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Radial Versus Femoral Randomized Investigation in ST-Segment Elevation Acute Coronary Syndrome

The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) Study

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Objectives The purpose of this study was to assess whether transradial access for ST-segment elevation acute coronary syndrome undergoing early invasive treatment is associated with better outcome compared with conventional transfemoral access.

Background In patients with acute coronary syndrome, bleeding is a significant predictor of worse outcome. Access site complications represent a significant source of bleeding for those patients undergoing revascularization, especially when femoral access is used.

Methods The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) was a multicenter, randomized, parallel-group study. Between January 2009 and July 2011, 1,001 acute ST-segment elevation acute coronary syndrome patients undergoing primary/rescue percutaneous coronary intervention were randomized to the radial (500) or femoral (501) approach at 4 high-volume centers. The primary endpoint was the 30-day rate of net adverse clinical events (NACEs), defined as a composite of cardiac death, stroke, myocardial infarction, target lesion revascularization, and bleeding). Individual components of NACEs and length of hospital stay were secondary endpoints.

Results The primary endpoint of 30-day NACEs occurred in 68 patients (13.6%) in the radial arm and 105 patients (21.0%) in the femoral arm ($p = 0.003$). In particular, compared with femoral, radial access was associated with significantly lower rates of cardiac mortality (5.2% vs. 9.2%, $p = 0.020$), bleeding (7.8% vs. 12.2%, $p = 0.026$), and shorter hospital stay (5 days first to third quartile range, 4 to 7 days] vs. 6 [range, 5 to 8 days]; $p = 0.03$).

Conclusions Radial access in patients with ST-segment elevation acute coronary syndrome is associated with significant clinical benefits, in terms of both lower morbidity and cardiac mortality. Thus, it should become the recommended approach in these patients, provided adequate operator and center expertise is present. (Radial Versus Femoral Investigation in ST Elevation Acute Coronary Syndrome [RIFLE-STEACS]; NCT01420614) (J Am Coll Cardiol 2012;60:2481–9) © 2012 by the American College of Cardiology Foundation

Bleeding complications in patients with acute coronary syndrome are a significant predictor of morbidity and mortality (1–3). In particular, patients with ST-segment elevation acute coronary syndrome (STEACS) constitute a high-risk subset of acute patients requiring more aggressive pharmacological treatment (e.g., glycoprotein IIb/IIIa inhibitors, thrombolysis) and urgent revascularization strategy (4,5). In these patients, access site complications still represent a significant source of bleeding, especially when femoral access is used (6,7).

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Abbreviations and Acronyms

CI = confidence interval

HR = hazard ratio

NACE = net adverse clinical event

PCI = percutaneous coronary intervention

STEACS = ST-segment elevation acute coronary syndrome

Notwithstanding the development of new more selective and safe antithrombotic agents, the use of radial access remains likely the best way to dramatically affect access site–related bleeding risk (7–12). Indeed, although technically more demanding, the transradial approach has been demonstrated feasible in the acute coronary syndrome setting and the safest in terms of local vascular complications (13–17).

Whether this evident access-site bleeding reduction may also have a positive impact on prevention of further cardiovascular events remains to be defined. The available clinical evidence summarized in a recent meta-analysis seems to suggest that the radial approach could also be associated with improved outcome (12). Moreover, the RIVAL (Radial Versus Femoral Access for Coronary Intervention) trial showed a clear benefit in terms of mortality in the subgroup of patients with STEACS undergoing percutaneous coronary intervention (PCI) (18). Nonetheless, the small sample size of conducted randomized trials, all underpowered to detect difference for hard clinical event (e.g., death), and the inevitable selection bias of observational studies included in the meta-analysis prevent any conclusion.

In this trial, we aimed to test, in an adequately powered study, whether transradial access for STEACS treatment was associated with better outcomes compared with the conventional transfemoral approach.

