Cardiovascular Revascularization Medicine 17 (2016) 295–301

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Clinical

Radial versus femoral access for percutaneous coronary intervention in ST-elevation myocardial infarction patients treated with fibrinolysis: Results from the randomized routine early invasive clinical trials

John J. Graham [a,b], Andrew T. Yan [a,b], Mary K. Tan [c], Warren J. Cantor [b,d], Carlo DiMario [e], Sanjit S. Jolly [f], Sigrun Halvorsen [g], Francisco Fernandez-Aviles [h], Michel R. Le May [i], Bruno Scheller [j], Francesco Borgia [k], Federico Piscione [l], Mina Madan [m], Shaun G. Goodman [a,b,c,*]

[a] Terrance Donnelly Heart Centre, St. Michael's Hospital, Toronto, Canada
[b] University of Toronto, Toronto, Canada
[c] Canadian Heart Research Centre, Toronto, Canada
[d] Southlake Regional Health Centre, Newmarket, Canada
[e] Royal Brompton Hospital and Imperial College, London, United Kingdom
[f] Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, Canada
[g] Oslo University Hospital Ulleval, Oslo, Norway
[h] Hospital General Universitario Gregorio Marañón, Madrid, Spain
[i] University of Ottawa Heart Institute, Ottawa, Canada
[j] Innere Medizin III, Universitat des Saarlandes, Homburg, Germany
[k] Federico II University, Naples, Italy
[l] University Hospital San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy
[m] Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 7 December 2015
Received in revised form 11 March 2016
Accepted 21 March 2016

Keywords:
Radial access
Fibrinolysis
Bleeding
PCI

ABSTRACT

Background: To investigate the relationship between arterial access site choice (radial versus femoral) and clinical outcomes among STEMI patients undergoing routine PCI after fibrinolysis.
Methods: Patient-level data from trials of STEMI patients evaluating routine PCI after fibrinolysis were included. The primary endpoint was 30-day major bleeding; secondary endpoints included 30-day death and re-infarction.
Results: 1891 patients underwent PCI (trans-radial n = 338, trans-femoral n = 1553). Trans-radial PCI patients were less likely to be >75 years (2% vs. 8%, p = 0.0001), heavier (median weight 82 [72–90] vs. 80 [70–90] kg, p = 0.0013) and more likely in Killip class I at presentation (87% vs. 82%, p = 0.03). At 30 days, trans-radial PCI was associated with a similar unadjusted risk for major bleeding (3.7% vs. 1.2%, Odds Ratio [OR] 0.43 [95% CI 0.13–1.48], p = 0.18), mortality (3.4% vs. 1.2%, OR 0.34 [0.09–1.28], p = 0.11) and re-infarction (3.9% vs. 4.7%, OR 1.25 [0.60–2.58], p = 0.56). In multivariable analysis, radial access was associated with similar estimates for bleeding and death/reinfarction risk.
Conclusions: In STEMI patients treated with fibrinolysis and undergoing an early routine invasive strategy, radial compared to femoral PCI is chosen in younger, less ill patients and is independently associated with similar risk of bleeding, re-infarction, and mortality.
Summary: This study evaluated the relationship between arterial access choice (radial versus femoral) and in-hospital and 30-day outcomes in patients undergoing routine PCI after fibrinolysis for STEMI. We included patient-level data from trials evaluating a strategy of routine PCI after fibrinolysis for STEMI. Of 1891 patients undergoing PCI, trans-radial access (n = 338) was chosen in younger, lower risk patients. At 30 days, trans-radial access was associated with a similar unadjusted and adjusted risk of major bleeding, re-infarction and mortality.

