Emerging risk factors for venous thromboembolism: The role of commonly prescribed drugs for cardiovascular disease and inflammatory disorders

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Chapter 2

Statin therapy to revert hypercoagulability and prevent venous thromboembolism: a narrative review

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Summary

Venous thromboembolism (VTE) causes a major disease burden worldwide, so that effective preventive measures may be warranted. Although oral anticoagulation is effective in preventing VTE episodes, bleeding complications are a major concern that may lead to treatment avoidance. Statin therapy, which is widely used for prevention of arterial cardiovascular disease, is a promising alternative treatment for VTE prophylaxis, as the drug may affect hemostasis without increasing the risk of bleeding. In the past years, clinical studies have suggested that statins can interfere with blood coagulation and, in turn, reduce the risk of VTE. These effects, however, are still regarded with skepticism, as the underlying mechanisms by which statins may affect hemostasis in humans are not clear and data showing that statin therapy reduces VTE risk mostly came from observational studies, while only one randomized trial was conducted to evaluate this issue. In this review, we summarize the currently available evidence regarding the effect of statin therapy on coagulation and on VTE prevention. Recent randomized data show that statin therapy, in particular rosuvastatin, leads to decreased levels of coagulation factors in patients with prior VTE. This evidence provides a reasonable basis for interventional studies necessary to establish the efficacy of statins on reducing the risk of incident of recurrent VTE.

Keywords: blood coagulation, epidemiology, hydroxymethylglutaryl-CoA reductase inhibitors, prevention, venous thrombosis

INTRODUCTION

Venous thromboembolism (VTE) is a condition that comprises deep vein thrombosis (DVT), pulmonary embolism (PE) or both. The reported annual incidence of VTE ranges from 7.5 to 26.9 per 10,000 individuals in the population, with the highest rates being reported in the elderly [1]. In addition, VTE mortality rates range from 0.94 to 3.23 per 10,000 per year, varying across countries [2]. Due to the high incidence rates, associated disabilities and mortality, VTE causes a major disease burden worldwide [1], which underscores the necessity of effective preventive measures and adequate treatment.

Approximately 50-60% of VTE episodes are provoked by major risk factors, such as cancer, surgery, immobilization, estrogen therapy and pregnancy. Cases in which a transient or a persistent risk factor cannot be identified are categorized as unprovoked VTE [3, 4]. Because the risk of recurrent VTE is higher after an unprovoked event compared with a provoked one, categorizing VTE episodes is important to determine the duration of anticoagulation treatment [5]. After anticoagulation therapy is discontinued, the risk of VTE recurrence is up to 10% per year in patients with unprovoked VTE [6] and extended use of oral anticoagulants is associated with a 7-fold decrease in the risk of recurrent VTE [7, 8]. Prolonged oral anticoagulant therapy increases by 2-3 fold the risk of having a clinically significant bleeding episode compared with placebo [7, 8], which may result in treatment avoidance. Therefore, the search for new medications capable of decreasing VTE risk without increasing the risk of bleeding is warranted.

In this context, statins could be an alternative medication for VTE prophylaxis because they may have antithrombotic effect without causing bleeding complications [9]. Although results from the SPARCL trial [10] indicated that atorvastatin at 80 mg per day was associated with a 66% increase in the risk of hemorrhagic stroke compared to placebo (hazard ratio, 1.66; 95% confidence interval [CI] 1.08 to 2.55), these observations were not confirmed in other trials.[11-14] This suggests that results from SPARCL were due to a type I error. In the Heart Protection Study [11] no difference in hemorrhagic stroke was observed between simvastatin at 40 mg per day and placebo (incidence rate ratio, 0.95; 95% CI: 0.65 to 1.40). The JUPITER trial found no difference between rosuvastatin at 20 mg per day and placebo in the rates of intracranial hemorrhage [12] or other bleeding episodes [13]. A meta-analysis of randomized trials and observational studies [14] demonstrated that statins were not associated with an increased risk of intracerebral hemorrhage. The pooled risk ratio for bleeding on statin in randomized trials was 1.10 (95% CI: 0.86 to 1.41) and was 0.94 (95% CI: 0.81 to 1.10) in

cohort studies. Finally, the American Heart Association/American Stroke Association guidelines[15] state that there is insufficient data to recommend restrictions on use of statin agents for the management of intracerebral hemorrhage. In addition, long term use of statins, which is required for prophylactic treatments, is well tolerated and side effects are manageable [16].

