Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials

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Summary

Background Bivalirudin is an alternative to heparin in patients undergoing percutaneous coronary intervention (PCI). We aimed to define the effects of a bivalirudin-based anticoagulation regimen compared with a heparin-based anticoagulation regimen on ischaemic and bleeding outcomes.

Methods We searched Medline, the Cochrane Library, and relevant meeting abstracts (search done on April 9, 2014) for randomised trials that assessed bivalirudin versus heparin in patients planned for PCI. The primary efficacy endpoint was the incidence of major adverse cardiac events (MACE) up to 30 days. Secondary efficacy endpoints were death, myocardial infarction, ischaemia-driven revascularisation, and stent thrombosis. The primary safety endpoint was major bleeding up to 30 days. We calculated pooled risk ratios and 95% CIs using random-effects models.

Findings We included data from 16 trials involving 33,958 patients, of whom 2,422 experienced MACE and 1,406 had a major bleed. There was an increase in the risk of MACE with bivalirudin-based regimens compared with heparin-based regimens (risk ratio 1.09, 95% CI 1.01–1.17; p=0.0204), which was largely driven by increases in myocardial infarction (1.12, 1.03–1.23) and seemingly also by ischaemia-driven revascularisation (1.16, 0.997–1.34) with bivalirudin compared with heparin, with no effect on mortality (0.99, 0.82–1.18). Bivalirudin increased the risk of stent thrombosis (risk ratio 1.38, 95% CI 1.09–1.74; p=0.0074), which was primarily due to an increase in acute cases in ST-segment elevation myocardial infarction (4.27, 2.28–8.00; p<0.0001). Overall, bivalirudin-based regimens lowered the risk of major bleeding (risk ratio 0.62, 95% CI 0.49–0.78; p=0.0001), but the magnitude of this effect varied greatly (p<0.0001) depending on whether glycoprotein IIb/IIIa inhibitors were used predominantly in the heparin arm only (0.53, 0.47–0.61; p=0.0001), provisionally in both arms (0.78, 0.51–1.19; p=0.25), or planned in both arms (1.07, 0.87–1.31; p=0.53).

Interpretation Compared with a heparin-based regimen, a bivalirudin-based regimen increases the risk of myocardial infarction and stent thrombosis, but decreases the risk of bleeding, with the magnitude of the reduction depending on concomitant glycoprotein IIb/IIIa inhibitor use. Physicians should weigh the trade-off between ischaemic and bleeding events when choosing between different anticoagulant regimens.

Funding None.

Introduction Bivalirudin is an intravenous direct thrombin inhibitor that is used as an alternative to heparin in patients undergoing percutaneous coronary intervention (PCI). Most phase 3 trials of bivalirudin compared with heparin have used a composite primary endpoint of ischaemic and bleeding outcomes. Findings from these trials showed that, with regard to the aforementioned composite endpoint, bivalirudin was superior or at least non-inferior to heparin. Nevertheless, interpretation of such a net clinical outcome endpoint can be challenging because the amount of anticoagulation between the two treatment arms would be expected to have completely opposing effects on the incidence of thrombotic and bleeding complications.

Specifically, in many of these trials, a numerical excess of myocardial infarction (MI) or stent thrombosis was reported in patients treated with bivalirudin, although these excesses were often not statistically significant in the individual trials. In these same studies, bivalirudin-based regimens consistently and substantially reduced the risk of bleeding. However, most trials mandated routine glycoprotein IIb/IIIa inhibitor (GPI) use in the heparin-based arm and only provisional GPI use in the bivalirudin-based arm. Since GPIs increase bleeding, differences in bleeding between bivalirudin-based arms and heparin-based arms might have been secondary to differential use of GPIs. Moreover, use of P2Y₁₉ inhibitors has become standard practice, and data support their use on presentation as well as use of more potent inhibitors in patients presenting with acute coronary syndrome (ACS). For this reason, routine use of a GPI upstream does not seem to be as beneficial as it was previously thought to be, and thus has become less common. Such shifts in practice have prompted the development of new trials to compare bivalirudin with heparin in the setting of only provisional GPI use in both arms.
We therefore sought to define more precisely the effects of a bivalirudin-based anticoagulation regimen compared with a heparin-based anticoagulation regimen on specific ischaemic and bleeding outcomes, with particular attention to differential use of GPIs with regard to bleeding.

