Influence of Access, Anticoagulant, and Bleeding Definition on Outcomes of Primary Percutaneous Coronary Intervention: Early Experience of an US Academic Center

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Abstract

Background We aimed to carry out comparison of different bleeding avoidance strategies in doing primary percutaneous coronary intervention (PPCI) using either radial or femoral as access of choice and either bivalirudin or unfractionated heparin as anticoagulant of choice. In this analysis, we analyzed the influence of major bleeding definition on bleeding outcomes as well.

Methods We did a retrospective analysis of 139 patients with ST-segment elevation myocardial infarction (STEMI) who had PPCI in our academic center from January 2010 till October 2013. The primary outcome at 30 days was a composite of death from any cause or stent thrombosis or non-coronary artery bypass grafting (CABG) related major bleeding (CathPCI Registry definition) and secondary outcomes were individual components of primary outcome and the hospital length of stay.

Results There was no significant difference among different access/anticoagulant combinations with regards to primary outcome (22% in radial/bivalirudin vs. 5% in radial/heparin vs. 17% in femoral/bivalirudin vs. 28% in femoral/heparin group; $p = 0.2$) as well as its individual components except the hospital length of stay (2.56 vs. 3 vs. 3.97 vs. 4.4 days each; $p < 0.0001$). The overall rate of major bleeding was 11.5%. When we use HORIZON-AMI bleeding definition, it went up to 25 % due to one particular component ($p < 0.004$).

Keywords

- radial access
- bivalirudin
- bleeding definition

Conclusions This single center observational study doing PPCI did not show any superiority of one bleeding avoidance strategy over others with regard to primary outcome and its individual components except the hospital length of stay. It also shows the importance of bleeding definition on bleeding outcomes.

Background

Primary percutaneous coronary intervention (PPCI) has been established as a standard therapy for ST elevation myocardial infarction (STEMI). There are multiple variables that influence the PPCI outcomes, including access site, antiplatelet

agents, and anticoagulants. In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors (GPI), resulted

in significantly reduced 30-day rates of major bleeding and net adverse clinical events where most of the patients had transfemoral PPCI.¹ In a recent meta-analysis report of STEMI patients undergoing PPCI, the radial approach was found to be associated with reduced risk of mortality and major bleeding, with slightly prolonged procedure times as compared with femoral approach.² An observational analysis of CathPCI registry (the Society for Cardiovascular Angiography and Interventions collaborates with the American College of Cardiology, NCDR, Washington, United States) suggested that the combination of bivalirudin and radial access was associated with reduced bleeding, when compared with either combination of heparin and radial access or the combination of femoral access, vascular closure devices, and bivalirudin even in high-bleeding risk patients.³ In a recent multicenter registry from Italy of PPCI performed through the radial approach, bivalirudin was not associated with a significant reduction in major bleeding or major adverse cardiovascular event (MACE) compared with heparin and provisional GPIs.⁴ There is no clear data on the superiority among different access and anticoagulant combinations in doing PPCI in exclusive STEMI patients. In this single-center retrospective analysis, we are presenting the outcomes of our experience in doing PPCI using four different combinations of bleeding avoidance strategies such as radial access with bivalirudin (RAB), radial access with heparin (RAH), femoral access with bivalirudin (FAB), and femoral access with heparin (FAH). There are differences in "major bleeding" definitions used in the previous trials which can affect the outcomes. Therefore, we analyzed the influence of a component of major bleeding definition on our outcomes.

Methods

Our institutional review board approved this project and determined that this study qualified for an exempt status for obtaining the patient consent. We included all the STEMI patients who underwent PPCI between January 2010 and October 2013. Our primary PCI service is led by three interventional cardiologists who are high-volume operators performing more than 200 PCI procedures each year. Our center has been performing radial PCI since July 2010 and started radial primary PCI in STEMI patients since June 2011. Baseline characteristics and procedural data of all the patients were entered prospectively at the time of procedure by qualified cardiac catheterization laboratory personnel and doctors, into our dedicated cardiac service database system (XIMS, Xper Information Management System by Philips, Andover, MA). All patients undergoing PCI were loaded with different combinations of antiplatelet agents, such as clopidogrel or ticagrelor or prasugrel along with 325 mg of aspirin before the procedure. Heparin was administered as an intravenous bolus of 60 IU/kg of body weight, with subsequent boluses targeted to an activated clotting time of 250 to 300 seconds. Bivalirudin was administered as an intravenous bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h. Either abciximab or eptifibatide were used as GPIs. Choice of access site, anticoagulant, antiplatelet agents, GPI, closure

device in femoral approach, and the type of stent implanted were at the discretion of the operator. All patients were maintained on dual antiplatelet agents, including clopidogrel or ticagrelor or prasugrel along with 81 to 325 mg of aspirin daily.