1. Introduction

Combined antithrombotic/antiplatelet therapy is a mainstay of treatment in patients presenting with acute coronary syndromes (ACS) [1]. Although proven to reduce recurrent ischemic events, these therapies are associated with excess bleeding, a complication associated with subsequent adverse outcomes [2,3]. In patients presenting with ST-elevation myocardial infarction (STEMI), the use of fibrinolytic

Abbreviations: **ACS**, acute coronary syndrome; **STEMI**, ST elevation myocardial infarction; **MI**, myocardial infarction; **PCI**, percutaneous coronary intervention; **TIMI**, Thrombolysis-In-Myocardial-Infarction; **GUSTO**, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial; **DES**, drug eluting stent; **BMS**, bare metal stent; **eGFR**, estimated glomerular filtration rate; **OR**, odds ratio; **CI**, confidence interval; **CABG**, coronary artery bypass grafting.

* Corresponding author at: Terrence Donnelly Heart Centre, St. Michael's Hospital, Toronto, Ontario M5B 1W8. Tel.: +1 416 864 5722; fax: +1 416 864 5722.
E-mail addresses: goodmans@chrc.net, goodmans@smh.ca (S.G. Goodman).

http://dx.doi.org/10.1016/j.carrev.2016.03.008
1553-8389/

therapy is associated with a lower risk of mortality (compared to placebo/control) but a higher risk of major bleeding [4]. Primary percutaneous coronary intervention (PCI) has however superseded fibrinolysis as the preferred mode of reperfusion when delivered in a timely fashion [5]. When access to primary PCI within current recommended timelines is not possible, fibrinolysis as the initial reperfusion strategy followed by routine angiography/PCI is associated with reductions in the rates of re-infarction and recurrent ischemia with no increase in the rates of stroke or major bleeding [6], and recent guideline recommendations for pursuing an invasive strategy post-lysis have reflected these data [7].

For ACS patients undergoing invasive therapy, bleeding complications occur in up to 5% with approximately one-third of major bleeds being related to the arterial access site [8,9]. When compared to trans-femoral access, trans-radial access is associated with significant reductions in vascular access complications and bleeding [10–12]. In STEMI patients undergoing primary PCI, trans-radial access leads to decreased bleeding and may result in a reduction in mortality [13–15]. However, the impact of access-site choice on outcomes in STEMI patients undergoing routine PCI following fibrinolysis is unknown. This study analyzes patient-level data from the trials of routine PCI following fibrinolysis for STEMI in an attempt to further address this question.

2. Methods

Patient-level data from trials (6 of 7 where arterial access site was recorded) of STEMI patients receiving fibrinolysis and randomized to an early invasive approach vs. standard care were included (trials included: SIAM III, GRACIA-1, CAPITAL AMI, WEST, CARESS-in-AMI, TRANSFER-AMI, and NORDISTEMI) [16–22]. The inclusion of patient-level data, as part of a wider research collaboration, provided a unique opportunity beyond that of simple aggregation of different clinical trial results (Collaborative analysis ClinicalTrials.gov Identifier: **NCT01014182**; see Appendix) [23]. Only data from patients who underwent PCI (either as part of a routine invasive strategy or standard treatment arm) were included for analysis. Patients who did not undergo PCI, with unknown arterial access site, or those with a history of prior aorto-coronary bypass surgery (CABG) were excluded from the current analysis. The primary endpoint was 30-day major bleeding (TIMI major or GUSTO severe, according to definition used in each separate trial). Secondary endpoints were 30-day rates of death, re-infarction and death/re-infarction. Since arterial access site choice was not randomized, the association between major bleeding and access site was also evaluated in multivariable models with propensity score adjustment.

2.1. Statistical analysis

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (25th, 75th percentile). Chi-square test or Fisher's exact test was used for comparison of categorical variables, whereas continuous variables were compared using Wilcoxon rank-sum test. Multivariable logistic regression models, stratified by trials, were performed to determine the relationship between arterial access site and outcomes. Adjustment for possible confounding factors was performed via stepwise selection using an inclusion criteria of $\alpha = 0.05$. For the primary outcome (30-day major bleeding), covariates adjusted included female, age, weight, initial creatinine, initial hemoglobin, diabetes, hypertension, time from fibrinolysis to PCI (≤24 h, >24 h, unknown), use of glycoprotein IIb/IIIa inhibitors and choice of anti-coagulant (heparin vs enoxaparin vs both vs none). For the secondary outcome (30-day death/reMI), covariates considered were age, weight, heart rate, systolic blood pressure, Killip class and initial creatinine. Some of these variables were not available across all trials; thus, to ensure missing data did not create a biased sample, we explored different ways of handling missing data such as single or multiple imputations, or datasets that contain only certain trials. In addition, linearity and interaction of these factors were assessed in the models.