**Methods**

**Study design**

We undertook a systematic review and meta-analysis of relevant randomised controlled trials and stratified analyses by important differences in trial characteristics. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses. We did a computerised literature search of the Medline and Cochrane databases on April 9, 2014, with the following search terms: “bivalirudin”, “Angiomax”, “Hirulog”, “stent”, “percutaneous coronary intervention”, “acute coronary syndromes”, “ST-elevation myocardial infarction”, “non-ST-elevation myocardial infarction”, and “unstable angina”. No other search restrictions were applied. Additionally, both authors reviewed abstracts from major cardiology meetings held between March, 2013, and April, 2014.

Trials were included if they enrolled individuals with planned PCI (for ACUITY, we used the prespecified subgroup of patients who underwent PCI) and randomly assigned patients to treatment with bivalirudin (using the approved dosing regimen) or heparin (mostly unfractionated heparin [UFH], but also low-molecular-weight heparin) with or without a GPI. Trials that did not report clinical outcomes, involved fibrinolitics, were done before coronary stenting was available, or compared bivalirudin with anticoagulant regimens other than heparin or low-molecular-weight heparin were excluded from the analysis. For trials in which there were three arms, the relevant pairwise comparisons were assessed separately.

**Outcomes**

The primary efficacy endpoint was the incidence of major adverse cardiac events (MACE) up to 30 days (or to the latest timepoint if less than 30 days). Secondary efficacy endpoints were death, MI (including Q wave and non-Q wave), ischaemia-driven revascularisation, and stent thrombosis (including acute [within 24 h] and subacute [24 h to 30 days]). The primary safety endpoint was major bleeding up to 30 days (or to the latest available timepoint if less than 30 days). Information on these endpoints was abstracted by MAC and MSS independently into a structured dataset and compared. All disagreements were resolved by reaching consensus and there was complete agreement on abstracted results in the final dataset.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Year</th>
<th>Population</th>
<th>ACS (%)</th>
<th>PCI (%)</th>
<th>Radial (%)</th>
<th>Pretreatment with P2Y12 inhibitors</th>
<th>Mean age (years)</th>
<th>GPI (%)</th>
<th>GPI (%)</th>
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<tr>
<td>CACHET (2002)†</td>
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<td>59* 94</td>
<td>0%</td>
<td>100%</td>
<td>NR</td>
<td>Encouraged</td>
<td>63</td>
<td>3%</td>
<td>100%</td>
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<td>REPLACE-2 (2003)</td>
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<td>297 290</td>
<td>22%</td>
<td>98%</td>
<td>NR</td>
<td>Encouraged (86% received)</td>
<td>63</td>
<td>7%</td>
<td>97%</td>
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<tr>
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<td>532 524</td>
<td>17%</td>
<td>100%</td>
<td>NR</td>
<td>Encouraged (55% received)</td>
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<td>71%</td>
<td>73%</td>
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<td>284 573</td>
<td>NSTEMI 100%</td>
<td>100%</td>
<td>NR</td>
<td>Permitted</td>
<td>60</td>
<td>3%</td>
<td>99%</td>
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<td>2007</td>
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<td>NSTEMI 100%</td>
<td>100%</td>
<td>6%†</td>
<td>Per investigator (69% received)</td>
<td>63</td>
<td>9%</td>
<td>97%</td>
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<td>2569</td>
<td>NSTEMI 100%</td>
<td>100%</td>
<td>6%†</td>
<td>Per investigator (68% received)</td>
<td>63</td>
<td>97%</td>
<td>97%</td>
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<tr>
<td>HORIZONS-AMI (2008)§</td>
<td>2008</td>
<td>1800 1802</td>
<td>STEMI 100%</td>
<td>93%</td>
<td>NR</td>
<td>Mandated</td>
<td>60</td>
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<td>2008</td>
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<td>STEMI 100%</td>
<td>18%</td>
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<td>Mandated</td>
<td>67</td>
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<td>2009</td>
<td>167 168</td>
<td>Elective or urgent PCI 15%</td>
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<td>3%</td>
<td>Mandated</td>
<td>65</td>
<td>1%</td>
<td>100%</td>
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<td>2011</td>
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<td>Elective or urgent PCI 74%</td>
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<td>NR</td>
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<td>100%</td>
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<td>99%</td>
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<td>Mandated</td>
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<td>0%</td>
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<td>2012</td>
<td>49 52</td>
<td>Elective or urgent PCI 43%</td>
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<td>NR</td>
<td>Mandated</td>
<td>56</td>
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<td>100%</td>
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<td>STEMI 100%</td>
<td>86%</td>
<td>46%</td>
<td>Mandated</td>
<td>62</td>
<td>12%</td>
<td>59%</td>
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<tr>
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<td>2014</td>
<td>729 724</td>
<td>AMI 100%</td>
<td>97%</td>
<td>79%</td>
<td>Mandated</td>
<td>58</td>
<td>4%</td>
<td>100%</td>
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<tr>
<td>BRIGHT (heparin alone; 2014)§</td>
<td>2014</td>
<td>729 725</td>
<td>AMI 100%</td>
<td>97%</td>
<td>79%</td>
<td>Mandated</td>
<td>58</td>
<td>4%</td>
<td>6%</td>
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<tr>
<td>HEAT PCI (2014)§</td>
<td>2014</td>
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<td>STEMI 100%</td>
<td>82%</td>
<td>81%</td>
<td>Mandated</td>
<td>63</td>
<td>13%</td>
<td>15%</td>
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<tr>
<td>NAPLES III (2014)§</td>
<td>2014</td>
<td>418 419</td>
<td>Elective or urgent PCI 23%</td>
<td>99%</td>
<td>6%</td>
<td>NR</td>
<td>78</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