Statins are widely used in patients with cardiovascular risk factors for prophylaxis of cardiovascular disease [17]. Since cardiovascular disease and VTE have some common risk factors, such as older age, male sex, smoking history, sedentary lifestyle, obesity and hypercoagulability [18-21], statins are frequently recommended anyway to patients requiring VTE prophylaxis. Thus, the possibility of using one single drug to prevent arterial cardiovascular diseases and VTE would diminish the pill burden associated with the use of several classes of drugs. Therefore, statin therapy could become an alternative treatment for VTE prophylaxis if statins are proven to downregulate hemostasis and prevent VTE episodes.

In this article, evidence of association between statins, hemostasis and VTE risk will be reviewed. For this purpose, we searched MEDLINE electronic databases to select the manuscripts. The searches combined the MESH terms related to the intervention (i.e., hydroxymethylglutaryl-CoA reductase inhibitors) and outcomes (i.e., hemostasis, blood coagulation, venous thromboembolism, embolism and thrombosis). Basic science studies and clinical studies, particularly meta-analysis and systemic reviews, were selected for this review.

THE EFFECT OF STATINS ON HEMOSTASIS

Statins are a class of drugs that decrease the serum levels of cholesterol through the inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. By inhibiting this enzyme, statins reduce the hepatocyte cholesterol content, thus promoting enhanced expression of low-density lipoprotein (LDL) receptors on the cell membrane. The increased expression of this receptor leads to increased receptor-mediated endocytosis of LDL and, in turn, to decreased serum levels of LDL [22].

Statin use decreases the risk of CVD not only because of the lipid lowering effect but also because of an anti-inflammatory effect.[23] Results from the JUPITER trial demonstrated that the risk of CV events decreased by 79% in participants who achieved the targets of hsCRP less than 1 mg/L and LDL cholesterol less than 1.8 mmol/L (hazard ratio 0.21, 95% CI: 0.09

to 0.51). While the CV risk reduction was 51% (hazard ratio 0.49, 95% CI: 0.37 to 0.66) in those who achieved only the target of LDL cholesterol [23].

Besides the lipid lowering and the anti-inflammatory effects, statins are alleged to have pleiotropic effect on the process of hemostasis. Basic research and clinical studies have investigated whether statins can interfere with platelet activity, coagulation, thrombin generation and fibrinolysis. These studies will be reviewed in this topic.

Effects of statins on platelet activity

Studies *in vitro* and in animal models have demonstrated that statins can decrease platelet activation by several mechanisms. Rosuvastatin was shown to inhibit platelet degranulation in rat models of myocardial infarction [24], and atorvastatin to decrease platelet activation and upregulate the synthesis of *nitric oxide* (NO) by platelets and endothelial cells in mice models of cerebral ischemia [25-27]. Pravastatin was shown to suppress platelet-dependent procoagulant activity *in vitro* by decreasing the expression of P-selectin and the deposition of tissue factor (TF), thrombin and fibrin on adherent platelets [28, 29].

The first clinical study that evaluated the effects of statins on platelet activity enrolled patients with hypercholesterolemia, and showed that pravastatin could affect platelet aggregation and platelet-dependent thrombin generation in association with reduced serum cholesterol levels [30]. Atorvastatin, simvastatin, fluvastatin and cerivastatin were also shown to reduce P-selectin levels [31] and platelet aggregation with different agonists, such as arachidonic acid [32, 33], ADP, collagen, and epinephrine [34, 35]. Conversely, the discontinuation of statins led to increased platelet activity [33]. In patients with hypercholesterolemia, the effect of statins on platelet aggregation seemed to occur in association with increased platelet-derived NO release, in a dose-dependent manner and independently of cholesterol-lowering effect [34]. In healthy individuals, use of simvastatin for 7 days led to a reduction in platelet aggregation triggered by arachidonic acid [36]. Although these studies point to an effect of statins on platelet activity, most of the data came from non-randomized studies, and therefore these results may be biased by confounding or due to regression to the mean.

In the STAtins Reduce Thrombophilia (START) trial, in which individuals with prior VTE were randomized to receive either rosuvastatin at 20 mg daily for 28 days or no intervention, rosuvastatin use had no effect on platelet activation mediated by thromboxane A_2

(TxA_2) [37]. Although the observations from this randomized controlled trial (RCT) do not confirm that rosuvastatin decreases platelet activation mediated by TxA_2, it is not possible to exclude potential other antiplatelet effects of rosuvastatin since other platelet function assays were not performed.

