Impact of baseline hemorrhagic risk on the benefit of bivalirudin versus unfractionated heparin in patients treated with coronary angioplasty: A meta-regression analysis of randomized trials

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Background Bivalirudin significantly reduces 30-day major and minor bleeding compared with unfractionated heparin (UFH), while resulting in similar or lower rates of ischemic events in both patients with stable and unstable coronary disease undergoing percutaneous coronary intervention. We performed a meta-analysis of randomized trials to evaluate the impact of bivalirudin compared with UFH, with or without glycoprotein IIb/IIIa receptor inhibitors (GPI), on the rates of mortality, myocardial infarction (MI), and major bleeding.

Methods We searched electronic databases for randomized controlled trials with >100 patients comparing bivalirudin (±provisional GPI) with UFH with either routine or provisional GPI in patients undergoing percutaneous coronary intervention. The principal efficacy end points were mortality and MI within 30 day, whereas major bleeding was the principal safety end point. We assessed the benefit of bivalirudin for each efficacy end point relative to the baseline bleeding risk, using the control (UFH) major bleeding rate as proxy for that risk.

Results A total of 12 randomized trials that enrolled 33,261 patients were included. Overall, there was no significant difference in mortality and MI between bivalirudin monotherapy and UFH (±GPI), whereas major bleeding was significantly lower with bivalirudin. Bivalirudin reduced major and minor bleeding across the entire bleeding risk spectrum.

Conclusions Bivalirudin significantly reduces major and minor bleeding regardless of the estimated baseline hemorrhagic risk. (Am Heart J 2014;167:401-412.e6.)

Bivalirudin is a direct antithrombin inhibitor, which has been extensively investigated in patients undergoing percutaneous coronary intervention (PCI). Large scale studies have demonstrated that bivalirudin significantly reduces 30-day major and minor bleeding and thrombocytopenia compared with unfractionated heparin (UFH) plus a glycoprotein IIb/IIIa inhibitor (GPI), while resulting in similar rates of ischemic events in patients both with stable angina and unstable angina or non–ST-segment elevation myocardial infarction (UA/NSTEMI) undergoing PCI.[1-6] In ST-segment elevation myocardial infarction (STEMI), patients treated with bivalirudin alone as compared with UFH and GPI also had significant reductions in 30-day and 3-year cardiac and all-cause mortality.[7,8] Recent studies have shown that bleeding complications are consistently and independently associated with subsequent adverse cardiac events, including myocardial infarction (MI) and death.[9] In prior studies, major bleeding has been associated with 2- to 8-fold increase in subsequent mortality in acute coronary syndrome (ACS) and PCI.

The incremental risk of increased mortality in patients with major bleeding is equivalent to or greater than after

