

Rivaroxaban – a novel, oral, direct Factor Xa inhibitor – has no clinically relevant interaction with Aspirin or naproxen

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Introduction

Rivaroxaban (BAY 59-7939) is an oral, direct Factor Xa (FXa) inhibitor in advanced clinical development for the prevention of venous thromboembolism (VTE) in patients who have undergone major orthopaedic surgery. In these patients, administration of Aspirin® or non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen (Proxen®, Roche), for the relief of pain and inflammation is commonplace. Because rivaroxaban, Aspirin and NSAIDs may affect haemostasis, it is important to determine whether concomitant use of these drugs is feasible in the clinical setting.

Objective

To determine the effect of either Aspirin or naproxen on the safety, tolerability, pharmacodynamics and pharmacokinetics of rivaroxaban (and vice versa). Two studies were undertaken: one with Aspirin and one with naproxen.

Methods

Study participants and design

- Each study was a randomized, non-blinded, single-centre, two-way crossover study in young, healthy males, with a run-in period of Aspirin or naproxen (Figure 1)

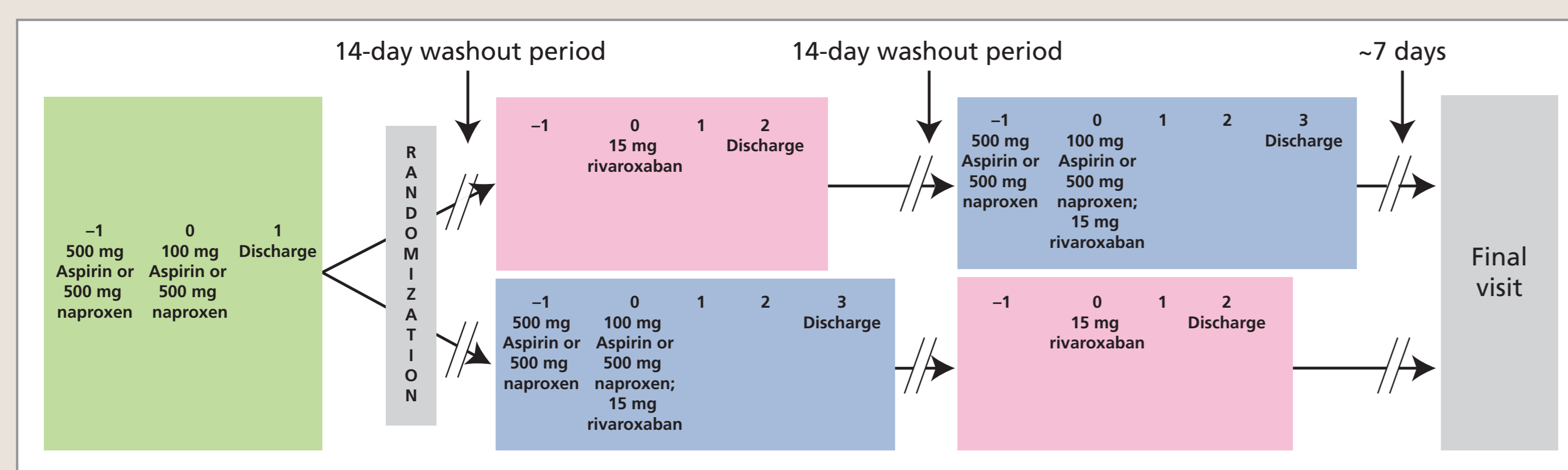


Figure 1. Study designs. Two studies, one with rivaroxaban and Aspirin and one with rivaroxaban and naproxen, were performed. Both had the same design

Assessment of study variables

- Safety and tolerability were assessed by adverse-event questioning, monitoring of vital signs, and laboratory tests, including haematology and clinical chemistry
- Anticoagulant activity was assessed by FXa activity and prothrombin time (PT). Quantitative assessment of collagen-activated platelet aggregation was also undertaken. Bleeding time was measured before and 4 hours after study drug administration, using the Surgicutt® device
- Pharmacokinetic evaluations, including area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}), were conducted after administration of rivaroxaban alone, or co-administration of rivaroxaban with Aspirin or naproxen