Methods

Study design and endpoints. The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) was a multicenter, randomized, parallel-group, investigator-initiated study. All patients with suspected STEACS planned for early revascularization strategy (within 24-h of symptom onset) were eligible for the study. Before arterial stick for percutaneous access, all enrolled patients were randomized (1:1 ratio) to radial or femoral access according to opaque, numbered, sealed envelopes with randomization based on a computer-generated random series and stratified by center. By protocol, contraindication to either radial or femoral vascular access (e.g., abnormal Allen's test or known severe peripheral vascular disease), recent stroke (within 4 weeks), anticoagulant therapy assumption with an international normalized ratio >2, or other severe bleeding diathesis were the pre-specified exclusion criteria adopted, whereas presentation with cardiogenic shock and/or hemodynamic instability did not preclude enrollment. The study protocol received ethical committee approval, and written informed consent was obtained by the patient or immediate family member in case the patient's clinical condition precluded the ability to provide written consent.

As the primary endpoint of the study, we assessed the 30-day incidence of net adverse clinical events (NACEs), defined as the composite of cardiac death, myocardial infarction, stroke, target lesion revascularization, and non–coronary artery bypass graft–related bleeding. Secondary endpoints were 30-day individual components of NACEs and hospital stay. Endpoint adjudication was performed by a blinded central independent clinical-event committee. Patients and investigators were not blinded to the procedure. No extramural funding was used to support this work, and authors are solely responsible for the design, conduct, and final contents of this study.

Population and procedures. The study population included patients undergoing primary/rescue PCI at 4 high-volume centers. Procedural anticoagulation was achieved with preliminary administration of an unfractionated heparin bolus at a dose of 70 UI/kg, supplemented during the procedure to maintain an activated clotting time of >250 s. The choice of additional periprocedural antithrombotic agents (e.g., glycoprotein IIb/IIIa inhibitors or bivalirudin) or different revascularization strategies (e.g., thrombectomy, direct stenting) was left to the operators according to the institution's standard procedure. Unless clinically contraindicated, all anticoagulants were discontinued at the end of the procedure, whereas glycoprotein IIb/IIIa inhibitor boluses were followed by a ≥12-h infusion. All patients were pre-treated with acetylsalicylic acid plus a loading dose of clopidogrel (300 to 600 mg) and were discharged on dual-antiplatelet therapy for ≥12 months at the discretion of the operator and depending on the stent implanted.

Before the procedure, bilateral femoral and radial pulses were evaluated by a physician. In particular, Allen's test was performed twice on both hands to exclude insufficient ulnar collateral circulation; in case of an abnormal Allen's test result, further evaluation with pulse oximetry or plethysmography was not precluded but not encouraged to prevent consistent time delay. In patients presenting with cardiogenic shock, radial pulse and Allen's test were assessed after intra-aortic balloon positioning or specific pharmacological treatment (i.e., inotropic drug administration); patients with persistent pulseless cardiogenic shock were excluded from the study.

All participating interventional cardiologists were high-volume operators (>150 PCIs/year) and had adequate expertise in both approaches, meeting minimal proficiency criteria of ≥50% interventional cases by radial approach per year.

Data collection and definitions. By design, ad hoc dedicated databases for data entry and explicit definitions for outcomes were adopted. Data on 30-day outcomes were obtained by direct patient visit or contact with referring physician in the absence of any adverse event. Source documentation was obtained for all clinical events and analyzed by the central clinical-event committee.

Cardiac death was defined as any death due to cardiac cause, procedure-related deaths, and death of unknown cause. Stroke was defined as the presence of a new focal neurological deficit thought to be vascular in origin, with sign or symptoms persisting >24 h and in the presence of cerebral lesions as assessed by imaging procedures. New myocardial infarction was defined as new ischemic symptoms lasting >20 min and new or recurrent ST-segment elevation or depression >1 mm in at least 2 contiguous leads, associated with a >20% increase of the cardiac biomarker values not attributable to the evolution of the index myocardial infarction (19). Target lesion revascularization was defined as any revascularization procedure performed because of angiographic restenosis or thrombosis at the site of the culprit lesion, associated with clinical and/or objective evidence of inducible myocardial ischemia. Stent thrombosis was classified using the Academic Research Consortium definition (20). Post-procedural bleeding (Table 1) was considered to be any overt and actionable hemorrhage not related to coronary artery bypass graft with ≥3 g/dl decrease in hemoglobin, requiring prompt evaluation by a health care professional and leading to an increased level of care. Bleeding was further categorized as access site and non–access site related according to its relationship to the arterial vascular access.

