rs4962153 showed an association with cryptogenic stroke (Table 1). This association is interesting in view of the fact that prothrombotic variants have been suggested as risk factors for cryptogenic stroke [8], but there are no studies on ADAMTS13 in this subtype. We found no significant associations for any of the other IS subtypes. However, whether this is due to a subtype-specific effect of *ADAMTS13* gene variation or a lack of statistical power in the smaller subgroups cannot be determined from these findings.

In conclusion, three SNPs in the *ADAMTS13* gene were found to be associated with IS in the present population of relatively young patients from western Sweden. The SNP rs4962153 showed significant associations with both overall ischemic stroke and the subtype cryptogenic stroke. To the best of our knowledge, this is the first study investigating *ADAMTS13* gene variants in a large cohort of patients with IS and in different subtypes of IS. Thus, further studies are needed in order to investigate whether the present finding can be replicated, and whether there are associations for other subtypes apart from cryptogenic stroke.

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Disclosure of Conflict of Interests

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Will oral rivaroxaban improve clinically relevant outcomes and thromboprophylaxis management in the orthopedic patient?

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The RECORD program comparing rivaroxaban, a new oral direct inhibitor of factor Xa, and enoxaparin in major orthopedic surgery has shown higher efficacy of rivaroxaban than of enoxaparin in reducing total venous thromboembolism (VTE) with no statistically significant increase in major bleeding [1–4]. Pivotal studies with new anticoagulants are usually powered to test the non-inferiority and/or superiority of the new compound as compared with the control drug with respect to total VTE (mainly driven by asymptomatic distal deep vein thrombosis), but underpowered to test

Table 1 Clinically relevant events with rivaroxaban and enoxaparin in the RECORD program (safety population)

Event	RIV, $n = 6183$	ENO, $n = 6200$	RR (95% CI)	*P*-value
Symptomatic VTE* [1–4]	38 (0.6)	68 (1.1)	0.56 (0.38–0.83)	0.004
Clinically relevant bleeding† [1–4]	201 (3.3)	160 (2.6)	1.26 (1.03–1.55)	0.026
Death related to VTE or bleeding [1–4]	8 (0.1)	12 (0.2)	0.70 (0.29–1.70)	0.432
Death by any cause [1–4]	10 (0.2)	15 (0.2)	0.69 (0.31–1.54)	0.368
Cardiovascular events‡ [1–4]	31 (0.5)	34 (0.5)	0.91 (0.56–1.49)	0.716
During therapy	14 (0.2)	24 (0.4)	0.59 (0.30–1.13)	0.110
After treatment cessation	17 (0.3)	10 (0.2)	1.92 (0.32–11.41)	0.472
Hepatic events§ [5]	7 (0.1)	3 (< 0.1)	2.34 (0.66–8.30)	0.226

CI, confidence interval; ENO, enoxaparin; RIV, rivaroxaban; RR, relative risk; VTE, venous thromboembolism. Data are no. (%). Events occurring during the first 2 weeks unless specified. Relative risks and *P*-values were calculated using the fixed effects model, with the exception of cardiovascular events after treatment cessation, which were calculated using the random effects model, owing to heterogeneity ($P < 0.1$). *Symptomatic VTE includes symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and VTE-related deaths. †Clinically relevant bleeding is the sum of major bleeding plus clinically relevant non-major bleeding. ‡Cardiovascular events include cardiovascular death, myocardial infarction, ischemic stroke, and unexplained death. §Alanine transferase $> 3 \times$ upper limit of normal (ULN) with total bilirubin $> 2 \times$ ULN and at least a possible relationship with the study drug according to the sponsor's liver advisory panel ('most relatedness' assignment by any adjudicator).

differences in clinical outcomes that may be relevant in real practice. We used meta-analysis techniques to analyze clinically relevant outcomes occurring during the RECORD program [1–4]. Two independent investigators collected the data on symptomatic VTE, clinically relevant bleeding (composite of major and clinically relevant non-major bleeding), total deaths, deaths due to VTE or bleed and total cardiovascular events during and after cessation of therapy in the safety population. Data on hepatic events were extracted from a recent review by the US Food and Drug Administration [5]. Relative risks and *P*-values were obtained using the fixed effects Mantel–Haenszel weighted model. Alternatively, the DerSimonian–Laird random effects weighted model was used in cases of heterogeneity between studies on a given outcome. Statistical calculations were performed using MIX software version 1.7.

Table 1 shows that, when compared to enoxaparin, rivaroxaban is associated with a lower rate of symptomatic VTE (number needed to treat: 207) and a higher rate of clinically relevant bleeding (number need to harm: 149) after hip or knee arthroplasty; data on mortality, cardiovascular events and hepatic events are inconclusive [1–5]. The reduction in symptomatic VTE afforded by rivaroxaban in our meta-analysis is a positive finding, being consistent with findings from a recent meta-analysis [6], which did not include the RECORD-4 study [4]. Our results on clinically relevant bleeding are consistent with the results from ancillary analyses by the US Food and Drug Administration using a different methodology (Cox regression analysis), which also showed a consistent increased bleeding risk with rivaroxaban as compared with enoxaparin in the RECORD program [5]. A recent study has shown differences between clinical trial (usually less frail patients) and real-life patient populations, which may result in a less favorable safety profile of the anticoagulant in real practice [7].