Effect of statins on coagulation

Evidence with regard to the effect of statins on coagulation was first demonstrated in the late 1990s and early 2000s. The first studies, performed *in vitro*, demonstrated that both simvastatin and fluvastatin were capable of reducing TF gene expression in human monocytes, endothelial cells and smooth muscle cells, in a dose dependent manner [38, 39]. Not only TF was suppressed but also thrombin formation could be inhibited by simvastatin *in vitro* [40]. Lovastatin, simvastatin and mevastatin were shown, *in vitro*, to enhance the activated protein C-mediated suppression of thrombin generation, in part via increased levels of thrombomodulin, in a concentration-dependent manner, that is dependent on inhibition of the Rho/Rho-kinase pathway [41]. Later on, the inhibitory effect of statins on TF expression was replicated *in vivo*. Studies in hyperlipidemic mice models, showed that statins diminished the expression of TF in atherosclerotic lesions and monocytes [42] independently of the reduction in plasma lipids [43, 44]. The mechanisms of statin-induced TF inhibition involved a direct inhibitory effect on Rho/Rho-kinase pathway and, in turn, TF expression [39, 45]. This lipid-independent mechanism was further confirmed in a study with a atherosclerotic rabbit model showing that fluvastatin directly interfered with the transcriptional activation of *TF* gene, by downregulating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway in endothelial cells [46]. Therefore, basic research studies consistently demonstrated that statins can downregulate TF expression [38, 39, 42] through a direct pathway, independent of the lipid-lowering mechanism [45, 46].

Clinical trials have also demonstrated that statin therapy, either with simvastatin [47], atorvastatin [48-50] or cerivastatin [35, 51] affects coagulation factors and thrombin generation, although the mechanisms behind these effects are less clear. The first study, published in 1997 [52] showed that simvastatin treatment decreased plasma levels of prothrombin fragment F1+2 (F1+2) by 35% and monocyte TF antigen and activity by 68% and 61% , respectively, in hypercholesterolemic patients. The effect of simvastatin and cerivastatin in reducing tissue factor pathway inhibitor (TFPI) and factor (F) VII was also demonstrated in

crossover studies [35, 51] and in a small randomized trial [53]. In an RCT aimed to compare atorvastatin with placebo in patients eligible for two-step carotid endarterectomy (CEA), atorvastatin reduced TF and TFPI antigen levels in blood (29% and 18% reduction respectively), and TF activity (56% reduction) in plaques removed at the second CEA, as compared with placebo [48]. Further clinical studies demonstrated that 12 weeks of atorvastatin therapy could lead to decreased FVII levels and activity [49, 50], coinciding with a decrease in the serum levels of LDL-cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and triglycerides [32]. The effect of statin on TF was also evaluated in individuals without dyslipidemia or cardiovascular disease. In a study of experimental endotoxemia, 20 healthy men were randomized to receive either simvastatin (80 mg/d) or placebo for 4 days before intravenous administration of l*ipopolysaccharide*s (LPS). Simvastatin premedication attenuated the increase in monocyte TF expression and reduced the formation of F1+2 in response to LPS without affecting platelet aggregation [54].

The effect of statin therapies on FV [55-57], von Willebrand factor (VWF) [55, 58, 59], and natural anticoagulants [59] has also been reported in several studies [55-59]. Two small clinical studies performed in patients with cardiovascular disease [56, 57] showed that early simvastatin therapy decreased FVa generation and increased FVa inactivation by protein C in blood samples collected from sites of microvascular injury (bleeding-time wounds). Simvastatin and pravastatin reduced VWF levels in patients with hypercholesterolemia after 3 months of therapy. In a clinical trial, 45 patients with unstable angina were randomized to receive either atorvastatin or placebo for 6 weeks. Levels of coagulation markers, such as plasminogen activator levels (tPA), protein C, protein S, FV, FVII and VWF, were measured after 1 week and 6 weeks with treatment and compared with baseline [55]. In the placebo arm, all coagulation markers, except for protein S, increased from baseline to the end of the first week with treatment. At six weeks, protein C and antithrombin remained elevated in patients receiving placebo, when compared to baseline. These parameters did not change substantially in patients who received atorvastatin, suggesting that atorvastatin could regulate the levels of liver-derived coagulation markers [55]. Furthermore, in a randomized trial conducted with 60 patients with acute coronary syndrome, both atorvastatin low (10 mg) and high (80 mg) dose prevented elevation of VWF from baseline to the end of the first week with treatment, when compared to placebo [59]. After two weeks with treatment, levels of VWF were similar between both treatment arms and placebo [59]. Besides the reduction of some coagulation factors, simvastatin [47, 51, 56, 60], pravastatin [58] and atorvastatin [61, 62] therapies were

also shown to reduce the thrombin generation potential and the level of D-dimer [63], both markers of hypercoagulability. In the LIPID study, 9014 patients were randomized to pravastatin 40 mg or placebo for 3 to 36 months after an acute coronary syndrome. After one year of treatment, D-dimer levels in placebo group did not change from baseline (mean change of 1 ng/mL) while D-dimer levels in patients receiving pravastatin decreased significantly (mean change -12ng/mL). The difference between groups in absolute change of D-dimer levels from baseline to the end of the first year of the study was statistically different (mean levels at year 1 were 172ng/mL in placebo arm and 166ng/mL in patients receiving pravastatin) [64].