Results

- A total of 14 and 13 subjects were initially recruited into the Aspirin and naproxen studies, respectively
 - Safety analysis: 14 and 13 subjects were available (Aspirin and naproxen studies, respectively)
 - Pharmacodynamic and pharmacokinetic analysis: 13 and 11 subjects were available (Aspirin and naproxen studies, respectively)
- Age ranged from 18 to 45 years (mean values: 34.6 years in the Aspirin study and 32.5 years in the naproxen study)
- Body mass index ranged from 19 to 29 kg/m² (mean values: 24.6 kg/m² and 24.7 kg/m² in the Aspirin and naproxen studies, respectively)

Safety and tolerability

- All treatments, including the combination of rivaroxaban with either Aspirin or naproxen, were well tolerated; no serious adverse events were reported
- One subject withdrew from the Aspirin study due to a moderate adverse effect (vertebral disc prolapse) considered unrelated to treatment
- Two subjects withdrew from the naproxen study: one due to an adverse effect considered unrelated to treatment (impetigo contagiosa); the other withdrew consent
- Five mild, transient, drug-related adverse events were reported in four subjects in the Aspirin study
- No drug-related adverse events were reported in the naproxen study

Anticoagulant activity

- Neither Aspirin nor naproxen alone affected FXa activity or prolonged PT
- Rivaroxaban alone inhibited FXa activity to a maximum level of approximately 35% in both studies (Figure 2A and B)
- The inhibitory effect of rivaroxaban on FXa activity was not influenced by co-administration with Aspirin or naproxen (Figure 2A and B)
- PT was prolonged by rivaroxaban alone in both studies; there were no significant differences when either Aspirin or naproxen were co-administered (Figure 2C and D)

Platelet aggregation and bleeding time

- Rivaroxaban alone had no effect on collagen-stimulated platelet aggregation or bleeding time in either study, whereas both Aspirin and naproxen alone inhibited platelet aggregation and prolonged bleeding time (Figure 3)
- Co-administration of rivaroxaban with either Aspirin or naproxen did not significantly affect inhibition of platelet aggregation but did enhance bleeding time, compared with Aspirin or naproxen alone. These increases were small, with high inter-subject variability and, therefore, were not considered to be clinically relevant (Figure 3)

Pharmacokinetics

- Aspirin did not affect the pharmacokinetics of rivaroxaban when the two drugs were co-administered (Table 1)
- Co-administration of naproxen and rivaroxaban increased the bioavailability of rivaroxaban slightly, but this was not considered to be of clinical relevance (Table 1)