Definitions

STEMI patients were defined as having chest pain for at least 20 minutes with following electrocardiographic (ECG) changes: ST elevation ≥ 2 mm in two continuous precordial leads or ≥ 1 mm in two limb leads, new left bundle branch block or ECG changes compatible with true posterior MI. Major bleeding was defined using the CathPCI registry definition as the presence of ≥ 1 of the following: external bleeding at the access site, hematoma, retroperitoneal hemorrhage, gastrointestinal or genitourinary bleeding, cardiac tamponade (all of the above bleeding events had to be associated with ≥ 3 g/dL hemoglobin drop or blood transfusion or intervention/surgery to stop the bleeding, to qualify); intracranial hemorrhage, nonbypass surgery-related blood transfusion among patients with a preprocedure hemoglobin > 8 g/dL, or an absolute decrease in hemoglobin ≥ 3 g/dL from pre-PCI to post-PCI in patients with a preprocedure hemoglobin value ≤ 16 g/dL. Access site bleeding event was counted if at least one of the following was present: external bleeding at the access site, hematoma, or retroperitoneal hemorrhage. All other periprocedural bleeding events were considered nonaccess site bleeds. Death was defined as death from any cause up to 30 days following the index procedure. Stent thrombosis was defined according to the Academic Research Consortium criteria.⁵ Procedural success was defined as a final thrombolysis in a MI flow of three with residual stenosis of $< 30\%$. The length of stay at the hospital was defined as the number of days since the day of admission till the day of discharge from hospital. Door-to-balloon time was defined as the time interval from the point of arrival to the emergency department to the use of first balloon or thrombectomy device. Procedure time was defined as the time interval from the point patient received local anesthesia at the access site to completion of primary PCI.

Follow-Up Data and Study End Points

The primary outcome at 30 days was a composite of death from any cause or stent thrombosis or major bleeding not associated with coronary artery bypass grafting (CABG). The secondary outcomes were individual components of primary outcome and hospital length of stay. All the patients completed 30-day follow-up.

Statistics

Continuous data are presented as mean $\pm$ standard deviation (SD) and categorical outcomes are presented as percentages. Categorical outcomes were compared by using Fisher exact test while continuous variable outcomes were compared by using permutation unpaired *t*-test. Statistical significance was defined as $p \leq 0.05$. All statistical analyses were

performed by our biostatistics department using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Patients and Procedures

Between January 1, 2010 and October 31, 2013, a total of 162 patients with STEMI presented to the emergency department at our academic center. After emergent angiography, the primary management strategy was primary PCI in 150 patients, deferred PCI in 3 patients, primary CABG in 7 patients, and medical management in 2 patients. Among 150 PPCI patients, 13 patients who presented postcardiac arrest were excluded, leaving 139 patients in this retrospective observational analysis. Of these 139 patients, anticoagulant of choice was unfractionated heparin in 47 patients and bivalirudin in 92 patients, whereas access of choice was radial artery in 28 patients and femoral artery in 111 patients. We then subdivided whole data into four groups defined as, RAB ($N = 9$),

RAH ($N = 19$), FAB ($N = 83$), and FAH ($N = 28$). Baseline and procedural characteristics of all these patient subgroups are given in ►Tables 1 and 2, respectively. There were no statistically significant differences in the baseline characteristics between the four groups. In radial access patients we used only 6F sheaths, whereas 6 or 7F sheaths were used in femoral access patients. GPIs were administered in 84 out of the 92 patients in the bivalirudin group and all the 47 patients in the heparin group. Closure devices were used in 52 out of the 111 patients in femoral access group (46%). Post-PPCI, oral antiplatelet therapy included aspirin in all patients and additionally clopidogrel in 92 patients, prasugrel in 36 patients, and ticagrelor in 11 patients.

Outcomes

By Access

The overall rate of the primary outcome was 18%. It was 10.7% in the radial group and 20% in the femoral group ($p = 0.41$).