Statistical analysis. Assumptions for sample-size analysis were based, for the control event rate, on NACE rates reported in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial and pertinent meta-analyses (21–23) and, for the experimental event rate, on several meta-analyses on radial access (11,22,23). It must be emphasized that the concept of NACEs is a relatively novel one and that its absolute rates are highly variable, depending on the definitions of myocardial infarction, revascularization, and, most importantly, bleeding. Thus, the consensus among members of the steering committee was that assuming a 9.2% 30-day NACE rate in the control group and a 4.5% rate in the experimental group could be clinically and scientifically sound. Thus, aiming for 5% alpha and 20% beta errors and discounting for a likely 5% rate of losses to follow-up, 500 patients were included in each group (N = 1,000).

Table 1 Bleeding Definition

Overt and Actionable Bleeding Needing Evaluation by Physician and Fulfilling the Following Criteria		
Bleeding requiring blood transfusion		Leading to:
Bleeding requiring surgical repair		Unplanned diagnostic examinations and/or
Cerebral bleeding	+	Prolonged hospitalization and/or
Intracranial or retroperitoneal bleeding		Lifesaving drug discontinuation
Decrease in hemoglobin level ≥3 g/dl		
Intrapericardial with cardiac tamponade		
Fatal bleeding		

Baseline characteristics of the patients are summarized with mean ± SD for continuous variables with normal distribution, median (first to third quartiles) for those continuous but with skewed distribution, and number (percentage) for categorical variables; 95% confidence intervals (CIs) for proportions are calculated by the Wilson method. The Student *t*, Mann-Whitney *U*, and Fisher exact tests were computed when appropriate for bivariate analyses.

Combined adverse events were evaluated on a per-patient hierarchical basis; thus, each patient could provide only 1 hard event per event type. Analyses were conducted on intention-to-treat basis, regardless possible access site crossover or unneeded coronary revascularization. Cumulative event rates were compared with the log-rank test and summarized as Kaplan-Meier estimates.

All variables in Tables 2 and 3 were tested for bivariate association with NACEs, and nominally significant ($p < 0.05$) covariates were simultaneously forced into a Cox regression model to identify independent outcome predictors and to calculate their adjusted hazard ratios (HRs) with associated 95% CIs. A 2-tailed p value <0.05 was established as the level of statistical significance for all tests. All statistical analyses were performed using SPSS-PASW version 18.0 (IBM, Armonk, New York).

Results

Baseline population characteristics. Between January 2009 and July 2011, 501 patients were randomly assigned to femoral access and 500 to radial access (Fig. 1). The enrollment rate was >75% of all STEACS patients treated at the participating centers during the study period. There were no significant baseline demographic and clinical differences between the 2 study arms (Table 2). The prevalence of comorbidities and severity of coronary artery disease were comparable as well as acute clinical presentation with ~10% of patients in Killip class III/IV and 8% requiring intra-aortic balloon support during the procedure.

Procedural characteristics. There were no differences in the symptom-to-balloon and door-to-balloon times between the 2 study groups (Table 3), whereas the time from artery puncture to first balloon inflation was slightly longer in the radial group (10 min [range, 8 to 20 min] vs. 10 min [range, 8 to 15 min], p = 0.035). A sheath ≤6-F was used more frequently in the radial group than in the femoral group (90.8% vs. 81.4%, p < 0.001) (Table 3). The overall rate of vascular approach crossover was 6.1% (n = 61): 9.6% (n = 47) in the radial arm and 2.8% (n = 14) in the femoral arm. However, excluding cases of nonadherence to the randomized allocation by operators (Fig. 1), the actual access failure was 6% (n = 30) in the radial arm and 1% (n = 5) in the femoral arm. Cardiogenic shock at presentation (HR: 3.43; 95% CI: 1.7 to 7.1; p = 0.01), unknown peripheral vascular disease (HR: 2.55; 95% CI: 1.4 to 4.6; p = 0.02), and previous thrombolytic administration (HR:

