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Bivalirudin Use in the Elderly for Acute Coronary Syndrome

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Authors' contributions

This work was carried out in collaboration between all authors. Author OA designed the study, did the literature search and wrote the manuscript. Author RM assisted in the literature search and wrote the manuscript. Author GL mentored the design of the study and reviewed the manuscript.

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Review Article

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ABSTRACT

Introduction: Bivalirudin has been approved for use in acute coronary syndromes as part of the anticoagulation regimen. Elderly patients are at a higher risk for bleeding because of their co morbidities, decreased body mass and their age. Hence, this article reviews the landmark published papers on bivalirudin therapy in this patient population with the goal of understanding the particular benefits and risks.
Discussion: Several review articles suggest that the use of bivalirudin alone is associated with lower rates of major bleeding when compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndrome with invasive strategy planned. These beneficial effects span through the age ranges. Therefore, it is a good option for elderly patients. Decreased bleeding complications lead to better clinical outcomes in the elderly after percutaneous coronary intervention. It also leads to decreased length of stay in the hospital.

Keywords: Anticoagulants; elderly; acute coronary syndrome; ST elevation myocardial infarction.

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1. INTRODUCTION

Bivalirudin is a direct thrombin inhibitor. It inhibits both circulating and clot –bound thrombin directly by binding to the catalytic and anion-binding exosite. It undergoes extensive tissue distribution shown by its high volume of distribution compared to blood volume after either intravenous or subcutaneous administration. In contrast to unfractionated heparin (UFH), bivalirudin binds thrombin directly and reversibly in a mixed competitive/non-competitive manner. Its effect is irrespective of whether thrombin is free or fibrin-bound.

The drug is renally cleared, hence dosing needs to be adjusted in patients with renal impairment. The half-life is 25 minutes in individuals with normal renal function and up to 3.5 hours in end-stage renal disease patients [1]. This is particularly important as most of the elderly population experience a decline in their glomerular filtration rate (GFR) that puts them in the chronic kidney disease category (CKD) [2].

Changes in hemostatic mechanisms should also be considered in the elderly. Studies have shown decreased fibrinolytic activity and increased fibrin levels which could be related to the prothrombotic state in the elderly [3].

Therefore, our review will aim to discuss the risks vs benefits of bivalirudin use in the elderly in the setting of acute coronary syndrome (ACS).

2. DISCUSSION

Several studies have identified age as an independent predictor of non-coronary artery bypass graft (CABG) related bleeding after ACS [5,6,13], however, superiority of one anticoagulation regimen over another during ACS especially in the elderly is yet to be proven. Major bleed, composite ischemia and mortality were the endpoints in the vast majority of studies assessing the safety and efficacy of bivalirudin use in ACS. Major bleeding post percutaneous coronary intervention (PCI) or CABG was a key prognostic factor in determining mortality and morbidity at 30 days and 1 year. An analysis of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial defined major bleeding as one of the following: intracranial or intraocular bleeding, access site bleeding requiring intervention, reduction of hemoglobin of ≥4g/dl without or ≥ 3 with an overt bleeding source, reoperation for bleeding or blood product transfusion or ≥5 cm diameter hematoma [4,5].

Iijima et al. [6] evaluated the profile of bleeding and ischemic complication with bivalirudin and UFH after PCI. The study included 4570 patients with coronary artery disease (CAD) enrolled in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment Trial (ISAR- REACT) trial. They analyzed the safety and efficacy of bivalirudin vs UFH for seven independent correlates of major bleeding or myocardial infarction (MI): age, sex, body weight, cholesterol levels, multi-lesion intervention and complexity of lesions. Bivalirudin was superior to UFH with regard to major bleeding in patient's ≤75 years of age. Bivalirudin was associated with a reduction in major bleeding (3.1 vs 4.6%, P=0.008). That reduction, however, was most significant in subsets of patients considered at low risk of bleeding, and that bivalirudin was not efficacious in reducing the risk of bleeding in those patients at a higher risk. As for MI, there was a higher trend of MIs in most subsets treated with bivalirudin as compared to UFH, but that has only achieved statistical significance for only one variable, that is body weight >70 kg (5.4% with bivalirudin vs 4.0% with UFH). Hence, subsets that had the greatest reduction in risk of bleeding with bivalirudin had the greatest increase in the risk of MI as well.

The ACUITY trial is the largest randomized controlled trial (RCT) to date comparing the outcomes of different anti-coagulation regimen post PCI in patients with moderate to high risk NSTEMI. The study included 13,800 patients with moderate- to high-risk ACS who were prospectively randomized in 600 centers to one of three treatment regimens: UFH/enoxaparin + glycoprotein IIb/IIIa inhibitor (GPI) versus bivalirudin + GPI versus bivalirudin +/- provisional GPI. The patients had cardiac catheterization within 72hours, followed by percutaneous or surgical revascularization when appropriate. Patients then underwent a second randomization where patients assigned to receive GPI were sub-randomized to upstream drug initiation, versus GPI administration during angioplasty only. The primary end point was the composite of death, MI, unplanned revascularization for ischemia, and major bleeding at 30 days. Clinical follow-up continued for up to one year. This study was a very large study with several sub analyses which has helped emphasizing the utility of bivalirudin in

ACS. It has also helped in guiding the timing and necessity of GPI administration [7]. In a subgroup analysis of the ACUITY trial, the rates of composite endpoint of ischemia were similar for bivalirudin alone compared to UFH plus GPI, with statistically significant decreased rates of major bleeding in the bivalirudin monotherapy group and improved net clinical outcomes at 30 days [8].

