the formation of unstable non-occlusive thrombi,\textsuperscript{32} suggesting an impaired platelet function. Indeed, in these mice the activation of circulating platelets provoked by arterial injury, shown by increased glycoprotein (GP) IIb/IIIa activation, P-selectin expression and circulating platelet-leukocyte aggregates, was strikingly reduced as compared with control mice.\textsuperscript{32} It cannot be disregarded, however, that the assessment of in vivo platelet activation in mice by the measurement of these biomarkers may be prone to errors.\textsuperscript{33}

Moreover, the hypercoagulable state induced by sepsis was exacerbated in PCSK9 over-expressing mice, as shown by enhanced thrombin–antithrombin complexes and reduced protein C plasma levels,\textsuperscript{34} suggesting that changes in PCSK9 may also have an impact on blood coagulation.

Indeed, PCSK9\textsuperscript{-/-} mice developed significantly smaller venous thrombi as compared with wild-type mice after inferior vena cava ligation.\textsuperscript{35} Plasma factor VIII (FVIII) levels are known to modulate venous thrombosis in mice,\textsuperscript{36,37} and there are theoretical reasons to suppose that PCSK9 may modulate circulating FVIII levels (see later); thus, although no blood clotting factor measurements were made in this study,\textsuperscript{35} it is conceivable that an effect on FVIII may have contributed to reduce venous thrombosis. On the other hand, plasma levels of soluble P-selectin (sP-selectin), a platelet and endothelial activation biomarker,\textsuperscript{38} were significantly lower in PCSK9-deficient than in control mice after the induction of vena cava thrombosis,\textsuperscript{35} further suggesting that PCSK9\textsuperscript{-/-} mice have impaired platelet function, but also that PCSK9 deletion may reduce endothelial activation. In this regard, it is interesting that increased circulating sP-selectin was observed in humans with unprovoked deep vein thrombosis who have endothelial dysfunction.\textsuperscript{30,31}

**Studies in Humans**

The possible role of PCSK9 in modulating platelet function has been assessed also in humans. In a prospective, observational study in patients with a recent acute coronary syndrome (ACS) undergoing percutaneous coronary intervention and receiving P2Y\textsubscript{12} inhibitors, the PCSK9-REACT study, a direct correlation between PCSK9 plasma levels and high-on-treatment platelet reactivity was observed, suggesting that PCSK9 enhances platelet activation.\textsuperscript{39} Indeed, recent observations have shown that human recombinant PCSK9 pre-incubated in vitro with platelets potentiates aggregation, P-selectin expression and GP\textsubscript{IIb/IIIa} activation induced by a weak agonist,\textsuperscript{32} acting therefore as a primer of platelet activation.\textsuperscript{40}

In this regard, it is interesting that twice as much PCSK9 was found to be contained in platelets from type 2 diabetes mellitus (T2DM) patients with coronary artery disease (CAD) than in platelets from healthy controls,\textsuperscript{41} suggesting that PCSK9 may be released during platelet activation and contribute to the well-established T2DM-associated platelet hyper-reactivity and impaired responsiveness to anti-platelet agents.\textsuperscript{42,43}

Human megakaryocytes express messenger ribonucleic acid (mRNA) for PCSK9, although at low levels (A.S. Weyrich and R.A. Campbell, University of Utah, personal communication), but this is not found in platelets.\textsuperscript{44} It can therefore be hypothesized that mRNA for PCSK9 is handled by megakaryocytes similarly to mRNA for matrix metalloproteinase-2, with mRNA not sorted into platelets but the protein present,\textsuperscript{45} even if only in a platelet sub-population,\textsuperscript{41} as already reported for tissue factor (TF)\textsuperscript{46} and endothelial nitric oxide synthase.\textsuperscript{37}

It was found that PCSK9 plasma levels positively correlate with the platelet count and plateletcrit in patients with stable CAD, further suggesting a link between PCSK9 and platelets in patients with coronary disease.\textsuperscript{48} Furthermore, PCSK9 plasma levels have been recently reported to increase during an acute coronary event,\textsuperscript{49} a condition associated with a striking bout of in vivo platelet activation,\textsuperscript{50,51} and to positively correlate with the severity of coronary artery lesions evaluated by the SYNTAX score.\textsuperscript{49} On the other hand, platelet reactivity in ACS correlates positively with the SYNTAX score,\textsuperscript{52} further suggesting a role of enhanced circulating PCSK9 in platelet hyper-reactivity. Moreover, activated platelets of patients with CAD release soluble sortilin\textsuperscript{53} which is known to facilitate PCSK9 secretion,\textsuperscript{54} making even more plausible the hypothesis of a positive feedback activation of platelets through PCSK9 during ACS.