ACS=acute coronary syndrome. AMI=acute myocardial infarction. GPI=glycoprotein IIb/IIIa inhibitor. NR=not reported. NSTEMI=non-ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. *Patients in phase C. †Data from overall ACUITY trial because not reported in ACUITY-PCI. ‡P2Y12 inhibitors to be received before PCI, but not specified if before angiography. §Year presented.
We calculated pooled risk ratios using a random-effects model (Comprehensive Meta-Analysis 2-2-048, Biostat Inc, Englewood, NJ, USA) by the method of DerSimonian and Laird.16 We assessed heterogeneity using the Cochran $Q$ statistic, and when there was heterogeneity we assessed the amount with the $I^2$ measure (the percentage of total variability due to true between-study heterogeneity). We stratified results by key trial characteristics, including type of patient enrolled (predominantly ST-segment elevation MI [STEMI], predominantly non-ST-elevation [NSTE]-ACS, or predominantly elective or urgent PCI) and use of GPIs (predominantly planned in the heparin or bivalirudin arm versus provisional in the bivalirudin arm, provisional and use of GPIs (predominantly planned in the heparin arm, or planned in both arms)).

In sensitivity analyses, we included only trials with events in both arms, serially left one study out, partitioned the sole analysis to trials with at least 50 MACE events, and assessed heterogeneity on the basis of masking within the trial. We did meta-regression to examine two relations: (1) that of the natural log-transformed risk ratio of the effect of bivalirudin on mortality versus the natural log-transformed risk ratio of the effect of bivalirudin on major bleeding; and (2) that of the natural log-transformed risk ratio of the effect of bivalirudin on major bleeding versus the protocol-stipulated bolus dose of UFH among trials with provisional GPI use in both arms.

We assessed publication bias by visual inspection of funnel plots and by calculation of the $p$ value (one-sided) for Egger’s intercept. Asymmetry was addressed using Duval and Tweedie’s trim and fill method.17 All tests were two-sided, with $p$ less than 0·05 deemed significant.

### Figure 1: Major adverse cardiac events

There was no evidence of between-trial heterogeneity ($Q$ statistic 12·1, df 17; $p=0·79$). GPI=glycoprotein IIb/IIIa inhibitor. MACE=major adverse cardiovascular events.

### Figure 2: Major adverse cardiovascular events and individual cardiovascular events

![Figure 2](image-url)
Role of the funding source

There was no funding source for this study. Both authors (MAC, MSS) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 32 randomised clinical trials of bivalirudin, 16 of which met the inclusion criteria and were included in the meta-analysis (appendix), yielding a total of 33958 patients. The dosing regimens for bivalirudin were similar across trials, whereas the dosing regimens for heparin varied (appendix). The appendix also describes trial quality metrics.