Figure 1


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│ Search criteria:                                     │
│                                                      │
│ - Randomized clinical trials (RCTs) of Bivalirudin  │
│   vs Unfractioned Heparin                            │
│                                                      │
│ - Enrolling ≥ 100patients                            │
│                                                      │
│ - Follow-up ≤ 30 days                                │
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│ Search results:                                      │
│                                                      │
│ 20 potentially appropriate RCTs identified for       │
│ detailed evaluation                                  │
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                    │ 8 trials were excluded (small    │
                    │ sample size, no end-point ≤ 30   │
                    │ days)                            │
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│ 12 trials finally included in the meta-analysis      │
│ (n = 33261)                                          │
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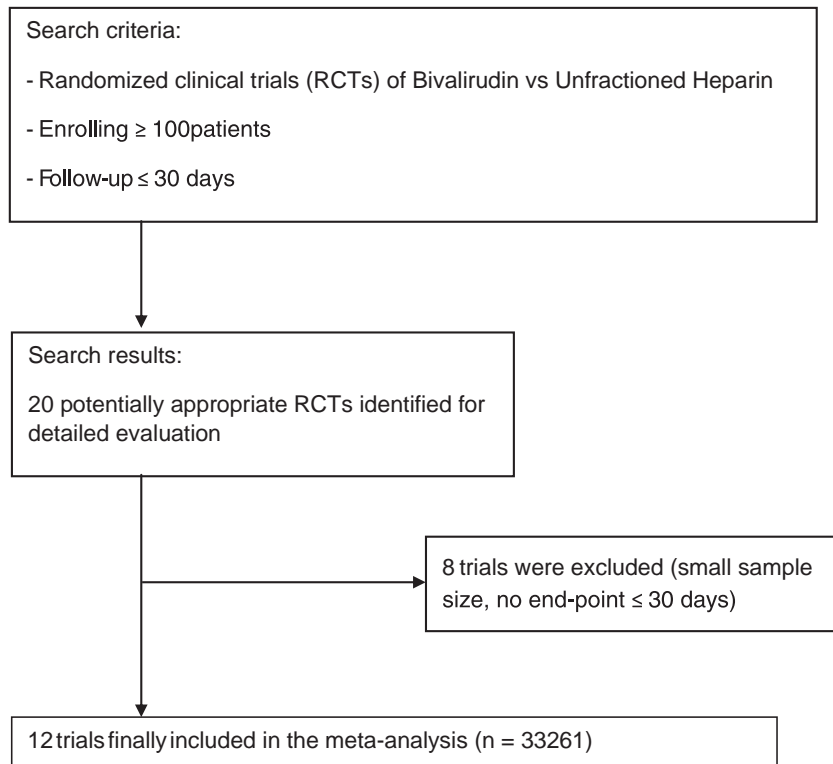
Diagram flow of the systematic overview process.

MI.[9] Despite the well-established benefits of bivalirudin in terms of bleeding complications, its benefit with respect to mortality is uncertain. Moreover, the impact of bivalirudin on mortality, MI, and even major bleeding complications as a function of baseline hemorrhagic risk has not been studied. We, therefore, performed a meta-analysis of randomized trials to evaluate the impact of bivalirudin use compared with UFH, with or without GPI, on the rates of mortality, MI, and major bleeding in patients treated with PCI. We evaluated also the effect of bivalirudin on primary end points as function of the baseline hemorrhagic risk profile of patients treated with PCI.

Methods

Three expert cardiologists (G.T., G.M., and E.P.N.) independently and systematically searched electronic databases (Medline, Central, Embase, the Cochrane Central Register of Controlled Trials, http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html and http://www.clinicaltrialresults.org) to identify randomized controlled trials using key words such as "bivalirudin," "unfractionated heparin," "randomized trials," "bleeding," "glycoprotein IIb/IIIa inhibitor," "percutaneous coronary angioplasty," "stent," "anticoagulation regimen." We also searched for abstracts of scientific sessions reported in *Circulation*, the *European Heart Journal*, the *Journal of the American College of Cardiology*, and the

American Journal of Cardiology. Reference lists of the identified reports, relevant studies, and meta-analyses were scanned. Furthermore, oral presentations and/or expert slide presentations identified at http://www.theheart.org, http://www.tctmd.com, http://www.crtonline.com, http://www.clinicaltrialresults.org, http://www.esccardio.org, http://www.europcr.com, and http://www.acc.org were examined. Non–English-language reports were also included. To be eligible for inclusion, studies had to be randomized controlled trials comparing bivalirudin monotherapy (provisional bailout use of GPI allowed) with UFH with either routine use or provisional bailout of GPI in patients undergoing PCI and had to enroll at least 101 patients and report the outcomes of interest. We excluded trials or arms of trials that used bivalirudin plus GPI in all patients because the latter strategy was associated with increased bleeding and is not recommended in the current guidelines.[10-12]

Data collection and quality assessment

After identification, each trial was independently evaluated by 3 investigators (G.T., E.P.N., and G.M.) for patient population, study treatment, protocol, and end point selection for data abstraction and inclusion into the final analysis. Discordances were resolved by consensus. The flow sheet of the trial selection process is shown in Figure 1. The listing, acronyms, and main characteristics of the selected randomized trials are reported in Table I. The ACUITY trial[4] included 3 randomized groups, but as