Table 1 Baseline characteristics across four subgroups

Variable	Overall cohort $N = 139$ (100%)	Radial access bivalirudin (RAB) $N = 9$ (6.5%)	Radial access heparin (RAH) $N = 19$ (13.5%)	Femoral access bivalirudin (FAB) $N = 83$ (59%)	Femoral access heparin (FAH) $N = 28$ (21%)	p-Value
Age, y; mean (SD)	58.8 (0.99)	59.4 (3.93)	61.1 (2.28)	57.9 (1.33)	59.7 (2.16)	0.70
Female sex, n (%)	40 (28.8)	2 (22.2)	5 (26.3)	23 (27.7)	10 (35.7)	0.84
Race, White (%)	6 (4.3)	1 (11.1)	2 (10.5)	3 (3.6)	0 (0)	0.25
Height, cm; mean (SD)	171 (1.18)	169.9 (3.01)	170.9 (2.62)	171.0 (1.78)	171.3 (1.79)	1.00
Weight, kg; mean (SD)	87 (1.65)	89.19 (5.8)	86.09 (4.57)	85.87 (2.08)	90.12 (4.14)	0.65
Diabetes, n (%)	32 (23)	1 (11.1)	5 (26.3)	17 (20.7)	9 (32)	0.52
Hypertension, n (%)	81 (58)	5 (55.6)	9 (47.4)	50 (60.5)	17 (60.7)	0.77
Hyperlipidemia, n (%)	55 (39.7)	4 (44.4)	8 (42.1)	33 (40)	10 (35.7)	0.94
Renal insufficiency, n (%)	5 (3.7)	0 (0)	1 (5.2)	1 (1.3)	3 (10.7)	0.11
Congestive heart failure, n (%)	22 (15.8)	0 (0)	1 (5.2)	3 (15.7)	8 (28.6)	0.11
Smoker, n (%)	54 (38.8)	4 (44.4)	7 (36.8)	29 (34.9)	14 (50)	0.52
Chronic lung disease, n (%)	12 (8.8)	0 (0)	1 (5.2)	7 (8.4)	4 (14.8)	0.67
Peripheral vascular disease, n (%)	6 (4.3)	0 (0)	1 (5.2)	3 (3.6)	2 (7.1)	0.72
Cerebrovascular accident, n (%)	5 (3.7)	1 (11.1)	1 (5.2)	2 (2.4)	1 (3.6)	0.40
Prior coronary-artery bypass grafting, n (%)	3 (2.2)	0 (0)	0 (0)	2 (2.4)	1 (3.6)	1.0
Prior percutaneous coronary intervention, n (%)	19 (14)	2 (22)	2 (10.5)	9 (10.8)	6 (21.4)	0.40
Kilip class II, III, or IV, n (%)	13(9.4)	0 (0)	1(5.2)	7(8.4)	5(17.9)	0.39

Abbreviation: SD, standard deviation.

Table 2 Procedural characteristics across four subgroups

Variable	Overall cohort N = 139 (100%)	Radial access bivalirudin (RAB) N = 9 (6.5%)	Radial access heparin (RAH) N = 19 (13.5%)	Femoral access bivalirudin (FAB) N = 83 (59%)	Femoral access heparin (FAH) N = 28 (21%)	p-Value
Sheath size used in French, 6 F (%)	89 (64)	9 (100)	19 (100)	36 (43.3)	25 (89)	0.001
Sheath size used in French, 7F (%)	50 (36)	0 (0)	0 (0)	47 (56.6)	3 (10.7)	0.001
IVUS used, n (%)	73 (52.5)	4 (44.4)	14 (73.7)	33 (39.85)	22 (78.6)	0.05
Closure device used, n (%)	52 (37)	0 (0)	0 (0)	47 (56.6)	5 (18)	0.0002
Heparin before procedure, n (%)	117 (84.2)	7 (77.8)	17 (89.5)	73 (88)	20 (71.4)	0.16
Glycoprotein IIB/IIIA inhibitor used, n (%)	131 (94.3)	9 (100)	19 (100)	75 (90.3)	28 (100)	0.23
Door-to-balloon time, min, mean (SD)	60.4 (2.25)	71.9 (6.36)	54.7 (4.44)	59.3 (3.06)	63.9 (5.27)	0.26
Fluoro time, min, mean (SD)	28.7 (1.09)	37.5 (4.08)	26.5 (3.31)	28.7 (1.37)	27.6 (2.37)	0.12
Procedure time, min, mean (SD)	98.1 (3.31)	106.5 (9.43)	80.5 (7.98)	103.8 (4.62)	90.2 (5.80)	0.09
Contrast volume, mL, mean (SD)	230 (7.64)	213 (25.0)	190.7 (23.1)	244.9 (9.43)	220.7 (17.6)	0.02
TIMI-3 flow post-PCI, n (%)	134 (96.4)	8 (88.9)	18 (94.7)	79 (95.4)	28 (100)	0.46
Hemoglobin before PCI, mean (SD)	14.5 (0.17)	14.6 (0.6)	14.9 (0.46)	14.5 (0.19)	14.3 (0.51)	0.59
Creatinine before PCI, mean (SD)	1.03 (0.068)	0.87 (0.079)	0.82 (0.054)	0.97 (0.029)	1.41 (0.32)	0.13
Culprit vessel—left anterior descending artery, n (%)	74 (53)	7 (78)	7 (37)	47 (57)	13 (46)	0.17
Left circumflex artery, n (%)	16 (11.5)	1 (11.1)	4 (21.1)	8 (9.6)	3 (10.7)	0.51
Right coronary artery, n (%)	49 (35.35)	1 (11.1)	8 (42.15)	28 (33.7)	12 (42.9)	0.33
Postprocedure—clopidogrel, n (%)	92 (66.2)	2 (22.2)	14 (73.7)	54 (65.1)	22 (78.6)	0.021
Ticagrelor, n (%)	11 (8.63)	4 (44.4)	1 (5.26)	4 (4.82)	2 (7.14)	0.006
Prasugrel, n (%)	36 (25.2)	3 (33.3)	4 (21.1)	25 (30.1)	4 (14.3)	0.4