The table lists the characteristics of the individual trials included in the meta-analysis. Nine trials enrolled patients undergoing urgent or elective PCI for unstable or stable angina2,5,18,19,21–24,27 and seven enrolled patients with ACS, either predominately STEMI (n=4)4,7,25,26 or NSTE-ACS (n=3)14–16 with planned PCI. In total across the 16 studies, 32936 (97%) of 33958 patients underwent PCI.

The composite primary endpoint of MACE typically included death, MI, ischaemia-driven revascularisation, and, in some trials, stroke, but was defined individually by each trial (appendix). 2422 patients had MACE. There was an increase in the risk of MACE with bivalirudin-based regimens compared with heparin-based regimens (risk ratio 1·09, 95% CI 1·01–1·17, p=0·0204; figure 1). These findings were consistent regardless of the type of patient the trial enrolled (ie, predominantly STEMI, predominantly NSTE-ACS, or predominantly elective or urgent PCI) or GPI use (predominantly planned in the heparin arm versus provisional in the bivalirudin arm, provisional in both arms, or planned in both arms; appendix).

There was no difference in risk of death between bivalirudin and heparin (risk ratio 0·99, 95% CI 0·82–1·18; figure 2; appendix). There was no significant relation between the reduction of bleeding and the reduction of mortality with bivalirudin across trials (p=0·21; appendix).

The increase in MACE with bivalirudin-based regimens was driven by an increase in MI (risk ratio 1·12, 95% CI 1·03–1·23; appendix) and seemingly also by ischaemia-driven revascularisation (1·16, 0·997–1·34). With regard to MI, among the trials that differentiated between Q-wave and non-Q-wave MI, 14% of MIs were attenuated in the two trials in which there was substantial use of third-generation P2Y12 inhibitors (47% in EUROMAX and 89% in HEAT PPCI). Ischaemia-driven revascularisation was higher with bivalirudin than with heparin in patients with ACS (risk ratio 1·26, 95% CI 1·02–1·56), but not in patients who underwent elective or urgent PCI (0·95, 0·68–1·32), although the test for heterogeneity did not reach significance (p=0·15; appendix).

The risk of stent thrombosis was higher with bivalirudin than with heparin (risk ratio 1·38, 95% CI 1·09–1·74; p=0·0074; appendix). More specifically, the risk of acute stent thrombosis was increased with bivalirudin (risk ratio 1·86, 95% CI 1·2–2·7; p<0·001), whereas there was no difference in the risk of subacute stent thrombosis (0·89, 0·53–1·49; p=0·66). The rates of stent thrombosis were highest in patients with STEMI, for whom the risk ratio with bivalirudin was 2·25 (95% CI 1·07–4·71; appendix). In patients with STEMI, bivalirudin increased the risk of acute stent thrombosis (risk ratio 4·27, 95% CI 2·28–8·00; p<0·0001) but not subacute stent thrombosis (1·06, 0·43–2·61; p=0·90).

The specific definition of major bleeding varied between trials (appendix), but most used a major bleeding definition based on either REPLACE-2 or
0.62, 95% CI 0.49–0.78; p<0.0001). However, there was significant heterogeneity between the trials (Cochran’s Q statistic 53.1, df 17; p<0.0001; I²=68.0%).

Specifically, the risk of bleeding with bivalirudin-based regimens versus heparin-based regimens significantly differed depending on concomitant GPI use (p<0.0001; figure 4). In trials in which GPI use was provisional in the bivalirudin arm but predominantly planned in the heparin arm, the risk ratio for bleeding for bivalirudin versus heparin was 0.53 (95% CI 0.47–0.61; p<0.0001). In trials that used GPIs on a provisional basis in both the bivalirudin and heparin arms, the risk ratio was 0.78 (95% CI 0.51–1.19; p=0.25). Among these latter trials, which included ISAR-REACT 3, in which a very high bolus dose of UFH (140 U/kg) was used, there was a possible association (p=0.065 from the meta-regression model) between the reduction in bleeding with bivalirudin and the dose of UFH (6–6% greater relative risk reduction for each increase of 10 U/kg in the protocol-stipulated bolus dose of UFH; appendix).

Lastly, there was no difference in bleeding in the trials in which GPI was used routinely with both bivalirudin and heparin (risk ratio 1.07, 95% CI 0.87–1.31; p=0.53).

