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Association between arterial access site and anticoagulation strategy on major bleeding and mortality: A historical cohort analysis in the Veteran population

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ABSTRACT

Background: Studies have shown reduction in major bleeding with trans-radial intervention (TRI) compared with trans-femoral intervention (TFI), and with use of bivalirudin compared with heparin + glycoprotein IIb/IIIa inhibitors (GPI). We compared major bleeding, mortality and the interaction between arterial access site and the anticoagulant used for PCI in Veterans.

Methods: A retrospective cohort of 1192 consecutive patients who underwent PCI at a VA hospital between 2006 and 2012 was divided into TFI-heparin (n = 192), TFI-bivalirudin (n = 272), TRI-heparin (n = 274) and TRI-bivalirudin (n = 454) groups. Primary outcomes were in-hospital major bleeding, in-hospital and 1-year all-cause mortality. Secondary outcomes were in-hospital MI, in-hospital and 1-year MACE and net adverse cardiovascular events (NACE - composite of major bleeding + MACE).

Results: Femoral access was associated with a significantly increased risk of major bleeding compared with radial access (OR 11.87, $p < 0.001$). Correspondingly, radial access was protective against major bleeding compared with femoral access (OR 0.128, $p < 0.01$), but did not lower mortality or MACE by itself. Severe anemia was the only predictor of in-hospital all-cause mortality (OR = 27.62, $p < 0.008$). Presence of anemia and age > 70 predicted 1-year mortality, whereas major bleeding and anemia predicted 1-year MACE. An interaction was noted between anticoagulant and access site, such that heparin showed significantly greater major bleeding in the femoral group compared with the radial group. Bivalirudin resulted in similar risk of bleeding, regardless of access site. There was a synergistic interaction between radial access and heparin (HR 0.38, $p < 0.05$), but not radial access and bivalirudin, on reduction in 1-year NACE.

Conclusion: Radial access for PCI is associated with reduction in major bleeding, but does not have an effect on in-patient or 1-year MACE and mortality. Major bleeding is associated with poor short and intermediate term outcomes. In addition, anemia is strongly associated with increased in-patient and 1-year mortality. There is a differential effect of heparin but not bivalirudin on major bleeding, depending on the access site. There is no synergism between radial access and bivalirudin in lowering the composite outcome of MACE and major bleeding at 1 year.

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1. Introduction

Major bleeding following percutaneous coronary intervention (PCI) is associated with increased short and long term mortality, especially in patients with acute coronary syndrome (ACS) [1–4]. Femoral arterial access for PCI (trans-femoral PCI or TFI) is associated with a significantly increased risk of major bleeding, especially when combined with the use of heparin and a glycoprotein IIb/IIIa inhibitor (GPI) for anticoagulation. Two main strategies have been studied to lower major bleeding and mortality that focus on alternate anticoagulation and arterial access. Strategies include: (1) use of a short acting direct anticoagulant such as bivalirudin, in place of a combination of heparin and GPI, and (2) radial arterial access (trans-radial PCI or TRI) in place of femoral access.

Bivalirudin reduces major bleeding compared to a combination of heparin and GPI [5]. Trans-radial access is associated with markedly reduced major bleeding and mortality compared to TFI PCI [6–12]. The impact of combining bivalirudin anticoagulation with TRI (TRI-bivalirudin) and its comparison with other combinations of arterial access and anticoagulation has not been studied extensively. Therefore, the aim of the present study was to investigate whether or not there was an interaction between arterial access and anticoagulation on bleeding and mortality. We compared major bleeding and mortality amongst four groups of patients treated with different anticoagulation and arterial access strategies.

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2. Materials and methods

2.1. Study population

We performed a retrospective analysis of 1201 consecutive patients treated with PCI at the Nashville Veterans Affairs hospital between January 1, 2006 and March 30, 2012. The patients were stratified into four cohorts based on the anticoagulant (heparin or bivalirudin) and arterial access site (femoral or radial) used for PCI. The choice of anticoagulant and access site was determined by the operator performing the PCI. Four treatment groups were identified: TFI - heparin, TFI - bivalirudin, TRI - heparin, TRI - bivalirudin. The only exclusion criterion was access other than TFI or TRI.

Patients undergoing only IVUS (intravascular ultrasound) or FFR (fractional flow reserve) were not included. The Nashville VA institutional review board approved the protocol and provided exemption for informed consent.