Since arterial access site was not randomized, we performed a secondary sensitivity analysis in the 3 trials where both radial access and femoral access were utilized (CARESS-in-AMI, NORDISTEMI and TRANSFER-AMI). Via logistic regression, a propensity score (PS) was computed using the 16 variables that were commonly available across the trials and have been shown previously to have an influence on the choice of access site [24–26]. These included sex, age, weight, diastolic BP, systolic BP, heart rate, initial creatinine, initial hemoglobin, Killip class, diabetes, hypertension, smoking, time from fibrinolysis to PCI, use of glycoproteinIIb/IIIa inhibitor, ASA, and choice of anticoagulant. Here, a conservative estimate of PS was assumed by using an imputed mean for continuous and a "No" for categorical variables for missing values. During the stepwise selection of variables, the PS, as a covariate, was forced to be retained for adjustment in the multivariable regression model. We also analyzed PS as a continuous or categorical (quantiles) variable. We also used it to create a case–control matched pair using the greedy matching techniques.

All analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA) and tested using 2-sided tests at a significance level of 5%.

3. Results

In total, 3011 patients were randomized in seven pharmaco-invasive trials. Of these, 1120 were excluded due to no access site recorded (WEST trial, n = 221 [22]), previous CABG (n = 8) and no PCI being performed (n = 891). This left 1891 patients whose data were available for analysis with 1553 (82%) undergoing trans-femoral access (1004 randomized to early PCI and 549 to standard therapy) and 338 in the tran-radial access group (183 randomized to early PCI and 155 to standard therapy) [Fig. 1].

Baseline characteristics of these patients are contained in Table 1. When compared to trans-femoral access patients, those undergoing PCI via the trans-radial route were less likely to be older than 75 years of age, had higher body weight and were clinically lower risk with lower heart rate, higher systolic and diastolic BP, and more likely in Killip class I. In addition, patients undergoing trans-radial access had a lower creatinine and resultant higher estimated glomerular filtration rate.

There were no differences between the trans-femoral and trans-radial access site groups with respect to frequency of prior MI, PCI or heart failure. The trans-radial access group was less likely to have a prior history of hypertension and dyslipidemia but more likely to have a smoking history, either current or former.

There was no difference between the groups in time from fibrinolytic therapy to angiography/PCI (Median time [IQR] 4.1 [2.6, 15.8] hours versus 3.8 (2.8, 5.9) hours, p = 0.27).

3.1. In-hospital interventions

Patients undergoing trans-radial access were less likely to receive a glycoprotein IIb/IIIa inhibitor or unfractionated heparin (Table 2). The majority of patients in each group received dual anti-platelet therapy with aspirin and ticlopidine/clopidogrel.

3.2. Outcomes

Trans-radial access was associated with similar risks of 30-day TIMI Major/GUSTO Severe bleeding (1.2% vs. 3.7%, Odds Ratio [OR] 0.43 [95% CI 0.13–1.48], p = 0.18), 30-day mortality (1.2% vs. 3.4%, OR 0.34 [0.091–1.28], p = 0.11), re-infarction (4.7% vs. 3.9%, OR 1.25 [0.60–2.58], p = 0.56), and death or re-infarction (5.6% vs. 7.0%, OR 0.80 [0.41–1.55], p = 0.51) (Fig. 2, Table 3).

In a multivariable model predicting 30-day major bleeding when adjusting for age, gender, body weight, prior diabetes and hypertension, initial creatinine and hemoglobin, time from fibrinolysis to