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Table 2 Baseline Patient Characteristics

	Overall (N = 1,001)	Femoral (n = 501)	Radial (n = 500)	p Value
Clinical characteristics				
Age, yrs	65 (55–76)	65 (55–77)	65 (56–75)	0.409
Female	267 (26.7)	141 (28.1)	126 (25.2)	0.317
Body mass index, kg/m^2	27.0 (25–30)	26.6 (24–30)	27.2 (25–30)	0.140
Left ventricular ejection fraction	45.0 (40–50)	45.0 (40–50)	45.0 (40–52)	0.175
CKD (GFR <60 ml/min/1.73 m^2)	238 (23.8)	127 (25.3)	111 (22.2)	0.156
COPD	71 (7.1)	40 (8.0)	31 (6.2)	0.325
Peripheral arterial disease	143 (14.3)	68 (13.6)	75 (15.0)	0.529
Previous myocardial infarction,	141 (14.1)	71 (14.2)	70 (14.0)	1.000
Previous cerebrovascular accident	41 (4.1)	22 (4.4)	19 (3.8)	0.750
Previous revascularization	117 (11.7)	52 (10.4)	65 (13.0)	0.202
Previous PCI	105 (10.5)	45 (9.0)	60 (12.0)	0.123
Previous CABG	19 (1.9)	12 (2.4)	7 (1.4)	0.355
Cardiac risk factors				
Hypertension	608 (60.7)	309 (61.7)	299 (59.8)	0.561
Hypercholesterolemia	417 (41.7)	199 (39.7)	218 (43.6)	0.223
Smoking	401 (40.1)	191 (38.1)	210 (42.0)	0.221
Family history of CAD	177 (17.7)	81 (16.2)	96 (19.2)	0.215
Diabetes	237 (23.7)	122 (24.4)	115 (23.0)	0.656
Severity of CAD (p = 0.471)				
No epicardial vessel disease	11 (1.1)	6 (1.2)	5 (1.0)	1.000
Isolated left main disease	2 (0.2)	1 (0.2)	1 (0.2)	1.000
Single-vessel disease	544 (54.3)	265 (52.9)	279 (55.8)	0.374
Double-vessel disease	285 (28.5)	149 (29.7)	136 (27.2)	0.401
Triple-vessel disease	159 (15.9)	80 (16.0)	79 (15.8)	1.000
Killip class presentation (p = 0.164)				
I	678 (67.7)	330 (65.9)	348 (69.6)	0.224
II	210 (21.0)	108 (21.5)	102 (20.4)	0.698
III	52 (5.2)	28 (5.6)	24 (4.8)	0.670
IV	61 (6.1)	35 (7.0)	26 (5.2)	0.290

Values are n (%) or median (quartiles).

CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; PCI = percutaneous coronary intervention.

2.22; 95% CI: 1.0 to 4.7; p = 0.041) were the main determinants of vascular access crossover.

Lesion and procedural characteristics for the 2 groups were also well balanced (e.g., target vessel distribution) with a culprit lesion clearly identifiable in 99% of cases (Table 3). The culprit vessel was occluded at the time of the procedure in 60% of patients; thrombectomy devices were used in 41%, whereas a direct stenting strategy was possible in 28% of patients. The angiographic successful result rate, no-reflow incidence, creatine kinase-myocardial band peak, and stent/patient ratio were also comparable (Table 3).

Notably, periprocedural anticoagulant and antithrombotic therapies were similar in the 2 groups: 8% of patients had received previous fibrinolytic treatment, the mean heparin dose administered was 76 ± 21 U/kg, and glycoprotein IIb/IIIa inhibitors were used in 69% of patients, whereas bivalirudin was used in only 8%.