At least one in four people are not compliant with drug therapy in clinical practice, and this is related to poorer outcomes [8]. Patients prefer oral medications over daily subcutaneous injections, and it is believed that new oral anticoagulants may help to improve compliance with thromboprophylaxis regimens [9]. Nevertheless, in the RECORD program, 80 patients in the rivaroxaban group and 61 patients in the enoxaparin group were excluded from the per-protocol population because of inadequate compliance (patients taking $< 80\%$ or $> 120\%$ of the scheduled doses) [1–4], and a pooled analysis of RECORD-1, RECORD-2 and RECORD-3 studies showed that 31 patients on rivaroxaban and 28 patients on enoxaparin withdrew prematurely because of non-compliance [6].

Although it is claimed that oral regimens could enable shorter hospital stays [4], mean duration of initial hospital stay in the RECORD-4 study was similar in the rivaroxaban and enoxaparin groups (8.0 vs. 7.9 days) [4]; hospital stay data from the three previous RECORD studies are not available from the publications. The available clinical data for rivaroxaban are promising and merit regulatory approval. Nevertheless, much more clinical experience is required before the role of rivaroxaban after hip or knee arthroplasty in standard clinical practice can be established with confidence.

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Disclosure of Conflict of Interests

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Contribution of magnesium in binding of factor IXa to the phospholipid surface: implications for vitamin K-dependent coagulation proteins

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In the current schemes of coagulation, the intrinsic tenase complex consists of factor IXa, FVIIIa and Ca^{2+} assembled on the phospholipid (PL) membrane containing phosphatidylserine (PS) [1]. This complex activates FX to FXa, and the PS-containing PL membrane surface *in vivo* is provided by the activated platelets [1]. In virtually all investigations, saturating levels of Ca^{2+}, ranging from 2 to 5 mM, are used to assemble the FIXa–FVIIIa–Ca^{2+}–PL complex [1]. However, the physiologic concentration of Ca^{2+} in plasma is 1.1 mM [2], which is suboptimal and does not support complete occupancy of the Ca^{2+}-binding sites in the γ-carboxyglutamic acid (Gla) domain of vitamin K-dependent clotting proteins [3–5]. However, plasma also contains 0.6 mM Mg^{2+} [2] and at this concentration, the Gla domain of prothrombin binds three Mg^{2+} [6]. Furthermore, although the Gla domain of prothrombin has seven Ca^{2+}-binding sites under Mg^{2+}-free conditions [7], it only binds four Ca^{2+} in the presence of Mg^{2+} [3]. Thus, the three Mg^{2+} in the Gla domain of prothrombin are not displaced by Ca^{2+}. In agreement with this, the Gla domains of FVIIa and FXa each bind three Mg^{2+} [4,8], whereas FIXa Gla domain binds three Mg^{2+} when bound to its binding protein in the crystal structure [9], and apparently four in solution when not bound to any ligands [5]. Thus, with suboptimal Ca^{2+} concentrations, Mg^{2+} occupies specific sites in the Gla domains of vitamin K-dependent proteins and could provide support for PL binding. In this study, we investigated whether Mg^{2+} enhances FIXa binding to PL at physiologic concentrations of Ca^{2+}; if so, it could facilitate assembly of the intrinsic tenase complex.

We measured dansyl-Glu-Gly-Arg (dEGR)–FIXa (FIXa with the active site blocked for stability) binding to PS/PC bilayers using surface plasmon resonance (SPR). In 1.1 mM Ca^{2+} (Fig. 1B), the k_{on} for binding was $(2.1 \pm 0.91) \times 10^3$ M^{-1} s^{-1} ($n = 3$), k_{off} was $(3.9 \pm 1.8) \times 10^{-3}$ s^{-1} ($n = 3$), and K_d was 1.9 ± 0.23 μM. In 5 mM Ca^{2+} (Fig. 1C), the k_{on} for binding was $(4.1 \pm 1.4) \times 10^3$ M^{-1} s^{-1} ($n = 4$), k_{off} was $(2.2 \pm 1.0) \times 10^{-3}$ s^{-1} ($n = 4$), and K_d was 0.54 ± 0.11 μM. In 1.1 mM Ca^{2+}/0.6 mM Mg^{2+} (Fig. 1D), the k_{on} for binding was $(3.6 \pm 1.2) \times 10^3$ M^{-1} s^{-1} ($n = 4$), k_{off} was $(2.4 \pm 0.75) \times 10^{-3}$ s^{-1} ($n = 4$), and K_d was 0.67 ± 0.18 μM. The k_{on} and k_{off} values were not notably affected when PL coupling to the L1 chip was varied from 4200 to 7200 relative units (RUs). In addition, we obtained K_d values using the equilibrium response (RU_{eq}) for each concentration of

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