Abbreviations: IVUS, intravascular ultra sound; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, thrombolysis in myocardial infarction.

For the individual components of primary outcome please refer to ►**Fig. 1**. The rate of access-site bleeding event was 0% in the radial group and 4.5% in the femoral group ($p = 0.58$). After excluding cardiogenic shock patients, the mean length of hospital stay was 2.85 days in the radial group and 4.06 days in the femoral group; $p < 0.0001$ (see ►**Fig. 4**).

By Anticoagulant

The overall rate of the primary outcome was 18%. It was 17.3% in the bivalirudin group and 19.1% in the heparin group ($p = 0.82$). For the individual components of primary out-

come please refer to ►**Fig. 2**. After excluding cardiogenic shock patients, the mean length of hospital stay was 3.81 days in the bivalirudin group and 3.74 days in the heparin group; $p = 0.73$ (see ►**Fig. 4**).

By Access and Anticoagulant Combination

The rates of primary outcome were 22% in the RAB group, 5.2% in the RAH group, 17% in the FAB group, and 28% in the FAH group ($p = 0.2$). For the individual components of primary outcome please refer to ►**Fig. 3**. After excluding cardiogenic shock patients, the mean length of hospital stay among

Fig. 1 Clinical outcomes according to the access site at 30 days.

Fig. 2 Clinical outcomes according to the anticoagulant at 30 days.

the four subgroups were 2.56 versus 3 versus 3.97 versus 4.4 days each, respectively, in the four groups as mentioned above; $p < 0.0001$ (see ►Fig. 4).

Bleeding Outcomes by Different Bleeding Definitions

Among the total population of 139 STEMI patients, a total of 16 major bleeding events (11.5%) were recruited using CathPCI registry definition, whereas a total of 35 bleeding events (25%) were recruited using the HORIZONS-AMI major bleeding definition ($p < 0.004$). The HORIZONS-AMI major bleeding events ($N = 35$) included all the same 16 major bleeding events captured by using the CathPCI registry definition and an additional 19 major bleeding events. These additional 19 bleeding events met one particular component of HORIZONS-AMI major bleeding definition which is “4 g hemoglobin drop without an overt source of bleeding.” After excluding those 16 bleeding events which met both HORIZONS-AMI and CathPCI registry major bleeding definition from total patients ($N = 139$), we did an analysis of procedure time on remaining patients ($N = 123$). The mean procedure time in those 19 patients who had “4 g hemoglobin drop without an overt source of bleeding” was 112.2 minutes ($SD \pm 7.94$) and the

Fig. 3 Clinical outcomes according to the access site and anticoagulant combination at 30 days.

remaining 104 patients was 90.6 minutes ($SD \pm 3.52$); $p = 0.017$ (►Fig. 5). There was 0% 30-day mortality rate in both groups ($p = 1$). The mean length of stay was 3.8 days in the former and 3.2 days in the latter group ($p = 0.9$).

Discussion

In this US academic center study evaluating our early experience of STEMI patients undergoing PPCI by radial access, there was no significant difference in the primary outcome, which is a composite of death from any cause or stent thrombosis or major bleeding at 30 days among different access/anticoagulant combinations. After excluding cardiogenic shock patients, the mean hospital length of stay was significantly reduced with radial combinations compared with femoral combinations. Our study also shows the influence of a

Fig. 4 The mean length of stay according to access alone, anticoagulant alone, and access + anticoagulant combination. On the right side of the figure the p -values of head-to-head comparison are given among different combinations. FAB, femoral access bivalirudin; FAH, femoral access heparin; RAB, radial access bivalirudin; RAH, radial access heparin.

