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Preinjury statin use and thromboembolic events in trauma: a 10-year retrospective evaluation

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ABSTRACT

Background: Traumatic injury is well known to increase the risk of venous thromboembolic events (VTEs), occurring in up to 58% of trauma patients. Statin medications have significant anti-inflammatory properties and have been shown to reduce the risk of VTE. We hypothesized that trauma patients who received statin medication before injury would have a lower incidence of VTE after injury.

Methods: A 10-y retrospective review identified all patients admitted to our trauma service with an injury severity score >9 and an intensive care unit stay of >3 d. This population was categorized as either "statin recipient" (SR) or "statin naïve," with subsequent categorical division by occurrence of VTE. Our primary outcome measure was the occurrence of documented VTE in both statin naïve and SR subjects.

Results: A total of 2519 trauma patients were included with 97 (3.8%) developing VTE. Pretrauma statin use in males remained as an independent predictor of VTE (odds ratio = 2.25, 95% confidence interval = 1.25-4.04, $P < 0.01$). The median time to VTE onset was 3 d longer in SRs (10.0 d; confidence interval = 7.3-12.7, $P < 0.05$).

Conclusions: Pretrauma statin use does not appear to have a protective benefit of VTE prevention in trauma patients, as we have shown pretrauma SR male trauma patients to have a twofold increased incidence of VTE. However, when considering the 3 d longer median time to VTE onset found in SRs, we consider the protective benefit of statin use reported in the current literature as likely attributable to this observed delayed onset.

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Introduction and military relevance

Venous thromboembolic events (VTEs) are responsible for up to 100,000 deaths annually.[1] Traumatic injury is well known to increase the risk of thromboembolic events with deep vein thrombosis (DVT) occurring in up to 58% of trauma patients not receiving prophylaxis.[2-5] Owing to the nature of their injuries, many trauma patients have an absolute or relative contraindication to anticoagulation or chemoprophylaxis.[6] This makes preventing and treating VTEs extremely difficult in trauma patients. While considering the significant anti-inflammatory properties of statin medications (Fig. 1), there is growing evidence to suggest that statins can confer a protective benefit, reducing the incidence of VTE within the hospitalized patients.[7-11] Therefore, we hypothesized that trauma patients who were on statins before injury would have a lower rate of VTE development.

The protective effects of statins against VTE have been demonstrated in two recent meta-analyses, where Pai *et al.*[9] show statin use associated with significantly reduced odds