30-day outcome. No patient was lost at 30-day follow-up; thus, all 1,001 patients were included in the final intention-to-treat-analyses. The primary endpoint of 30-day NACEs occurred in 173 patients (17.3%) and was significantly fewer in the radial arm compared with the femoral arm (13.6% vs. 21.0%, 95% CI: 2.7% to 12.0%; p = 0.003) (Table 4). A Kaplan-Meier curve of the incidence of 30-day NACEs is shown in Figure 2. Analysis of individual NACE components showed 72 deaths (7.2%) attributable to cardiac causes (Online Appendix 1) with a significantly lower incidence in patients randomized to the radial approach compared with the femoral approach (5.2% vs. 9.2%; 95% CI: 0.8% to 7.3%; p = 0.020); on the contrary, myocardial infarction (1.2% vs. 1.4%; 95% CI: −1.4% to 1.8%; p = 1.000), target lesion revascularization (1.2% vs. 1.8%; 95% CI: −1.0% to 2.3%; p = 0.604), and stroke (0.8% vs. 0.6%; 95% CI: −1.5% to 1.0%; p = 0.725) rates were comparable in the 2 study groups.

Bleeding occurred in 100 patients (10.0%) and was significantly less frequent in the radial arm than in the femoral arm (7.8% vs. 12.2%; 95% CI: 2.7% to 12.0%; p = 0.026) (Table 4). This difference was mainly due to a 60% decrease in access site–related bleeding in the radial group compared with the femoral group (2.6% vs. 6.8%; 95% CI: 1.6% to 7.0%; p = 0.002). Indeed, non–access site–related bleeding, accounting

Table 3 Lesion and Procedural Characteristics

	Overall (N = 1,001)	Femoral (n = 501)	Radial (n = 500)	p Value
Target vessel				
Left main trunk	6 (0.6)	4 (0.8)	2 (0.4)	0.687
Left anterior descending/diagonal artery	469 (46.9)	234 (46.7)	235 (47.0)	0.950
Left circumflex/obtuse marginal artery	163 (16.3)	75 (15.0)	88 (17.6)	0.267
Right coronary/posterior descending artery	342 (34.2)	177 (35.3)	165 (33.0)	0.464
Bypass graft	10 (1.0)	5 (1.0)	5 (1.0)	1.000
Target lesion				
Occlusive stenosis	597 (59.6)	299 (59.7)	298 (59.6)	1.000
Stent thrombosis treatment	51 (5.1)	21 (4.2)	30 (6.0)	0.200
High thrombotic burden (TS ≥3)	782 (78.1)	394 (78.6)	388 (77.6)	0.703
Bifurcation	184 (18.4)	85 (17.0)	99 (19.8)	0.254
Procedural characteristics				
Symptom-to-balloon time, min	207 (140–380)	198 (135–392)	214 (145–375)	0.290
Door-to-balloon time, min	56 (34–95)	53 (31–91)	60 (35–99)	0.175
Artery puncture-to-balloon time, min	10 (8–17)	10 (8–15)	10 (8–20)	0.035
Systolic blood pressure, mm Hg	129 (110–145)	123 (106–146)	130 (110–143)	0.104
Arterial sheath size				
≤6-F	862 (86.1)	408 (81.4)	454 (90.8)	<0.001
≥7-F	139 (13.9)	93 (18.6)	46 (9.2)	<0.001
Baseline TIMI flow grade	0.80 ± 1.1	0.76 ± 1.0	0.83 ± 1.1	0.309
0–1	719 (71.8)	367 (73.3)	352 (70.4)	0.326
2–3	282 (28.2)	134 (26.7)	148 (29.6)	0.326
Baseline creatinine, mg/dl	0.94 (0.8–1.1)	0.95 (0.8–1.2)	0.93 (0.8–1.1)	0.112
Baseline hemoglobin, g/dl	14.3 (13–15)	14.2 (13–15)	14.3 (13–15)	0.153
Stent/patient ratio	1.42 ± 0.9	1.41 ± 0.9	1.43 ± 1.0	0.745
Total stent length, mm	24 (18–38)	24 (18–38)	24 (18–40)	0.265
Drug-eluting stent implantation	243 (24.3)	111 (22.2)	132 (26.4)	0.122
Failed thrombolysis	76 (7.6)	35 (7.0)	41 (8.2)	0.477
Heparin, U/kg	71 (62–87)	70 (63–86)	71 (61–88)	0.973
Glycoprotein IIb/IIIa inhibitors	687 (68.6)	350 (69.9)	337 (67.4)	0.414
Bivalirudin	76 (7.6)	36 (7.2)	40 (8.0)	0.635
Thrombectomy device use	407 (40.7)	203 (40.5)	204 (40.8)	0.949
Direct stenting	281 (28.1)	140 (27.9)	141 (28.2)	0.944
IABP support	80 (8.0)	42 (8.4)	38 (7.6)	0.727
CK-MB baseline, ng/ml	5.1 (3–18)	5.2 (3–19)	5.1 (3–18)	0.112
Final TIMI flow grade	2.82 ± 0.56	2.81 ± 0.6	2.83 ± 0.6	0.657
0–1	37 (3.7)	19 (3.8)	18 (3.6)	1.000
2–3	964 (96.3)	482 (96.2)	482 (96.4)	1.000
Angiographic failure*	121 (12.1)	65 (13.0)	56 (11.2)	0.438