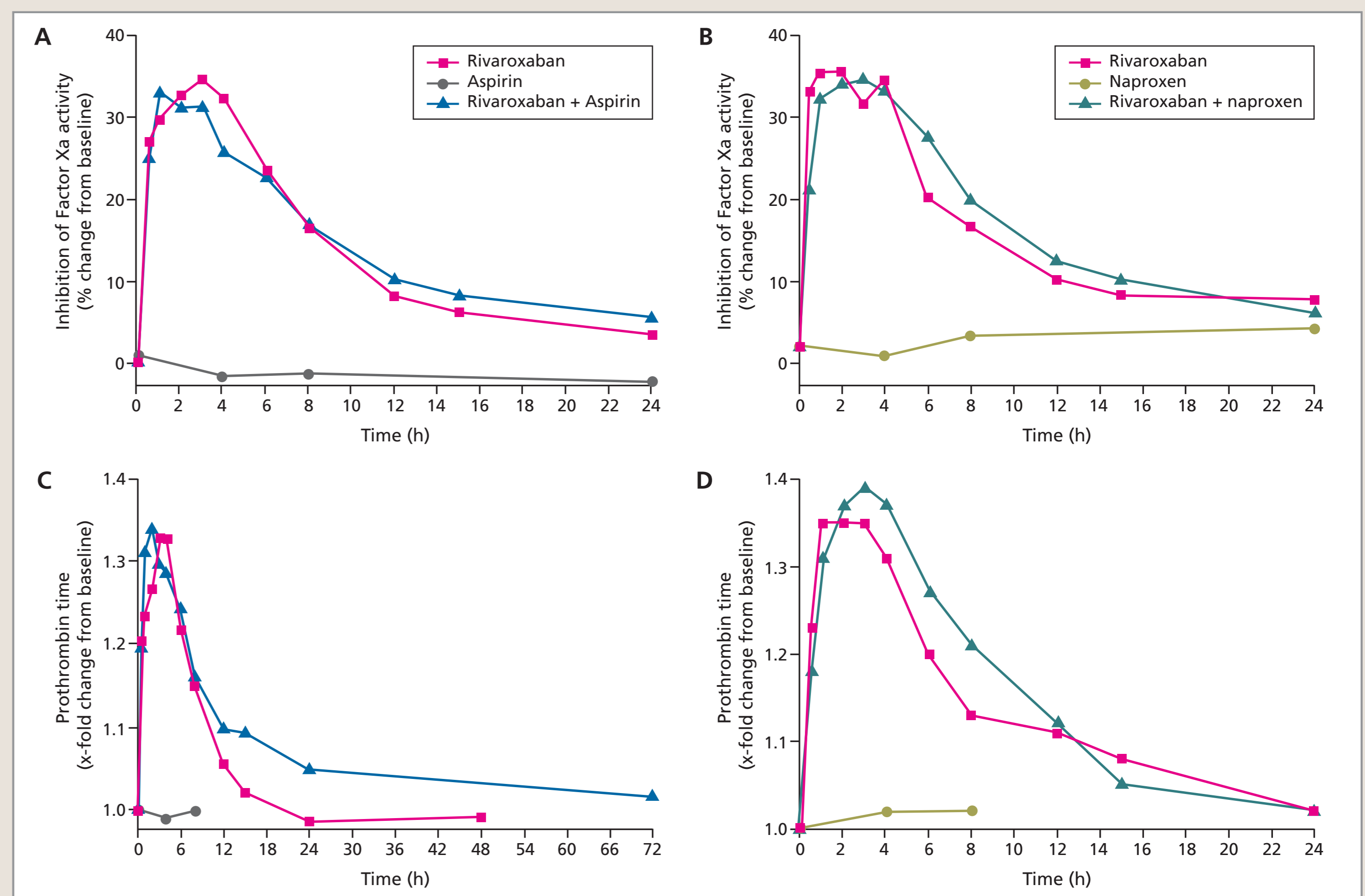


Figure 2. The effect of rivaroxaban and Aspirin, or rivaroxaban and naproxen, on median Factor Xa inhibition (A and B, respectively) or PT (C and D, respectively), compared with rivaroxaban or Aspirin/naproxen alone. (Administered doses: rivaroxaban 15 mg, Aspirin 100 mg, naproxen 500 mg; n=11)