Another important variable was evaluated in a study conducted by Feit et al. Of the 13,800 patients studied in the ACUITY trial, 3,852 had diabetes mellitus. Bivalirudin monotherapy was compared to bivalirudin plus GPI versus UFH plus GPI for the same outcomes; major bleeding and MI. This study used 75 years old as the cutoff point for age for the subgroups. Diabetes was defined as diagnosed hyperglycemia requiring therapy with diet, oral agents and/or insulin. Of the study population 690 patients were diabetic and 75 years of age or older, and were divided as follows: 239 (18.4%) received UFH plus GPI, 236(18.6%) received bivalirudin plus GPI, while 215(16.7%) received bivalirudin alone. In all age groups, composite ischemia was higher in the UFH plus GPI group (8.9% vs 7.9% RR 0.89, {95% CI: 0.69-1.15}). Composite ischemia events were not significantly different between the two age groups: <65 year old and ≥65 year old. However, major bleeding was the turning point as this event rate was found to be 3.7% for the bivalirudin monotherapy group versus 7.1% for the UFH + GPI group regardless of age (RR 0.53,{95% CI: 0.37-0.74}). This finding was even more significant in the subgroup analysis showing an event rate of only 5.4% in the bivalirudin arm compared to 10.4% with UFH + GPI in the ≥ 65 year old group (RR 0.52, {95% CI: 0.35-0.78}) [9].

Another sub-analysis of the ACUITY and the ISAR-REACT 4 trials supported the superiority of bivalirudin in the diabetic population in regards to major bleeding reduction and composite ischemia putting the superiority of GPI in diabetics under questioning. In this study, another variable was evaluated. 3789 patients presenting with non-ST elevation myocardial infarction (NSTEMI) were pretreated with clopidogrel before undergoing PCI. Patients were assigned to either bivalirudin monotherapy (n=1928) or UFH+ GPI (n=1870). Overall net adverse clinical events (NACE) in this analysis were as follows in all age groups: 258 patients (13.4%) in bivalirudin group versus 275 patients (14.7%) in the standard regimen group (OR 0.90, CI 0.76-1.06, p=0.21) .In patients older than 66 years of age, NACE rate was12% versus 13 %, indicating a slight advantage of bivalirudin use in this age group [10].

Low muscle mass have been associated with female gender and older age. Lansky et al studied this, as a variable, in a pooled analysis of the ACUITY trial. The study evaluated the impact of gender and antithrombin strategy on early and late clinical outcomes in patients with NSTEMI. Of the ACUITY study population 4,157 were women while 9,662 were men. In the female group, 25% were older than 75 while that was true only for 15 % of the male group. Women in this study were found to be older, have lower body weight and to have CKD, diabetes, hypertension, anemia, family history of CAD, baseline electrocardiogram (ECG) changes and higher ejection fraction (EF) compared to men. No significant difference was found in men vs women in regards to composite ischemia at 30 days and 1 year. Women had significantly higher 30-day non-CABG related major bleeding compared to men (8% vs 3% *p<0.0001)* with a resultant increase in net clinical outcomes (13% vs 10% $p<0.0001$). Bivalirudin monotherapy resulted in significantly lower major bleeding (5%) compared with UFH plus GPI (10%) and bivalirudin plus GPI (8%) [11].

White et al. [12] evaluated the safety and efficacy of bivalirudin with and without GPIs in ACS patients undergoing PCI. He conducted a pooled analysis of the ACUITY trial study outcomes at 12 months post PCI. Of the original study population 7,789 patients underwent PCI. Patients were assigned to 3 different treatment regimens as follows: 2,561 received a GPI combined with either UFH or enoxaparin; 2,609 received a GPI plus bivalirudin while 2,619 received bivalirudin monotherapy. At 1 year, no difference in mortality was found between the monotherapy group 3.1% vs the standard therapy group (UFH+GPI) 3.2%, this was specifically true in our study population with 5% mortality in both groups (RR 1.0, {95% CI: 0.7-1.43}). While composite ischemia was slightly higher in the monotherapy group (19.2%) vs UFH + GPI group (17.8%) in all age groups, no statistical difference was observed in patients ≥ 65 year old (RR 1.05, {95% CI: 0.9-1.24).

A practical risk score to predict the risk and implications of major bleeding in ACS was developed by Mehran et al [13]. The study looked at patients from both ACUITY and

Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials. Of the 17,421 patients in both studies, 744 (7.3%) had a non-CABG related major bleeding at 30 days. In a prospective analysis of those patients, 6 independent factors were determined to be strong baseline predictors of major bleeding. Those baseline characteristics were identified as gender, age, serum creatinine, white blood cell count, anemia and presentation (STEMI, NSTEMI with raised biomarkers, and NSTEMI with negative biomarkers). One treatment variable was added to complement the scoring system that is the use of bivalirudin monotherapy vs combination therapy (UFH+GPI).

Integer-Based Risk Score was developed and based on the previously mentioned predictors and total points scored, patients are divided (in terms of risk of non-CABG related major bleeding at 30 days) as follows: low risk <10, moderate 10-14, high 15-19 and very high >20.To note, bivalirudin monotherapy when combined with any other risk factor deducts 5 points from total score. This is most significant in the age group at the highest risk for bleeding; patients > 80 year old. This group is assigned 12 points solely based on age, this emphasizes the importance of using an anticoagulant with a low bleeding risk profile in such a high risk group [13].

3. CONCLUSION

Most of these studies have suggested that the use of bivalirudin alone is associated with lower rates of major bleeding when compared with UFH plus GPI in patients with ACS and planned invasive strategy. This effect spans through the age ranges and would be a good option for elderly patients. Decreased bleeding complications would lead to better clinical outcomes in the elderly after PCI. It would lead to decreased length of stay in the hospital.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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