Fig. 5 Relation between the mean procedure time of primary percutaneous coronary intervention and 4 g hemoglobin drop without an overt source of bleeding.

particular component of the bleeding definition on bleeding outcomes.

Bleeding is an important predictor for mortality and morbidity burden in PPCI.^{6–8} The HORIZONS-AMI trial compared bivalirudin versus heparin plus GPI use in PPCI and showed significant reduction of major bleeding events in patients who received bivalirudin, but the use of radial access was only 5.6 versus 5.4%, respectively.¹ The Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial compared radial access versus femoral access use in PPCI and showed a significant reduction of major bleeding events in patients who had PPCI by radial access, but the use of bivalirudin was only 8 versus 7.2%, respectively.⁹ Even in the Radial Versus Femoral Access for Coronary Intervention (RIVAL) trial, the use of bivalirudin was 2.2% in the radial group and 3.1% in the femoral group.¹⁰ In our study, the combination of radial access and bivalirudin did not show any significant difference in the major bleeding rates compared with other bleeding avoidance strategies possibly due to lack of power. From the recent observational analysis,³ the number needed to treat prevent one bleeding event in high-bleeding risk patients with radial and bivalirudin combination was 68. The total numbers of patients in our analysis with this combination were only nine.

In patients with acute coronary syndromes undergoing an early invasive management strategy by the femoral approach, the use of a vascular closure device minimized rates of major access site bleeding.¹¹ In our analysis, only 46% of the femoral group patients received the closure device which might be the reason for numerically more access site bleeding events in the femoral access group.

In this analysis, we used CathPCI registry major bleeding definition to recruit bleeding events. This definition does not include “4 g hemoglobin drop without overt source of bleeding” as a component. This particular component was a part of HORIZONS-AMI major bleeding definition which was also used in recent European Ambulance Acute Coronary

Syndrome Angiography Trial (EUROMAX).^{1,12} Bleeding academic research consortium recommended bleeding definition as well does not include hemoglobin drop without an overt source of bleeding as a component of bleeding definition at any level.¹³ Previous studies have shown that hemoglobin drop without an overt source of bleeding could be related to a variety of factors, including the initial hemoconcentration effect, large amounts of phlebotomy draw, and unobserved blood losses during catheter exchanges during the procedure.^{14–16} Catheterization procedures nowadays are performed on more complex lesions and may involve a variety of equipment exchanges associated with lengthy procedures which can lead to hemoglobin drop. We believe this component of bleeding definition could be related to the duration of the procedure rather than a bleeding complication of procedure. We found a significant interaction between procedure duration and 4 g hemoglobin drop without an overt source of bleeding. There was no difference observed in short-term mortality as well as hospital length of stay in those patients with 4 g hemoglobin drop compared with those without. Based on this, we need to carefully interpret the results of clinical trials which had “4 g drops in hemoglobin without an overt source of bleeding” as a bleeding endpoint.

Length of stay is a very important nonclinical outcome, especially in this era of economically driven health care.^{17,18} In our analysis, the combination of the RAB or heparin showed a significant trend in lessening the length of stay in the hospital compared with femoral combinations.

Limitations

Several important limitations of the present analysis should be discussed. As this is an observational study, the bias inherent in any observational data should be expected, such as individual bleeding risk differences, although STEMI itself is one of the components among various bleeding risk scores. We did collect bleeding risk score using Mehran bleeding risk calculator, but the sample size was too small to compare these subgroups. Although it represents real-life practice, the small sample size and the lack of long-term follow-up could have underestimated our results. This observational study lacked the statistical power to provide definite answers on hard clinical outcomes and should be viewed primarily as hypothesis generating. In this study, GPI usage in bivalirudin group is high compared with major randomized control trials of primary PCI patients which may represent the practice variations in the real-world setting. The early experience of operators performing radial PPCI may affect the outcomes by selection of sicker patients for femoral approach and less sick patients for radial approach.

Finally, our study represents a single center experience that may limit the generalizability of the results.

Conclusion

This single center early experience of STEMI patients undergoing PPCI by radial access, there was no significant difference in the clinical outcomes among different access/anticoagulant

combinations. Our study shows the influence of a particular component of the bleeding definition on bleeding outcomes. Given the limitations of this study, a well-designed randomized trial comparing femoral versus radial access in patients treated with bivalirudin versus unfractionated heparin plus GPI using well accepted bleeding definition is needed to assess the best combination of access and anticoagulant to improve outcomes in PPCI.

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