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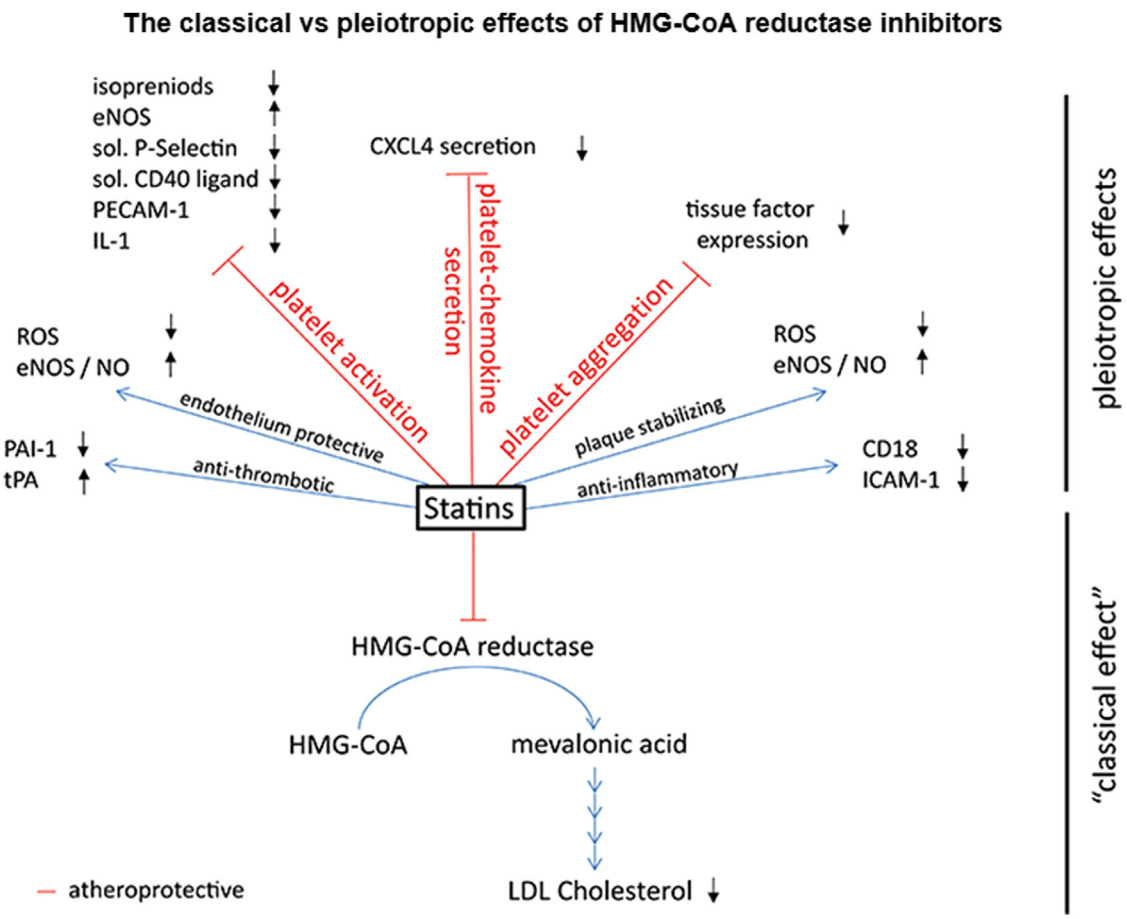

Fig. 1 – The classical *versus* pleiotropic effects of HMG-CoA reductase inhibitors. Citation: von Hundelshausen P and Schmitt MMN (2014) Platelets and their chemokines in atherosclerosis—clinical applications. *Front. Physiol.* 5:294. https://doi.org/10.3389/fphys.2014.00294. Taken from <http://journal.frontiersin.org/article/10.3389/fphys.2014.00294/full>. Copyright © 2014 von Hundelshausen and Schmitt. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution, or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution, or reproduction is permitted which does not comply with these terms. (Color version of figure is available online.)

of developing VTEs (odds ratio [OR] = 0.67), whereas Agarwal *et al.*[8] show statin use to be associated with lower rates of VTE (by 32%). While the strongest evidence to date is derived from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial published by Glynn *et al.*,[7] here we also see a decreased efficacy with increased age. In a large (n = 10,452) population-based case-control study (MEGA study), further evidence supporting the protective effects of statins is provided by Ramcharan *et al.*[12] where the use of statins was again associated with a reduced risk of VTE (OR = 0.45; 95% confidence interval [CI] = 0.36-0.56). In this same study, both the effect of age and medication class effect were examined, demonstrating that those over 60 y of age were shown to have a greater risk reduction than younger subjects (OR = 0.32, 95% CI = 0.29-0.51), while a reduced risk of venous thrombosis was shown with all different statin types.

While a recent prospective case-control study demonstrates that the abrupt withdrawal of statin treatment not only negates its beneficial effects but also additionally leads to further vascular injury[13] generating questions regarding the clinical impact of cessation of statin therapy in the hyperlipidemic trauma patients, there are currently very limited data exploring the role of statins in the trauma population.[14] In summary, we see the current evidence of the protective benefit of statin use as well defined,[7-9] and potential confounding factors of age and gender were identified.[3,12] In addition, our target subject demographics have been demarcated,[6] and although the anti-inflammatory properties of statin medications are the subject of current investigation,[10] the clinical impact of acute therapy withdrawal in the trauma setting is of developing consequence.[13] In addition, a potential gap in current therapy is observed.

The absence of a nonanticoagulant-based chemoprophylactic agent is a definitive void found when providers are faced with contraindications to chemoprophylaxis or anticoagulation in the trauma patient. A void potentially worsened as evolving evidence has shown that some pulmonary vascular