delirium reduction and improved sleep in patients from these two independent trials.[1,6]

It is true that hemodynamic disturbances are major concerns when using dexmedetomidine in ICU patients. Indeed, dexmedetomidine at such a low dose (0.1 μg kg^{-1} h^{-1}) slightly increased the occurrence of hypotension, although not statistically significantly,[6] indicating that close monitoring is necessary whenever dexmedetomidine is onboard. Last but not least, whether delirium prevention by dexmedetomidine ultimately improves patients' long-term outcome remains unknown and warrants further study.

Regarding the question of Dr. Reade, herein we confirm that these two studies[1,6] are completely independent trials in which each has an individual registration (Chinese Clinical Trial Registry [Chengdu, Sichuan, China; www.chictr.org.cn] Nos. ChiCTR-TRC-10000802 and ChiCTR-TRC-12002567). Patients who were recruited in one study were not enrolled the other one.

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Competing Interests

Dr. Wang reports that he has received lecture fees and travel expenses for lectures given at domestic academic meetings from Jiangsu Hengrui Medicine Co., Ltd. (Jiangsu, China). The other author reports no competing interests.

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Is the PeriOperative ISchemic Evaluation-2 Trial Equipoised?

To the Editor:

We read with interest the article by Eikelboom *et al.*[1] reporting the results of the PeriOperative ISchemic Evaluation-2 (POISE-2) trial regarding postoperative incidence of venous thromboembolism (VTE).

We had several concerns:

(1) It seemed to us unusual to report the findings of a randomized clinical trial and to pool its results immediately with previous trials and meta-analyses in the same article. Is there a rationale for not reporting the findings of POISE-2 alone, knowing that the pooling part was not specified in the protocol of the study posted on clinicaltrials.gov (NCT01082874)?

(2) Referring to the design of POISE-2 published in 2014,[2] the trial outcomes were listed in appendix A of that article. Pulmonary embolism and deep venous thrombosis at 30 days were defined as tertiary outcomes and pulmonary embolism and deep venous thrombosis at 1 yr as secondary outcomes. In this understanding, POISE-2 was not specifically designed to assess the effect of aspirin on VTE.

(3) Determination of the POISE-2 sample size was based on the assumption of a hazard ratio of 0.75 for the primary composite outcome (mortality and nonfatal myocardial infarction), two-sided α of 0.05, power of 0.80, and base incidence of composite outcome approximately 6%. However, as stated by the authors in the introduction, incidence of symptomatic postoperative VTE in noncardiac surgical patients is 1 to 5% in the absence of prophylactic anticoagulation, and one would be inclined to consider the lower bound with the current use of prophylactic anticoagulation (an assumption confirmed by the results of POISE-2,[1] reporting an incidence of 1.2%). Keeping the other parameters constant (α, power, and effect size), at least 36,000 subjects would be needed to enable rejecting the null hypothesis. As a corollary, the *post hoc* power determination yields a 30% power for POISE-2 to detect an effect of aspirin on VTE, far less than the 50% estimation given by the authors in the discussion.

Hence, POISE-2 was *a priori* severely underpowered to detect any effect of aspirin on VTE incidence, not due to the low incidence of VTE as stated by the authors, for it was known from previous publications, but due mainly to the insufficient sample size for VTE outcomes at 30 days. Of note, 1-yr VTE outcomes, although specified in the design, were not reported in the current paper.

(4) The authors report having used Cox models to assess the effect of various factors on VTE incidence. One shortcoming of Cox models is the assumption of proportional hazards, and it is not clear from the corresponding section whether any tests were performed to check this assumption.

(5) Pooling the results of POISE-2 with those of the Antiplatelet Trialists' Collaboration (APTC)[3] and Pulmonary Embolism Prevention (PEP) trial[4] raises several concerns. PEP patients were all orthopedic patients from the 1990s. APTC included more than 50 trials, a large number of them dating from the 1970s and 1980s. The profile of patients included in the older trials differs from that of current patients on several aspects, including a lack of prophylactic anticoagulation in older studies, different surgical and anesthetic techniques, different postoperative care and settings, and so forth. Although the authors admit the lower quality of some APTC trials due to dubious allocation concealment, lack of blinding, and other diagnostic issues, they unabashedly ignore patient-related, care-related, and trial-related differences and eventually proceed with pooling the trials. With this understanding, we are afraid that the assumption of comparability of PEP/APTC patients and those of POISE-2 is far from guaranteed and cannot be compensated for by metrics. The pooling approach altogether was not specified in the published protocol and deserves a separate, more in-depth assessment.

(6) Baseline characteristics were well balanced between the two arms. Of these, therapeutic dose anticoagulants during the first 3 days after surgery were used in 4.8% patients of the aspirin group and 4.4% of the placebo group. Referring to the design of POISE-2,[2] planned therapeutic anticoagulation in the 3 days after surgery was an exclusion criterion. We assume therefore that the 5% of patients under therapeutic anticoagulation in the 3 days after surgery were not planned to receive it but had it for other reasons that could place them at a higher risk of VTE. Was this subgroup prespecified, as is the case for patients with planned prophylactic anticoagulation from day 0 to day 3, and, if affirmative, how does it compare with the sample?

(7) The forest plot depicted in figure 2 of the article by Eikelboom *et al.*[1] shows overall no statistical significance. Looking closely to the 95% CIs of diabetics and patients younger than 75 yr, they merely cross the equivalence vertical bar. Had the sample size been larger to account for VTE outcome, these 95% CIs would have been potentially significant. Inspecting the horizontal bars for degrees of renal function reveals no events in the estimated glomerular filtration rate (eGFR) less than 30 group, which is a bit surprising. Recalling that incidence of VTE is 1 to 5%, one would expect to see 2 to 10 patients with VTE in aspirin patients with an eGFR less than 30 and the same figure for placebo with eGFR less than 30. Do the authors have any explanations for this observation? We would also like to point out that, after thorough inspection and manual check, it seems to us that almost all of the percentages reported in the forest plot do not correspond with the ratio of the number of events to the total number of patients in the corresponding subgroup.

In conclusion, POISE-2 was underpowered to assess the ability of aspirin to prevent VTE. From the authors' perspective, this major weakness was to be imputed to the low VTE rate. From ours, it stems from the insufficient sample size, for VTE rate was known *a priori*. Increasing sample size by pooling POISE-2 with PEP and APTC cannot fix this shortcoming due to different patient populations.

Competing Interests

The authors declare no competing interests.

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