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CLINICAL RESEARCH

CORONARY

Combined Use of Bivalirudin and Radial Access in Acute Coronary Syndromes Is Not Superior to the Use of Either One Separately

Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

OBJECTIVES The aim of this meta-analysis was to study the relation between access site and bivalirudin use on outcomes in patients with acute coronary syndrome (ACS).

BACKGROUND Bivalirudin and radial access use are 2 strategies that are increasingly used to lower major bleeding in patients with ACS undergoing invasive approaches. The interaction between these 2 strategies and the benefit of using them in combination are unclear.

METHODS This analysis included randomized controlled trials that compared bivalirudin to heparin with or without glycoprotein IIb/IIIa inhibitors in patients with ACS and reported outcomes stratified by arterial access site. Meta-analyses of outcome data were performed on the basis of access site and anticoagulation regimen. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from event rates using random-effects models.

RESULTS Eight trials with a total of 27,491 patients were included. Bivalirudin reduced major bleeding risk in patients with femoral access (OR: 0.51; 95% CI: 0.46 to 0.6; $p < 0.001$) but not in patients with radial access (OR: 0.75; 95% CI: 0.45 to 1.26; $p = 0.28$). Moreover, radial access reduced major bleeding risk in patients treated with heparin (OR: 0.57; 95% CI: 0.43 to 0.77; $p < 0.001$) but not in patients treated with bivalirudin (OR: 0.96; 95% CI: 0.65 to 1.41; $p = 0.83$). There were no differences in major adverse cardiovascular events or all-cause mortality between bivalirudin and heparin, regardless of access site.

CONCLUSIONS Bivalirudin reduces bleeding risk only with femoral access, and radial access reduces bleeding risk only with heparin anticoagulation. Therefore, there is no additional benefit to the combined use of bivalirudin and radial access strategies in patients with ACS. (J Am Coll Cardiol Intv 2016;9:1523–31) © 2016 by the American College of Cardiology Foundation.

Antithrombotic therapy and invasive approaches are the mainstay of management of acute coronary syndromes (ACS) (1,2). Those strategies improve ischemic outcomes and survival of patients with ACS (3,4). However, they come at the expense of increased incidence of bleeding, which by itself can increase acute morbidity and mortality (5,6). Therefore, adoption of bleeding

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

GPI = glycoprotein IIb/IIIa inhibitor

MACE = major adverse cardiovascular event(s)

OR = odds ratio

RCT = randomized controlled trial

avoidance strategies is essential to improve outcomes in patients with ACS (7).

Given that a substantial portion of bleeding in patients with ACS is related to access site (8), an effective strategy to avoid bleeding is the use of radial access, which is associated with lower major bleeding rates because of the smaller caliber and easier hemostasis of the radial artery compared with the femoral artery (9–11).

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Another bleeding-reducing strategy that has been proposed is the use of bivalirudin instead of heparin for anticoagulation (12). Randomized controlled trials (RCTs) have shown that bivalirudin reduces major bleeding compared with heparin plus glycoprotein IIb/IIIa inhibitors (GPIs). However, this bleeding-reducing effect was not evident when GPIs were used selectively in the heparin arm (13,14).

Even though outcomes of bivalirudin and radial access were evaluated separately in many RCTs, it is unclear if there is any additional benefit for using both strategies simultaneously. Therefore, we sought to evaluate, by meta-analysis, the relation between arterial access and the choice of anticoagulation regimen on outcomes in patients with ACS.

METHODS

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (15).

DATA SOURCE AND SEARCH METHOD. We searched PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for all studies comparing bivalirudin with heparin through December 2015. The following keywords were used: "bivalirudin," "Angiomax," "Hirulog," "heparin," "acute coronary syndromes," "ST-elevation myocardial infarction," "non ST-elevation myocardial infarction," "unstable angina," and "percutaneous coronary interventions." Only studies in English and studies with English translations were included. No other search restrictions were applied. Citations were screened at the title and abstract level, and relevant citations were retrieved as full reports. References of the included trials were also manually searched for relevant studies that might have been missed during the initial search. In addition, the "similar articles" search feature on PubMed was used.

STUDY ENDPOINTS AND SELECTION PROCESS. The endpoints studied in this meta-analysis were the incidence of major bleeding, major adverse cardiovascular events (MACE), and all-cause mortality at 30 days. Definitions of major bleeding and MACE varied among studies and are shown in Online Table 1. The BRIGHT (Bivalirudin in Acute Myocardial Infarction vs. Heparin and GPI Plus Heparin Trial) study (16) reported bleeding outcomes in patients with radial and femoral access as a combination of major and minor bleeding and therefore was excluded from major bleeding analyses.

Trials were included if: 1) they were RCTs comparing bivalirudin with heparin plus either routine or provisional or bail-out GPIs; 2) they included patients with ACS; 3) 1-month follow-up outcome data were reported; and 4) at least 1 of the studied outcomes was stratified by access site (whether in the original trial publication or in a subgroup analysis published at a later date). Both the ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment 4) (17) and BRAVE-4 (Bavarian Reperfusion Alternatives Evaluation) (18) trials included <1% patients with radial access and therefore were counted as femoral access-only trials in this meta-analysis.

Trials were excluded if: 1) there was no control group; 2) GPIs were mandated in the bivalirudin arm; 3) anticoagulant agents other than heparin or bivalirudin were used; 4) thrombolytic agents were used; or 5) only balloon angioplasty was done.

DATA EXTRACTION AND QUALITY ASSESSMENT. Data were independently extracted from the included trials by the first and second authors (G.S.M. and G.F.G.) on a pre-specified data sheet. Any discrepancy was discussed until there was complete agreement on all the results in the final data sheet. The potential risk for bias of the RCTs was assessed according to the Cochrane Collaboration guidelines (Online Table 2) (19).

STATISTICAL ANALYSIS. Access-based analysis was performed by comparing outcomes of bivalirudin with those of heparin in femoral and radial access patients. Anticoagulation-based analysis was then performed by comparing outcomes of radial access with those of femoral access in bivalirudin- and heparin-treated patients. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from rates or percentages using the more conservative DerSimonian and Laird random-effects model (20). All tests were 2 sided, and p values <0.05 were considered to indicate statistical significance. Heterogeneity was assessed using the Cochran Q test and the I^2 statistic, which describes the percentage of total variation across studies that is due to