A direct relationship between in vivo platelet activation and PCSK9 plasma levels has been reported also in atrial fibrillation. In this study, circulating PCSK9 correlated with urinary 11-dehydro- thromboxane B\textsubscript{2} excretion,\textsuperscript{55} an unbiased marker of in vivo platelet activation.\textsuperscript{56}

Several clues suggest that PCSK9 may also influence secondary haemostasis in humans. In fact, plasma levels of TF, a pro-coagulant glycoprotein triggering thrombin formation and playing a central role in atherothrombosis,\textsuperscript{57} positively correlated with plasma PCSK9 in patients with CAD and T2DM.\textsuperscript{58} Moreover, single nucleotide polymorphisms of the PCSK9 gene were shown to be associated with the development of thrombosis in carriers of anti-phospholipid antibodies,\textsuperscript{59} subjects characterized by a hypercoagulable state and in vivo platelet activation,\textsuperscript{60,61} confirming a link between PCSK9, platelets and blood coagulation.
Altogether, these data represent a strong hint that the association of PCSK9 with cardiovascular risk involves mechanisms that go beyond the mere regulation of circulating LDL-c and which include effects on the haemostatic system.

Modulation of Platelet Activation by Lipoproteins and the Possible Influence of PCSK9 Inhibitors

Dyslipidaemia may influence platelet reactivity and haemostasis by several mechanisms. Enhanced oxidative stress associated with high circulating LDL-c leads to the formation of oxidized-LDL (ox-LDL), which strongly contribute to inflammation-driven thrombosis by activating CD36 and LOX-1 receptors on platelets (►Fig. 1). CD36 is a member of the SRB-1 family which binds native- and ox-LDL and plays a role in thrombus formation, while LOX-1 (also called oLR-1) is a multi-ligand scavenger receptor whose expression is triggered by pro-inflammatory stimuli. In addition, activated platelets themselves oxidize LDL generating ox-LDL, in this way propagating platelet activation. Another mechanism by which dyslipidaemia may affect platelet reactivity is through the generation of lipid peroxide-modified phospholipids, which activate platelets by acting on Toll-like receptor 2.

Oxidized phospholipids are transported by Lp(a), and the latter may also directly activate platelets by not yet unravelled mechanisms.

Finally, HDL attenuate platelet function by interacting with the ApoER2 and SRB1 receptors, and also promoting cholesterol efflux from platelet membranes. Indeed, cholesterol incorporation in plasma membranes induces platelet hyper-sensitivity to stimuli, whereas its depletion strikingly reduces platelet reactivity. Moreover, HDL inhibit platelet fibrinogen binding and aggregation in response to thrombin via decreased formation of the second messengers diacylglycerol and inositol trisphosphate, and enhance platelet NO generation, thus increasing cyclic guanosine monophosphate, by acting on the apoER2 receptor. Finally, HDL also down-regulate the coagulation cascade and stimulate fibrinolysis.

Considering the above summarized mechanisms, PCSK9 inhibition may modulate the effects of lipoproteins on platelets at various levels, thus reducing platelet activation. By strikingly decreasing plasma LDL-c, PCSK9 inhibitors may deplete platelet membranes of cholesterol, thus reducing platelet reactivity and pro-coagulant activity. In this regard, it is interesting that treatment of hypercholesterolaemic subjects with rosuvastatin, a powerful cholesterol-lowering statin, reduced platelet membrane cholesterol, TF expression and generation of FXa.

Fig. 1 Hypothetical effects of proprotein convertase subtilisin/kexin type-9 (PCSK9) and its inhibition on platelets. (1) PCSK9 inhibition strikingly reduces low-density lipoprotein cholesterol (LDL-c) levels, thus potentially depleting platelet membranes of cholesterol, a mechanism reducing platelet reactivity. Moreover, the inhibition of platelet activation by PCSK9 inhibitors (2), a result of the various effects shown in the figure, may also reduce the ability of platelets to oxidize LDL thus decreasing the platelet stimulating activity of the latter through CD36 and LOX-1 receptors (3). Furthermore, PCSK9 inhibition reduces lipoprotein (a) [Lp(a)] levels, the main carriers of ox-phospholipids, thus potentially blunting their ability to activate platelets either through the TLR2 receptor (4) or directly (5). Finally, PCSK9 inhibition increases high-density lipoprotein (HDL) which reduces platelet activation acting on apoER2 and SRB1 receptors (6), and scavenging cholesterol from platelet membranes (7). +, stimulation; –, inhibition.
In addition, given that PCSK9 and LOX-1 positively influence the expression of each other, it can be envisaged that PCSK9 inhibitors may reduce platelet LOX-1.