It is noteworthy that most of these data came from non-randomized studies in which confounding and regression to the mean cannot be ruled out. Stronger evidence that statins can affect coagulation came from two meta-analyses of randomized trials [65, 66]. These meta-analyses demonstrated a significant decrease in the plasma levels of VWF (standardized mean difference [SMD] -0.54, 95 %CI: -0.87 to -0.21) [65] and D-dimer (SMD -0.988 µg/ml, 95% CI: -1.590 to -0.385) [66] following statin therapy. In both studies, the effects on VWF and D-dimer levels were more evident after atorvastatin or simvastatin therapy was commenced, when compared to no statin use. Limitations of the two meta-analyses are the inclusion of heterogeneous patient populations and treatment assignments and, according to funnel plot analyses, the possibility of publication bias.

Evidence of the effect of statin therapy on coagulation factors recently came from the START trial, in which patients with a prior VTE were randomized to rosuvastatin treatment or non-statin [67]. The mean FVIII:C levels decreased 7.2 IU/dL (95% CI: 2.9 to 11.5) in rosuvastatin users from baseline to the end of treatment, while among non-users, no change in FVIII:C was observed (mean difference -0.1; 95% CI: -3.0 to 2.9). Rosuvastatin therapy also decreased the levels of FVII:C (mean change -3.6 IU/dL; 95% CI: -0.2 to -7.1) and FXI:C (mean change -5.9 IU/dL; 95% CI: - 2.7 to -9.0) from baseline to the end of the study. Subgroup analyses revealed that the effect of rosuvastatin on decreasing the levels of coagulation factors was more pronounced in participants with unprovoked VTE or with cardiovascular risk factors [67]. The results are illustrated in Figure 1.

Effect of statins on fibrinolysis

Clinical studies that evaluated the effect of statins on fibrinolysis have presented controversial results. In a study with 46 patients with coronary artery disease randomized to receive either

placebo or fluvastatin, patients receiving fluvastatin had a decrease in tPA and an increase in plasminogen activator inhibitor-1 (PAI-1) activity [68]. Pravastatin decreased tPA [69] and PAI-1 [69, 70] levels by 10-20% among hyperlipidemic patients, accompanied by a decrease in LDL-C levels. Atorvastatin also increased the levels of plasmin-antiplasmin complex (PAP) by 50%, decreased PAI-1 activity by 34% and decreased platelet-dependent thrombin generation by 48% in hyperlipidemic patients [71]. A shift to a pro-fibrinolytic profile related to statin therapy was also observed in sets of patients with coronary disease undergoing coronary artery bypass grafting [72] in hyperlipidemic women [73] in patients with essential hypertension [74] and in patients with chronic obstructive pulmonary disease (COPD) [75]. In healthy individuals, a large cohort study showed that participants using statins had lower levels of D-dimer and FVIII and higher levels of fibrinogen and PAI-1, in comparison with non-statin users [76]. These results, however, seem contradictory since lower D-dimer and FVIII suggest a decrease in hemostatic activity, while higher fibrinogen and PAI-1 levels suggest hypercoagulability.

The strongest evidence for the effect of statin therapy on fibrinolysis came from a recent meta-analysis of RCTs, where the pooled analysis revealed that statin therapy reduced plasma levels of PAI-1compared with no statin therapy [77]. Although these findings suggest that statins stimulate fibrinolysis, result could also be plagued by publication bias. No additional evidence from RCTs of the effect of statin therapy on fibrinolysis has been published recently.

The importance of the lipid-lowering effect on hemostasis

Basic research studies have consistently shown that the effect of statins on hemostasis is independent of the drug-related lipid-lowering effect. Studies *in vitro* have confirmed that statins can directly inhibit the Rho/Rho-kinase pathway and consequently NF-kB activity and TF expression in monocytes and endothelial cells [39, 40, 45, 46]. Such mechanisms of action are different from that involved in the lipid-lowering process [22].

Additionally, studies in hyperlipidemic mice and rabbits have shown that statins can decrease the expression of TF in atherosclerotic lesions and monocytes independently of the decrease in plasma lipids [43, 44]. The effect of statins on increasing platelet-derived NO release and, in turn, decreasing platelet activity was also shown to be independent of the lipid-lowering effect [26, 34].