We found similar overall results after excluding each individual study and after excluding trials with no events in a treatment arm (appendix). When the meta-analysis was limited to only those studies with at least 50 MACE (ten studies with 31748 patients), the results were similar (appendix). There was no evidence that masking in the trial affected the results (appendix). For trials with three arms, similar results were noted when the sole comparator was partitioned (appendix). There was no evidence of publication bias having a significant effect on the results (appendix).

Discussion
In this meta-analysis of 16 trials involving nearly 34000 patients, treatment with a bivalirudin-based regimen compared with a heparin-based regimen resulted in 0.47–0.61

Figure 4: Major bleeding, stratified by use of glycoprotein IIb/IIIa inhibitors
p for heterogeneity by trial design <0

$0\cdot 0001$.

Within trial design groupings, there was no evidence of between-trial heterogeneity in the trials with predominantly planned GPI in the heparin arm compared with provisional GPI in the bivalirudin arm (Q statistic 6.8, df 8; p=0.56), trials with provisional GPI in both arms (Q statistic 7.9, df 4; p=0.094, or trials with planned GPIs in both arms (Q statistic 3.0, df 3; p=0.39). GPI=glycoprotein IIb/IIIa inhibitor. PCI=percutaneous coronary intervention.
Articles

in a 9% relative increase in the risk of MACE. This difference was mainly due to an increase in MI and ischaemia-driven revascularisation. Bivalirudin also substantially increased the risk of stent thrombosis overall, and specifically, acute stent thrombosis in patients with STEMI. There was no difference in the incidence of death in patients treated with bivalirudin compared with heparin.

Overall, bivalirudin-based regimens substantially reduced the risk of bleeding; however, the magnitude of the reduction depended on concomitant GPI use. When GPI use was provisional in the bivalirudin arm but predominantly planned in the heparin arm, the risk of bleeding was 47% lower in the bivalirudin arm than in the heparin arm. By contrast, when GPI use was provisional in both arms there was a non-significant 22% reduction, and when it was routine in both arms there was no difference in risk of bleeding. Moreover, as one might expect, in trials with provisional GPI use in both arms the relative reduction in bleeding with bivalirudin seemed to depend on the dose of UFH used in the control arm (p=0.065). Thus, when considering the risk–benefit profile of a bivalirudin-based regimen versus a heparin-based regimen in terms of ischaemic events and bleeding, one must consider the patient presentation and whether the heparin would be coupled with routine GPI use. In the setting of upstream P2Y₉ inhibition, routine GPI use before PCI does not seem to be as beneficial as was previously thought. Those findings, along with the advent of more potent P2Y₉ inhibitors, have led to recommendations for more selective GPI use.

Our findings, which include data from more recent trials than did a previous meta-analysis, should help clinicians make a more informed decision when selecting an anticoagulant regimen to support PCI in patients with ACS, the exact dosing of an anticoagulant is especially important. That being said, the point estimate for the relative excess in MACE with provisional GPI use was close to 10% among almost all of the large, multicentre trials, and we did not identify high levels of heterogeneity for ischaemic events such as periprocedural MI and bleeding complications. The long-term sequelae of non-fatal events such as periprocedural MI and bleeding continue to be debated. Findings from some studies show a mortality risk among patients who bleed that is comparable to those who have an MI; however, observational studies such as these can only show associations and cannot assess causality. Nonetheless, the worse outcomes reported in patients who bleed might be related to either treatment strategies for bleeding or the discontinuation of evidenced-based antithrombotic treatments as a consequence of the bleeding. As we continue to strive towards personalised medicine, further work is needed to understand better the patient populations at high risk of ischaemic events who warrant more intensive antithrombotic therapy versus those patients at high risk of bleeding who might benefit more from less intensive regimens.

When comparing heparin and bivalirudin, we found no difference in death overall. However, in one of the clinical trials (HORIZONS-AMI, a large, multicentre trial), which examined bivalirudin plus provisional GPI versus heparin plus mandated GPI in patients with STEMI, there was a significant 34% reduction in 30-day mortality in the bivalirudin arm. A similar effect with bivalirudin was not reported in the other STEMI trials, even though some of them had similar or greater reductions in bleeding. How differences in trial design, patient characteristics, anticoagulant use before randomisation, or concomitant treatments might have played a part is unclear. Nonetheless, going forward, understanding how to reliably achieve a mortality benefit with bivalirudin-based regimens would be of great interest.