Moreover, the blunting of platelet activation by PCSK9 inhibitors may decrease ox-LDL generation, interrupting the vicious circle that propagates platelet activation. Indeed, treatment of hypercholesterolaemic patients with alirocumab or evolocumab was shown to reduce platelet activation.

Finally, cell apoptosis is known to favour thrombosis, in part through the release of pro-coagulant microparticles, and PCSK9 was found to enhance apoptosis in vascular smooth muscle and endothelial cells. In this context, PCSK9 inhibitors, by mitigating apoptosis, might indirectly prevent thrombosis.

Regulation of FVIII Levels by LDLR and the Hypothetical Effect of PCSK9 Inhibitors

Blood clotting FVIII is a key plasma protein, encoded by a gene located on chromosome X, which plays a central role in coagulation. FVIII acts as a co-factor for FIX, thus favouring thrombin generation. FVIII is transported in the circulation by von Willebrand factor (VWF) which stabilizes it and reduces its clearance.

Epidemiologic studies have shown an association between increased FVIII plasma levels and arterial thrombosis, and elevated FVIII levels were found to correlate with a higher recurrence rate in patients with a prior myocardial infarction or ischaemic stroke. In contrast, haemophilia patients appear to be protected from ischaemic heart disease.

Experimental studies in animal models, although often involving the use of supra-physiologic concentrations, provide further evidence in support of the role of FVIII in arterial thrombosis. The increased risk of arterial thrombosis associated with enhanced FVIII levels is thought to be due to the combination of increased thrombin generation and enhanced platelet adhesion/aggregation, the latter being induced by the concomitant increase of VWF.

Circulating levels of FVIII are regulated by its biosynthesis and by its clearance through hepatic LDLR and lipoprotein receptor-related protein 1 (LRP1), both members of the LDLR family. In vivo has been confirmed by the strong elevation of circulating FVIII levels in LRP-deficient mice as well as in mice with adenovirus-mediated over-expression of receptor-associated protein, a chaperone for LRP1 which blocks the binding of all ligands to the receptor. On the other hand, LDLR plays a role in FVIII clearance too because the simultaneous deletion of the LDLR and LRP1 genes in mice (double LRP1/LDLR) further enhanced FVIII levels by 4.2-fold, while the

Fig. 2 Hypothetical effects of proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors on factor VIII (FVIII), von Willebrand factor (VWF) and tissue factor levels. Hepatic low-density lipoprotein receptor (LDLR) and lipoprotein receptor-related protein 1 (LRP1) are both involved in the clearance of FVIII and VWF by the liver. PCSK9 inhibitors enhance the expression of hepatic LDLR, and possibly also of LRP-1(1), by both intra- and extracellular mechanisms (2), thus potentially enhancing FVIII internalization and degradation leading to a decrease in FVIII plasma levels. Moreover, the possible enhancement of LRP1 by PCSK9 inhibitors in monocytes (3), might reduce circulating tissue factor (TF) through its accelerated clearance. +, stimulation; –, inhibition.
Several clues suggest that PCSK9 represents a major actor in cardiovascular disease, in part independently from its effects on lipid metabolism. Data from observational studies in humans and from experimental research in animals imply that PCSK9 may modulate both primary and secondary haemostasis either indirectly, through its effect on LDL-c, or directly by influencing platelet activation and plasma levels of FVIII. Previous observations, showing that the benefits of statins on cardiovascular events occur before any significant changes in lipid profile have taken place, have opened the way to a series of studies which unravelled several cholesterol-independent actions of this class of drugs, including the stabilization of atherosclerotic plaques, the improvement of endothelial function, the modulation of immune responses, the inhibition of oxidative stress and inflammation and the prevention of thrombosis. These studies not only lead to an advancement in our understanding of the role in inflammation in atherothrombosis, but also to the development of innovative therapeutic approaches targeting inflammation, like the anti-interleukin-1β MoAb canakinumab. A complete unravelling of the possible pleiotropic activities of PCSK9 inhibitors, and in particular of their possible anti-thrombotic effects, may potentially widen the indications for this new therapeutic class and clarify their potential role in the treatment of the acute phase of ischaemic cardiovascular disease. The recent publication of the ODYSSEY Trial shows that alirocumarb reduced cardiovascular events and mortality in patients with a recent acute coronary syndrome and not on target for LDL-c on statin therapy, confirming that PCSK9 inhibitor therapy has an important role in secondary cardiovascular prevention in patients at high risk.

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Conflict of Interest
None declared.

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Abbreviations: FVIII, factor VIII; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein (a); LRP1, lipoprotein receptor-related protein 1; TF, tissue factor; TFPI, tissue factor pathway inhibitor; PCSK9, proprotein convertase subtilisin/kexin type-9.


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