In the clinical data, the distinction between a potential direct effect of statin and the lipid-lowering effect on hemostasis is less clear. Most of the studies were conducted in patients with dyslipidemia, and although studies in individuals without dyslipidemia have also demonstrated an effect of statin therapy on hemostasis [54, 67, 76], it is not possible to rule out that the observed effect was due to decreased serum levels of lipids, since many lipoproteins are related to coagulation activity [29].

THE EFFECT OF STATINS ON THE RISK OF VENOUS THROMBOEMBOLISM

Evidences from basic research studies

Data on the effect of statins on *in vivo* venous thrombosis are limited to few studies. In a mouse model of venous thrombosis, mice treated with high dose atorvastatin or rosuvastatin displayed 25% reduction in venous thrombus mass and accelerated thrombus resolution, compared to control animals treated with saline [78]. The reduction in thrombus formation observed in statin treated mice was accompanied by several changes in platelet activity, fibrinolysis and coagulation factors [78]. More recently, a study in a murine model of hyperlipidemic *APOE* knock-out mice showed that mice treated with high doses of rosuvastatin had a 12% decrease in venous thrombus formation compared to controls [79]. The effect of statin on reducing thrombus formation occurred independently of the effect on lipid levels [79]. Results from these animal studies confirm a biological effect of statins on venous thrombus formation. However, supratherapeutic doses of statins were used in the studies, and doses currently used in the clinical scenario were not tested.

Statins to prevent first venous thromboembolism

The first study to suggest that statin therapy was associated with a reduced risk of VTE was conducted in a selected population of postmenopausal women [80]. Since then, several population-based studies have aimed to evaluate the effectiveness of statin therapy on VTE prevention. Most of them are observational studies and were performed in selected populations of patients with cardiovascular disease [81].

The only RCT supporting the effect of statins on decreasing VTE risk was published in 2009. In the JUPITER trial [13] 17,802 apparently healthy individuals, with normal cholesterol levels, were randomized to receive rosuvastatin at 20 mg per day or placebo and were followed

for a median period of 1.9 years. Rosuvastatin reduced the incidence of VTE by 40% (hazard ratio: 0.57; 95% CI: 0.37 to 0.86) compared to placebo.

Since the results of the JUPITER trial were published, additional evidence of the association between statin therapy and reduced VTE risk came from at least four meta-analyses of observational studies and clinical trials. A meta-analysis of RCTs, published in 2012, compared statin use with no statin (20 trials), and also high dose versus standard dose statin (7 trials) [82]. Results from the pooled analysis did not confirm a risk reduction of VTE by statin treatment. Albeit the confidence intervals were wide, the point estimates suggest that rosuvastatin, which is the statin that is most related with halting/regression of atherosclerosis, dyslipidemia, and inflammation [23, 83, 84] also provides the largest risk reductions for the occurrence of VTE. The results are illustrated in Figure 2.

A meta-analysis of 36 studies (13 cohort studies and 23 RCTs) of statin treatment versus no-statin (placebo or control) was published in 2017 [85]. When evaluating RCTs, the meta-analysis demonstrated a pooled relative risk for VTE of 0.85 (95% CI: 0.73 to 0.99) when statin was compared with a non-statin treatment. The lowest relative risk for VTE was observed in individuals who were randomized to rosuvastatin (relative risk, 0.57; 95% CI: 0.42 to 0.75). Among observational studies, the pooled relative risk for VTE was 0.75 (95% CI: 0.65 to 0.87). A stronger effect, i.e. a 54% risk reduction, was observed in populations with pre-existing disease or at high VTE risk, in contrast with a 14% VTE risk reduction in studies that recruited participants from the general population. These results are in line with those from a previous meta-analyses of 7 observational studies that demonstrated that statin therapy was associated with a 40% decrease in VTE risk, as compared to no statin use [86].

Although the results from the JUPITER trial and the meta-analyses of observational studies and RCTs might encourage the use of statins for VTE prevention, these data must be interpreted with caution for several reasons. First, meta-analyses of observational studies have limitations that are related to potential biases in the studies. Some examples: 1) the underlying disease severity in patients selected for statin therapy may be different, even milder than that in patients for whom statin was not indicated (healthy user effect) [87], 2) the inclusion of prevalent statin users results in missing the events that occurred in statin users before the inclusion, early after starting treatment (survivor bias), and 3) observational studies are not able to control for those patients who adhere or not to statin treatment (adherence bias) [88]. Second, the meta-analyses of RCTs included non-published data and were influenced by the results of the JUPITER trial. Finally, the results on VTE from the JUPITER trial came from the analysis

of a secondary endpoint in the trial, in which the primary outcome was the occurrence of a first major cardiovascular event. These results may have run into the statistical problem of small numbers, since in the statin treatment arm only 34 participants developed a venous thrombotic event, and randomness, or a type I error, may have influenced this result. Replication of the results from the JUPITER trial is important, therefore, to confirm that statin therapy reduces the risk of VTE.

