Radial versus femoral access, bleeding and ischemic events in patients with non–ST-segment elevation acute coronary syndrome managed with an invasive strategy

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Background Bleeding is a major limitation of antithrombotic therapy among invasively managed non–ST-segment elevation acute coronary syndromes (NSTE-ACS) patients; therefore, we examined the use of radial access and its association with outcomes among NSTE-ACS patients.

Methods Clinical characteristics and geographic variation in radial access were examined, as well as its association with bleeding, red blood cell transfusion and ischemic outcomes (96-hour death/myocardial infarction/recurrent ischemic/thrombotic bailout; 30-day death/myocardial infarction; 1-year death) in the EARLY versus delayed, provisional eptifibatide in acute coronary syndromes trial.

Results Of 9126 patients, 13.5% underwent radial-access catheterization. Female sex, age, weight, and prior revascularization were inversely associated with radial access, and its use varied widely by country (2%-97%). There were fewer GUSTO severe/moderate bleeds and red blood cell transfusions in the radial access group; however, it was attenuated after adjustment (odds ratio 0.73, 95% confidence intervals [CI] [0.50-1.06], $P = .094$ and 1.00 [0.71-1.40] $P = .991$). Ischemic outcomes did not differ by access site.

Conclusions In this post hoc analysis of a large clinical trial, there was significant international variation in use of radial access for NSTE-ACS patients undergoing invasive management, and it was preferentially used in those at lower risk for bleeding. Radial approach was not associated with a significant reduction in either bleeding or ischemic outcomes. Further study is needed to determine whether wider application of radial approach to acute coronary syndrome patients at high risk for bleeding improves overall outcomes. (Am Heart J 2013;165:583-590.e1.)

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Bleeding is a common adverse event associated with increased morbidity and mortality in patients with acute coronary syndromes (ACS) undergoing cardiac catheterization and percutaneous coronary intervention (PCI).[1–4] Hemorrhagic complications in this patient population can occur either at the vascular access site or remotely from the access site; however, both are associated with increased risk for long-term mortality.[5] Several strategies can decrease bleeding risk. Because a large proportion of bleeding events in invasively managed patients are related to vascular access,[2,6,7] use of radial access instead of femoral access is one such strategy that has been associated with a marked decrease in access site bleeding and vascular complications.[8] Some observational studies indicate that the radial approach is also associated with a reduced risk of

death or re-infarction at 1 year,[9] and potentially even mortality alone.[10] However, the adoption of transradial procedures is limited in many countries such as the United States,[11] and radial access is associated with higher rates of procedure failure in some studies.[8] Moreover, it is not clear whether these associations are due to the reduction in bleeding and blood transfusions, or due to selection of low-risk patients for transradial procedures and the confounding effect this may have on the analysis. Indeed, it is possible that minor levels of access site bleeding that are not associated with transfusion, hemodynamic compromise, or hemoglobin decreases are not predictive of increased mortality or morbidity.[12,13] If there is an association between transradial procedures and reduced mortality that is mediated through an effect on bleeding, it would likely be most evident in patients at high risk for hemorrhagic complications, like those with ACS managed invasively.

The EARLY-ACS trial was a multicenter, multinational study that enrolled patients with non–ST-segment elevation ACS (NSTE-ACS) for whom an invasive strategy was planned.[14] Given that it included contemporary antithrombotic strategies, the EARLY-ACS trial was a platform from which to examine the association between transradial versus femoral angiography (and intervention) and subsequent outcomes.

Methods

Patient population

The EARLY-ACS trial (clinicaltrials.gov identifier NCT00089895) was a prospective, randomized, double-blind, multicenter, international study that included 9406 high-risk NSTE-ACS patients, for whom an invasive strategy was planned, randomly assigned to either early, routine administration of eptifibatide or early placebo with delayed, provisional administration of eptifibatide after angiography but before the patient underwent PCI.[14] Our current analyses focused on 9126 (97.0%) patients who underwent coronary angiography via a radial (including brachial) or femoral access site. Patients were excluded if they did not have complete access site data.

All patients provided written informed consent to participate in the EARLY-ACS trial, and the trial was approved by the institutional review board or ethics committee of each participating site. The current analyses were approved by the Duke University Institutional Review Board.

Concomitant treatment

All treatment decisions, including choice of vascular access site, were at the discretion of the treating physician. In addition to randomized eptifibatide treatment strategy, investigators were encouraged to use other medications according to existing North American and European guidelines recommendations, including other antithrombotic strategies aspirin, clopidogrel, and primarily unfractionated or low molecular weight heparin (an amendment to the protocol allowed the use of bivalirudin or fondaparinux upon their approval by regulatory authorities for use in practice).

Endpoints

The primary endpoint of the current analysis was any bleeding occurring within 120 hours of the catheterization procedure. The pre-specified bleeding definitions used in the EARLY-ACS trial were TIMI major and GUSTO severe/moderate bleeding and red blood cell (RBC) transfusion. We further classified bleeding according to access-site related (local hematoma >5 cm, retroperitoneal hemorrhage) or non-access site related (intracranial, gastrointestinal, genitourinary or respiratory tract) bleeding events. GUSTO bleeding was reported by the investigator on the case report form. Determination of TIMI bleeding category required an overt clinical bleeding event and was assigned by a programmed algorithm that assessed hemoglobin and/or hematocrit and red blood cell transfusion data. For cases that the algorithm could not classify, independent reviewers blinded to treatment assignment assigned TIMI bleeding category by manual review of the case records.

Secondarily, we examined rates of ischemic endpoints and the relationships between the use of radial versus femoral access and the occurrence of ischemic endpoints: all-cause death, myocardial infarction (MI), recurrent ischemia requiring urgent revascularization (RIUR) or thrombotic bailout (TBO) from catheterization procedure through 96 hours, death or MI from randomization through 30 days, and mortality within 1 year.

Statistical analysis

Baseline characteristics, concomitant treatments, procedural characteristics and outcomes were reported as medians (25th, 75th percentiles) for continuous variables and percentages for discrete variables. The Wilcoxon rank sum test was used to test differences between groups for continuous variables, and the χ^2 test for discrete variables.

Because the use of radial or femoral access was not randomized, we used multivariable logistic regression modeling to determine a patient's propensity to undergo either radial or femoral access at cardiac catheterization. The model included patient and clinical factors most strongly associated with use of radial versus femoral access for cardiac catheterization. Because the adoption of radial access potentially increased over time, year of enrollment was included in the propensity model. Associations of access site with bleeding and ischemic endpoints were examined by logistic regression modeling that included the propensity to undergo radial or femoral access as well as other factors predictive of these endpoints in models previously created in the EARLY-ACS patient population (see the online Appendix for model details). Given the variation in the assess site across countries, "country" was included as strata in the models. Short-term associations are reported as ORs and 95% CI; long-term associations (ie, death within 1 year) are reported as HR and 95% CI via multivariable Cox proportional hazards regression. We repeated the analysis after excluding any patient that underwent in-hospital CABG and again among patients undergoing PCI (since they were more likely to receive eptifibatide).

All statistical tests were two-sided with $P < .05$ indicating statistical significance. No adjustments were made for multiple comparisons. All analyses were performed using SAS version 9.2 (Cary, NC).

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