Our findings should also serve as impetus to continue to investigate specific strategies to minimise thrombotic complications during PCI without substantially increasing the risk of bleeding. Prolonging bivalirudin infusion after PCI could decrease the risk of acute stent thrombosis; however, this strategy would need to be studied with rigorous clinical outcomes trials before being used. In theory, more potent P2Y₉ inhibition might mitigate the increased risk of MI and stent thrombosis noted with bivalirudin. We did not identify such an effect in the two studies within our meta-analysis that had substantial use of third-generation P2Y₉ inhibitors; and, among patients with ACS, the time to achieve meaningful platelet inhibition with these oral drugs seems to be longer than previously thought. Cangrelor, an experimental intravenous P2Y₉ inhibitor, reduces peri-procedural MI and intraprocedural stent thrombosis compared with clopidogrel given at the time of PCI. The results of ongoing trials of bivalirudin will provide further understanding of the clinical outcomes with this antithrombotic drug in patients undergoing PCI (NCT01084993, NCT01433627).

This meta-analysis has several limitations. First, as is the case for any meta-analysis, data were combined from different studies, each of which had its own protocol and definitions. In particular, the exact dosing of an anticoagulant is especially important. That being said, dosing protocols were mostly similar across the trials and outcomes were generally defined similarly. Furthermore, the point estimate for the relative excess in MACE with bivalirudin was close to 10% among almost all of the large, multicentre trials, and we did not identify high levels of heterogeneity for ischaemic outcomes when analysed by patient type or trial design. Further analyses based on achieved amounts of anticoagulation might provide further information on this concern, but would entail analysis of a post-randomisation variable. Second, we used trial-level data because patient-level data were not available. Additionally, some of the included trials have been presented but not yet published. However, patient-level data are unlikely to change the overall findings. Moreover, the effect of one of the key factors, GPI use, is properly analysed by trial design (ie, allocation to provisional or planned GPI use) rather than by whether a patient actually received a GPI—a decision that is
non-randomised and therefore subject to substantial confounding by indication. In EUROMAX," GPI use in the heparin arm was left to physician preference. In most cases, physicians chose to add a GPI to heparin, whereas it was not permitted upstream in the bivalirudin arm. Thus, there was a large imbalance in GPI use (69% vs 11%), and for that reason this trial was included in the category of GPI use being predominantly planned in the heparin arm versus provisional in the bivalirudin arm. Although subgroup data are available by GPI use, these represent a post-randomisation subgroup analysis in an unmasked trial.28 The potential for confounding is shown by the fact that the rate of major bleeding was 6·3% in patients who received bailout GPI and 5·9% in patients who received routine GPI. Nonetheless, access to patient-level data would permit analysis of subgroups and other combina-
tions of individual endpoints and would allow for the creation of prediction models to identify individuals or groups who are at particularly high risk of harm or benefit from the respective treatments. Third, we presented data for outcomes at 30 days because data were available at that timepoint in most trials and it was a logical timepoint for a drug only given during the peri-PCI period. In the few trials with longer term data, the results were similar to the 30-day data.29 30 However, as more long-term data emerge, a dedicated analysis would be helpful.

In summary, in patients undergoing PCI, a bivalirudin-based regimen compared with a heparin-based regimen increased MACE. Conversely, there was a decrease in bleeding, at least when a GPI was predominantly routinely used with heparin and only provisionally with bivalirudin; this benefit was attenuated when GPI use was provisional in both groups. When choosing between different anticoagulant regimens in patients undergoing PCI, physicians should weigh the tradeoff between ischemic and bleeding events.

Contributors
Both authors did the literature search, analysed the data, interpreted the findings, and drafted the manuscript.

Declaration of interests
MSS has received research grant support through Brigham and Women’s Hospital from Abbott Laboratories, Accumetics, Amgen, AstraZeneca, Bristol-Myers Squibb, Critical Diagnostics, Daiichi-Sankyo, Eisai, Genzyme, GlaxoSmithKline, Intarcia, Merck, Nanosphere, Roche Diagnostics, Sanofi-Aventis, and Takeda; and has done consulting for Aegerion, Amgen, AstraZeneca, Bristol-Myers Squibb, Cubist, GlaxoSmithKline, Intarcia, Merck, MyoKardia, Pfizer, Quest Diagnostics, Sanofi-Aventis, Vertex, and Zeus Scientific. MAC declares no competing interests.

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