Statins to prevent recurrent venous thromboembolism

Over the last years, clinical studies have aimed to determine the role of statins in preventing VTE recurrence, with heterogeneous results. Cohort studies that observed a protective effect of statin therapy on the risk of recurrent VTE have reported a risk reduction that varies from 26 to 38% [89-91]. A recently published meta-analysis of observational cohort studies demonstrated that the pooled relative risk for VTE recurrence was 0.73 (95% CI: 0.68-0.79) in statin users in comparison with no use [92]. Statin therapy reduced the risk for recurrent PE by 25% and the risk of recurrent DVT by 34%, in comparison with no statin [92].

A more detailed analysis of the cohort studies, however, reveals that the results may have been affected by the inclusion of long-term (or prevalent) statin users. Long-term statin users may be healthier than non-users and less susceptible to VTE recurrence, which results in survivor bias and healthy user effect [93]. As an example, in a large cohort study, Schmidt et al [90] reported a 29% decrease (hazard ratio, 95% CI: 0.58–0.87) in the risk of recurrent VTE in long-term statin users as compared with non-users, while among new users the relative risk reduction dropped to a non-significant 17% (0.45–1.52). Therefore, a biased association between statin use and prevention of VTE recurrence cannot be ruled out.

SUMMARY AND CONCLUSIONS

Several studies have consistently demonstrated that statins affect hemostasis, particularly by downregulating TF expression on endothelium cells and monocytes through a direct, lipid-lowering independent effect on transcriptional activation of *TF* gene. This drug effect is, thus far, the best described mechanism by which statins may reduce thrombus formation. Additionally, statins were also shown to impair platelet activation, decrease multiple coagulation factors and increase fibrinolysis. A summary with documented biological influence of statins on the different phases of hemostasis is provided in Figure 3.

Recent data from randomized trials pointed to a potential effect of statins on decreasing the levels of coagulation factors. Although these studies have provided stronger evidence that statins may affect coagulation in humans, the exact mechanisms by which this happens are not elucidated. Furthermore, the question whether the observed effect of statin therapy on coagulation is sufficient to prevent VTE is still open.

From the clinical perspective, recent meta-analyses of randomized trials have demonstrated that rosuvastatin therapy may reduce the risk of incident VTE, reinforcing the results reported by the JUPITER trial. However, a direct relation between statin therapy and recurrent VTE risk cannot be assumed from the current clinical data, since the results still need to be replicated. The lack of randomized data also provides uncertainty about the effect of statin therapy on reducing the risk of recurrent VTE.

Clinical trials are currently underway for assessing whether rosuvastatin (NCT01524653) or simvastatim (NCT02285738) therapy would reduce the risk of incident VTE in patients with cancer. The two studies have surrogate biomarkers of hypercoagulability as a primary endpoints, D-dimer levels and soluble P-selectin levels respectively. A third study aims to evaluate whether rosuvastatin can reduce post-thrombotic syndrome in VTE patients (NCT02679664). A fourth trial (NCT02331095) aims to determine whether atorvastatin plus anticoagulation can reduce the thrombin generation potential in patients with acute VTE compared to anticoagulation alone. The results of these trials will contribute to the body of evidence on the association between statin therapy and hemostasis. However, the question whether statin therapy is effective to prevent incident or recurrent VTE will probably remain unanswered for the following years, since no studies on this issue have been started yet.

In conclusion, findings from clinical studies point to a potential effect of statins on decreasing the levels of coagulation factors and reducing the risk for VTE. These effects were mainly attributed to rosuvastatin, which is the most potent LDL-C and atherosclerosis reducing statin. However, stronger evidence on efficacy of statins in preventing VTE, in particular the recurrent events, is still lacking. Recent data showing the effect of rosuvastatin on levels of coagulation factors in patients with prior VTE provides a solid basis for interventional studies necessary to establish the efficacy of statins on reducing the risk of incident of recurrent VTE.