Values are n (%), median (quartiles), or mean ± SD. *Angiographic failure = TIMI flow grade <3 and/or residual stenosis >30%.
CK-MB = creatine kinase-myocardial band; IABP = intra-aortic balloon pump; TIMI = Thrombolysis In Myocardial Infarction; TS = thrombus score.

for 53% of total bleeding events, were similar in the 2 study groups (5.2% vs. 5.4%; 95% CI: −2.7% to 3.0%; p = 1.000). The clinical relevance of this decrease in access site bleeding was underscored by less need for blood transfusion in patients undergoing a transradial procedure (1.0% vs. 3.2%; 95% CI: 0.4% to 4.2%; p = 0.025). Post hoc bleeding analysis according to the Thrombolysis In Myocardial Infarction classification showed a comparable rate of major Thrombolysis In Myocardial Infarction bleeding between the 2 groups (2.8% vs. 1.8%; 95% CI: −0.9% to 3.0%; p = 0.399), but a significantly lower rate of minor Thrombolysis In Myocardial Infarction bleeding in the radial arm (7.2% vs. 4.0%; 95% CI: 0.3% to 6.1%; p = 0.038) (Table 4).

Hospital stay was shorter in the radial group than in the femoral group (Table 4). Indeed, a significant reduction in coronary care unit stay (3 days [range, 2 to 4 days] vs. 4 days [range, 3 to 5] days, p < 0.001) after a transradial procedure led to earlier discharge than after a transfemoral procedure (5 days [range, 4 to 7 days] vs. 6 days [range, 5 to 8 days], p = 0.008). The differences in terms of outcome between the 2 study groups became more evident when data were analyzed according to a per-protocol basis (Online Appendix 2).

Outcome predictors. Multivariate analysis confirmed the radial approach as an independent predictor of 30-day NACEs (HR: 0.7; 95% CI: 0.5 to 0.9; p = 0.028) together with female sex (HR: 1.4; 95% CI: 1.1 to 2.0; p = 0.037),

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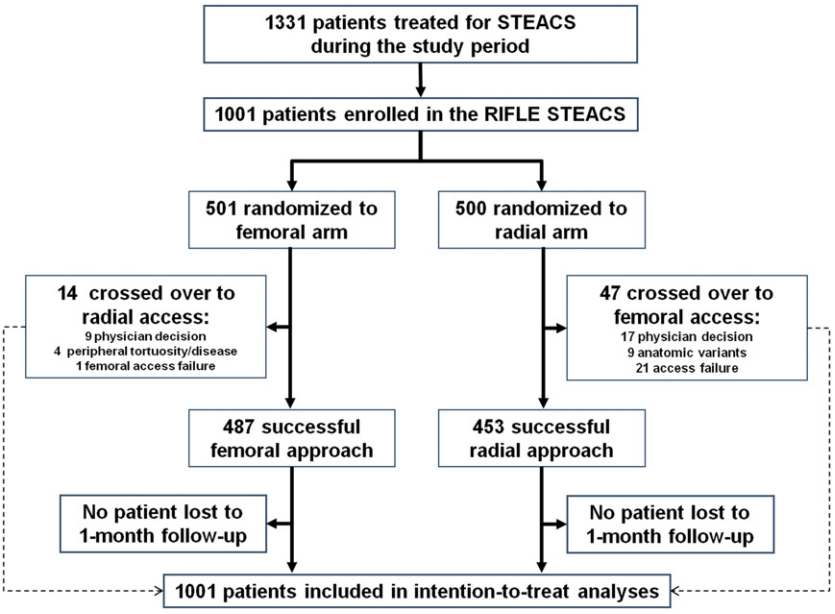