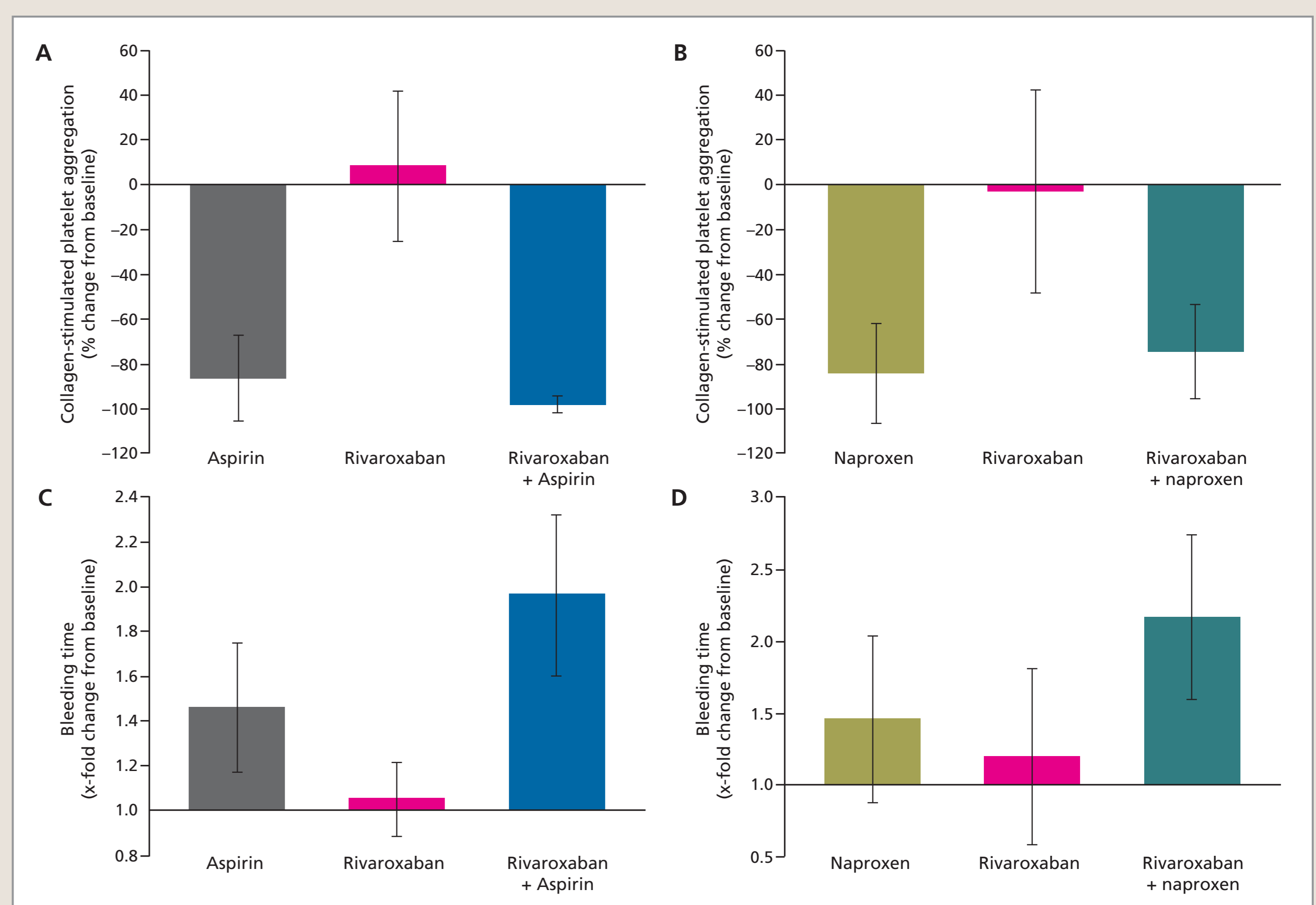


Figure 3. The effect of rivaroxaban and Aspirin, or rivaroxaban and naproxen, on maximum collagen-stimulated platelet aggregation (percentage change from baseline; A and B, respectively) or bleeding time (x-fold change from baseline; C and D, respectively) compared with rivaroxaban or Aspirin/naproxen alone. (Administered doses: rivaroxaban 15 mg, Aspirin 100 mg, naproxen 500 mg; n=11)

Table 1. Pharmacokinetics of rivaroxaban after administration alone (15 mg) or in combination with either Aspirin (100 mg; n=13) or naproxen (500 mg; n=11). Area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}) were calculated. These parameters were then analysed by ANOVA, from which least-squares (LS) mean ratios (with 90% confidence intervals [CIs]) were generated

Parameter	Rivaroxaban alone ^a	Rivaroxaban + drug ^a	LS mean ratio (90% CI)
Aspirin study			
AUC $\mu\text{g}\cdot\text{h/L}$	1156/30.62	1053/22.58	0.908 (0.819, 1.006)
C_{max} $\mu\text{g/L}$	126.3/30.01	133.4/26.44	1.052 (0.945, 1.171)
Naproxen study			
AUC $\mu\text{g}\cdot\text{h/L}$	1250/28.56	1396/26.30	1.125 (0.995, 1.271)
C_{max} $\mu\text{g/L}$	152.9/31.51	165.3/27.69	1.095 (0.905, 1.325)

^aMean/coefficient of variation

Conclusions

- The studies suggest there is no clinically relevant interaction between rivaroxaban and either Aspirin or naproxen at the doses tested in these trials
- These data are corroborated by clinical data
 - Phase II studies investigating rivaroxaban (twice daily) for the prevention of VTE after major orthopaedic surgery demonstrated that co-administration of NSAIDs with rivaroxaban (5–20 mg total daily dose) did not place patients at an increased risk of bleeding (combined bleeding rates: 1.1–5.2% in patients receiving rivaroxaban alone vs 2.9–4.8% in patients receiving rivaroxaban + NSAIDs)^{1,2}
 - In phase II studies investigating up to 3 months' rivaroxaban for the treatment of VTE, patients were permitted to receive concomitant low-dose Aspirin with no apparent effects on rivaroxaban safety and efficacy^{3,4}
- Ongoing phase III studies of rivaroxaban for the prevention of VTE after major orthopaedic surgery (the RECORD studies) should confirm the tolerability of the combination of rivaroxaban with either Aspirin or NSAIDs

References

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