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Legends to Figures

Figure 1 Effects of rosuvastatin on coagulation factors VIII, XI, VII, von Willebrand Factor and D-dimer according to (A) VTE classification (unprovoked and provoked) and (B) the presence/absence of cardiovascular risk factors. Results from the START (STAtins Reduce Thrombophilia) trial.[63]

CI confidence interval. CV cardiovascular

Figure 2 Effect of rosuvastatin, pravastatin, atorvastatin and simvastatin on VTE [77,78].

[a] excluding results from the JUPITER (The Justification for the Use of *Statins* in Prevention: an Intervention *Trial* Evaluating Rosuvastatin) trial. CI confidence interval.

Figure 3 Biologically documented effects of statins on distinct phases of the process of hemostasis.

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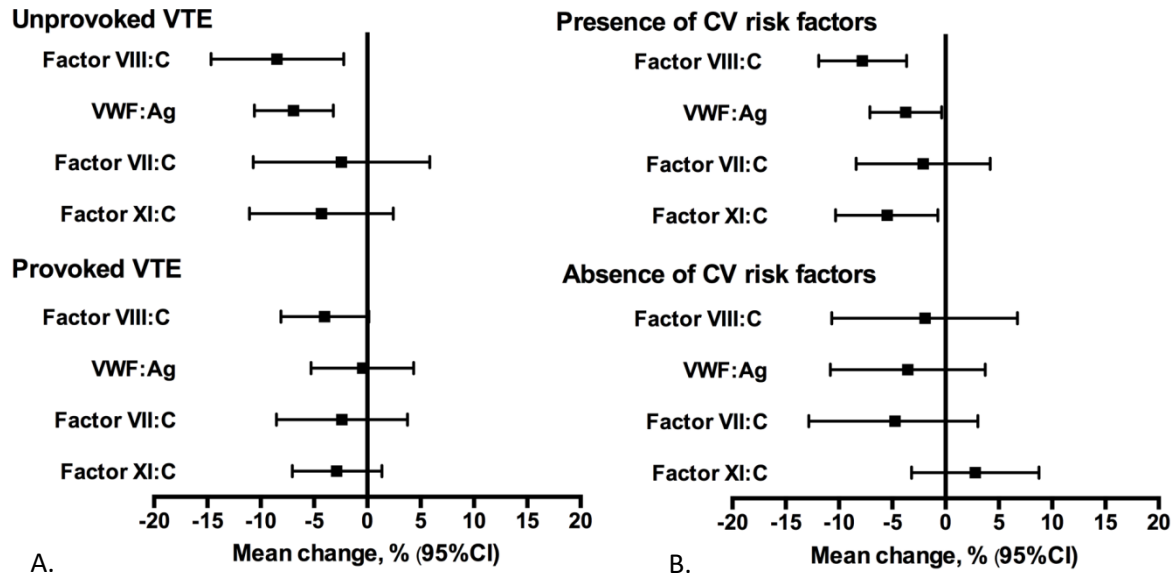

Figure 1 Effects of rosuvastatin on coagulation factors VIII, XI, VII, von Willebrand Factor and D-dimer according to (A) VTE classification (unprovoked and provoked) and (B) the presence/absence of cardiovascular risk factors. Results from the START (STAtins Reduce Thrombophilia) trial.[63]