2.2. Study end points

The primary endpoints included major bleeding occurring during hospital stay following the index PCI, in-hospital all-cause mortality and one year all-cause mortality. Major bleeding was defined as in the ACUITY trial, and included any of the following: access-site hemorrhage requiring medical, surgical or endovascular intervention, hematoma > 5 cm, drop in hematocrit (Hct) by 12% or more without an overt source of bleeding or drop in Hct concentration by 9% or more with an overt source of bleeding, need for blood transfusion, reoperation for bleeding, intraocular or intracranial hemorrhage [5]. Bleeding was categorized into access-site and non-access site. In nine patients, a significant decrease in Hct was clinically judged to be due to procedural blood loss during a lengthy PCI, chronic illness or bone marrow suppression. These patients had no evidence of overt bleeding, and were not adjudicated as a major bleeding event, even though blood transfusion was required in 4 out of these 9 patients. Coronary artery bypass graft (CABG) related bleeding was not included. Secondary endpoints included in-hospital major adverse cardiovascular events (MACE), which included all-cause death, MI, stroke and unplanned urgent target vessel revascularization, in-hospital net adverse clinical events (NACE), which included a composite of MACE and major bleeding, in-hospital MI, in-hospital peripheral vascular complications (pseudoaneurysm, arterial dissection, arteriovenous fistula, retroperitoneal bleeding), contrast induced nephropathy, 1-year MACE, 1-year NACE and 1-year cardiac mortality. We also performed an analysis to study the interaction between anticoagulation and arterial access site. In other words, we sought to determine if the benefit of one anticoagulant over another depends on the type of arterial access. In the same way, we wanted to evaluate if the benefit of one method of arterial access over another depends on the anticoagulant used for PCI. Finally, we wanted to investigate the synergistic beneficial interaction of a particular combination of anticoagulant and arterial access (specifically TRI-bivalirudin) over other combinations.

2.3. Statistical analysis

Contingency table analysis was used to analyze categorical data, and tested with chi-square or Fisher exact tests, where appropriate. Stepwise binary or multinomial logistic regression was used for multivariable analysis of the odds ratios (OR) of outcomes that were not time-dependent, where appropriate. Entry criteria for Cox and logistic regression variable selection were entry probability of 0.10, and removal was set at 0.15. Stepwise Cox regression analysis was used for multivariable analysis to estimate the hazard ratios (HR) for time dependent outcomes with Kaplan Meier curves. Only statistically significant results from the stepwise analyses are reported. The initial regression models included body surface area (BSA), age > 70, anemia, non-ACS, ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), GPI use, access site, anticoagulant used, creatinine > 1.3 mg/dl. Analyses were performed with IBM SPSS V. 22 (IBM SPSS, Chicago, Ill USA) and SAS V9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline characteristics

Amongst the 1201 consecutive patients on whom data was collected, 9 patients were female and were excluded from analysis for statistical reasons. The remaining 1192 subjects were stratified into the following groups - TFI-heparin (n = 192), TFI-bivalirudin (n = 272), TRI-heparin (n = 274) and TRI-bivalirudin (n = 454). Unadjusted analysis of baseline variables demonstrated a significantly increased frequency of ACS (STEMI and NSTEMI) and GPI use in the TFI-heparin group compared to other cohorts. Consequently the percentage of non-ACS cases was significantly lower in the TFI-heparin group. The frequency of chronic kidney disease (CKD), defined as creatinine (Cr) > 1.3 mg/dl, was lower in the TRI-bivalirudin group compared with the other three groups. The frequency of moderate anemia (hematocrit 30–35) was significantly lower in the TRI-Heparin group compared with the other three groups. These differences are summarized in Table 1.

3.2. Clinical outcomes

3.2.1. Unadjusted analysis of primary and secondary outcomes

Unadjusted frequencies of primary and secondary outcomes between the groups are compared in Tables 2A and 2B. The frequency of in-hospital major bleeding was numerically higher in the TFI-heparin group compared with other groups, but due to presence of zero events in the TRI-heparin, we were unable to test for statistical significance. The same limitation was noted in analysis of in-hospital all-cause death and 1-year cardiac death. There was a significantly higher frequency of in-hospital NACE in the TFI-heparin group and a significantly lower frequency of 1-year NACE in the TRI-heparin group.

3.2.2. Multivariable logistic regression analysis of primary and secondary outcomes

3.2.2.1. Major Bleeding. Increased likelihood of major bleeding was significantly associated with femoral access, age > 70 years, Cr > 1.3 mg/dl, STEMI, heparin anticoagulation, and GPI use. The factor that posed the greatest risk for major bleeding was STEMI (OR = 13.59, $p < 0.009$). Femoral access was associated with a significantly increased risk of major bleeding compared with radial access (OR 11.87, $p < 0.001$). Correspondingly, radial access was protective against major bleeding compared with femoral access (OR 0.128, $p < 0.01$). Older patients (age > 70 years) were at greater risk (OR = 2.88, $p < 0.03$) for major bleeding, as were those who had impaired renal function (OR = 4.40, $p < 0.003$). Heparin increased the risk of major bleeding (OR = 3.17, $p < 0.06$) compared with bivalirudin, but not significantly. Bivalirudin was protective against major bleeding compared with heparin, however the effect was of borderline statistical significance (OR = 0.3, $p < 0.042$). Similarly, GPI use increased the risk of major bleeding, but not significantly (OR = 5.52, $p < 0.08$).

3.2.2.2. In-hospital all-cause mortality. Severe anemia was the only predictor of in-hospital all-cause mortality (OR = 27.62, $p < 0.008$), and the effect was highly significant and large.

3.2.2.3. One year all-cause mortality. The factors that predicted one year all-cause mortality included two effects: anemia (moderate, severe, and mild) and age > 70 years. Moderate anemia was the strongest predictor for one year all-cause mortality (OR = 15.17, $p < 0.0001$),

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