Figure 1 **Study Flowchart**

Flowchart of patients with ST-segment elevation acute coronary syndrome (STEACS) enrolled in the study.

chronic kidney disease (HR: 1.8; 95% CI: 1.3 to 2.5; p = 0.001), left descending artery as the culprit vessel (HR: 1.5; 95% CI: 1.1 to 2.0; p = 0.020), Killip class at presentation (HR: 1.5; 95% CI: 1.3 to 1.8; p < 0.001), impaired left ventricular ejection fraction (HR: 1.6; 95% CI: 1.1 to 2.3; p = 0.027), and angiographic no reflow (HR: 1.9; 95% CI: 1.3 to 2.7; p = 0.001).

Discussion

The present multicenter randomized clinical trial has the following implications. First, systematic use of transradial access for STEACS treatment translates into an evident clinical advantage in terms of NACEs, cardiac mortality, and bleeding; second, the radial approach in these patients is associated with a substantial decrease in access site hemorrhagic events compared with the femoral approach; third, patients undergoing a transradial procedure need shorter intensive coronary care unit and hospital stays.

Hemorrhagic complications constitute an important risk factor for a worse outcome in STEACS (1–3). Due to the strict correlation among bleeding, ischemic events, and mortality, more attention has been recently paid to the reduction of all avoidable iatrogenic hemorrhagic complications. Several bleeding risk score models have been developed to define the patient risk profile and facilitate a personalized decision-making process (24–26), but the urgency of care and the unavoidable need to minimize ischemic risk often limit the applicability of standardized treatment, especially in terms of antithrombotic regimens.

In this context, use of the transradial approach for acute patients undergoing early invasive treatment has undoubtedly a key role in the prevention of access site–related bleeding, accounting for as many as 40% of all causes of bleeding in acute coronary syndrome patients (1,2,6,27). Several studies have strongly emphasized the possible link between the decrease in major vascular complications and improved outcome associated with the transradial approach, especially in patients with STEACS (18,28). Nonetheless, the currently available evidence in this context is limited by the small number of patients and/or the observational study design. More recently, the RIVAL study (18) and a post-hoc analysis of the HORIZON-AMI trial showing improved event-free survival in patients undergoing primary PCI by the transradial approach (28) raised the question about the best vascular access in acute patients.

The RIFLE-STEACS is the first large randomized clinical trial specifically designed to compare the radial and femoral approaches for primary/rescue PCI. The RIFLE-STEACS is also the first randomized study to demonstrate an improved outcome in terms of NACEs and cardiac survival associated with the radial approach in patients with STEACS. This result is consistent with data emerging from meta-analyses and pooled analyses demonstrating in STEMI patients a 46% to 48% reduction in risk of mortality associated with the transradial approach compared with transfemoral access (23,29). The 30-day rate of 7.2% of cardiac deaths seen in this trial is higher than the rate of 2.9% reported in the heparin plus glycoprotein IIb/IIIa inhibitors group in HORIZON-AMI trial (21); neverthe-