CI confidence interval. CV cardiovascular

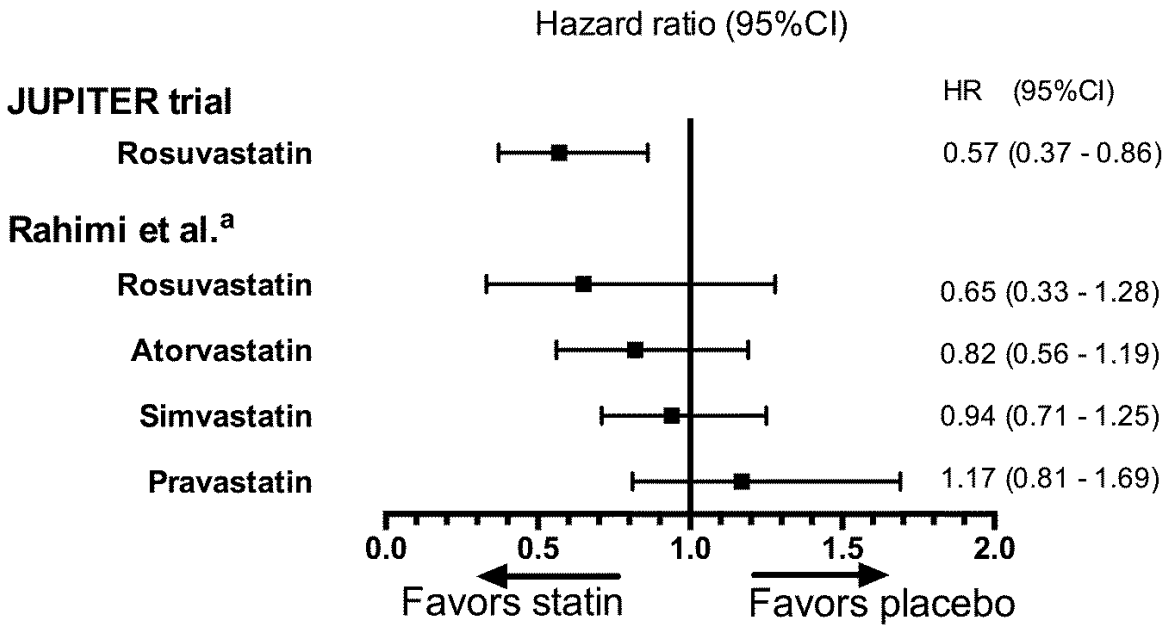

Figure 2 Effect of rosuvastatin, pravastatin, atorvastatin and simvastatin on VTE risk [77,78]. CI confidence interval. [a] excluding results from the JUPITER (The Justification for the Use of *Statins* in Prevention: an Intervention *Trial* Evaluating Rosuvastatin) trial.

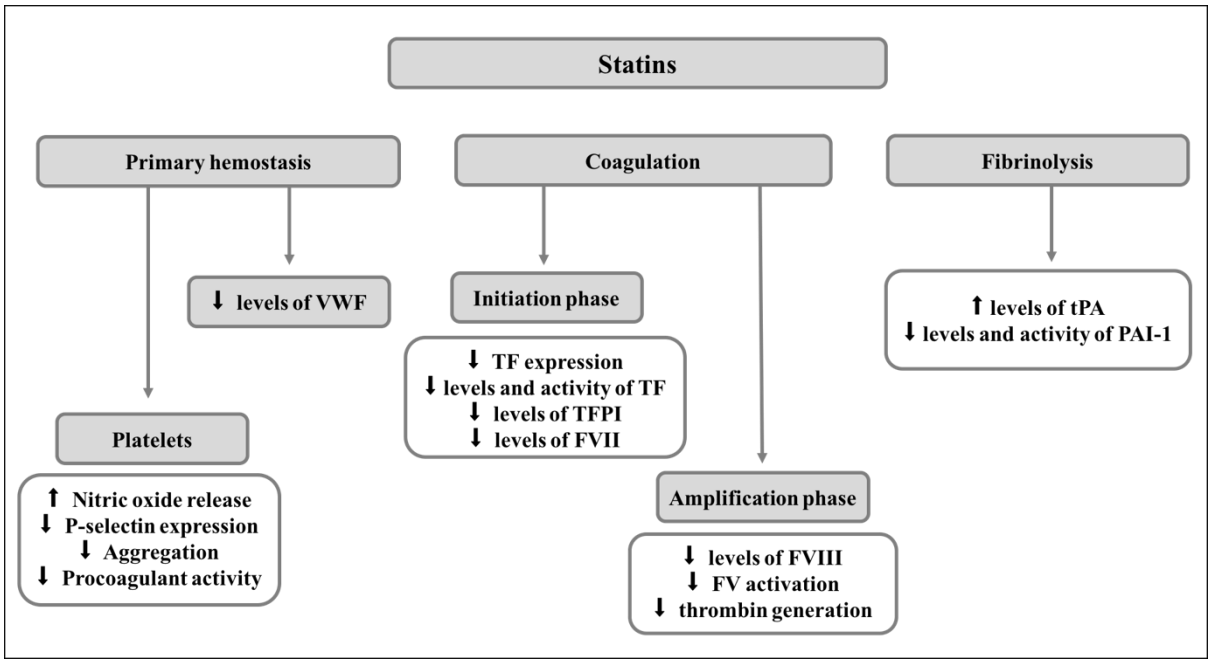

Figure 3 Biologically documented effects of statins on distinct phases of the process of hemostasis. Data from basic research and clinical studies have suggested that statins can decrease platelet activity, downregulate both initiation and amplification phases of coagulation and stimulate fibrinolysis. So far, the best known mechanism by which statins may impair hemostasis is the direct downregulation of TF expression on endothelial cells and monocytes through a direct inhibitory effect on transcriptional activation of *TF* gene. VWF von Willebrand factor, TF tissue factor, TFPI tissue factor pathway inhibitor, FVII factor VII, FVIII factor VIII, FV factor V, tPA tissue plasminogen activator levels, PAI-1 plasminogen activator inhibitor-1