Table 4 In-Hospital and Follow-Up Clinical Outcomes

	Overall (N = 1,001)	Femoral (n = 501)	Radial (n = 500)	p Value
30-day outcome (hierarchical)				
NACE	173 (17.3)	105 (21.0)	68 (13.6)	0.003
MACE	93 (9.3)	57 (11.4)	36 (7.2)	0.029
Cardiac death	72 (7.2)	46 (9.2)	26 (5.2)	0.020
Stroke	7 (0.7)	3 (0.6)	4 (0.8)	0.725
Myocardial infarction	13 (1.3)	7 (1.4)	6 (1.2)	1.000
Target lesion revascularization	15 (1.5)	9 (1.8)	6 (1.2)	0.604
Stent thrombosis	15 (1.5)	9 (1.8)	6 (1.2)	0.604
Definite	12 (1.2)	7 (1.4)	5 (1.0)	0.773
Probable	1 (0.1)	1 (0.2)	0 (0.0)	1.000
Possible	2 (0.2)	1 (0.2)	1 (0.2)	1.000
Non-CABG bleeding	100 (10.0)	61 (12.2)	39 (7.8)	0.026
Access site related	47 (4.7)	34 (6.8)	13 (2.6)	0.002
Non–access site related	53 (5.3)	27 (5.4)	26 (5.2)	1.000
TIMI major bleeding	23 (2.3)	14 (2.8)	9 (1.8)	0.399
TIMI minor bleeding	56 (5.6)	36 (7.2)	20 (4.0)	0.038
TIMI bleeding requiring medical attention	21 (2.1)	11 (2.2)	10 (2.0)	0.502
Blood transfusion required	21 (2.1)	16 (3.2)	5 (1.0)	0.025
Surgical repair required	3 (0.3)	2 (0.4)	1 (0.2)	0.999
Cerebral bleeding	1 (0.1)	0 (0.0)	1 (0.2)	0.999
Intracranial or retroperitoneal bleeding	2 (0.2)	1 (0.2)	1 (0.2)	0.480
Decrease in hemoglobin level ≥3 g/dl	79 (7.9)	49 (9.8)	30 (6.0)	0.036
Intrapericardial with cardiac tamponade	5 (0.5)	3 (0.6)	2 (0.4)	0.998
Fatal bleeding	6 (0.3)	3 (0.6)	3 (0.6)	0.684
Hospital stay, days (range)				
Total hospital stay	6 (5–8)	6 (5–8)	5 (4–7)	0.008
Intensive coronary care unit	3 (2–4)	4 (3–5)	3 (2–4)	<0.001
Cardiology ward	3 (1–4)	3 (1–4)	2 (1–4)	0.472

Values are n (%) and median (quartiles).

MACE = hierarchical major adverse cardiac event (cardiac death, nonfatal myocardial infarction, target lesion revascularization, stroke); NACE = net adverse clinical event (MACE + bleeding); other abbreviations as in Tables 2 and 3.

less, the less stringent selection criteria and the inclusion of patients with critical conditions such as cardiogenic shock and failed thrombolysis may explain this significant difference in cardiac mortality (23,29).

Possible explanations for this beneficial effect on outcome seem to be the lower rate of bleeding-related hemodynamic compromise, need for blood transfusion, and lifesaving drug discontinuation. Indeed, in this nearly all-comers study, radial access reduced the odds of clinically relevant access site bleeding by 60%, with a significant decrease in the need for transfusion. These data are consistent with the results of previous reports showing as much as a 55% reduction in the rate of non–coronary artery bypass graft–related bleeding (23,28). To overcome the evident limit of the heterogeneous bleeding classifications adopted in previous studies (30) and to focus only on hemorrhagic complications potentially affecting the outcome (31,32), the RIFLE-STEACS considered only overt bleeding events causing substantial blood loss and requiring increased level of care (e.g., unplanned diagnostic exam) and/or specific treatment (e.g. antithrombotic therapy modification); thus, ordinary access site local hematomas independently from its dimensions were not considered for the primary outcome. Again, the high patient risk profile and the extensive use of glycoprotein IIb/IIIa inhibitors (32), might partially explain the considerable hemorrhagic event rate recorded in this study population. Nonetheless, considering the inclusion of patients with failed thrombolysis (i.e., rescue PCI) and the low use of bivalirudin in the RIFLE-STEACS, the 10% bleeding rate at 30 days is to some extent comparable to the 7.3% reported in the post-hoc analysis of the HORIZON-AMI study (28). Notably, non–access site–related bleeding still accounted for >50% of all hemorrhagic events, underscoring the fact that the choice of the best antithrombotic regimen with the lowest bleeding potential remains a major issue to increase the safety margin in the treatment of patients with STEACS.

Thus, the reduction in cardiac mortality and bleeding found in the radial arm of the RIFLE-STEACS corroborates the link between mortality and "clinically relevant" access site bleeding (33,34). The multivariable analysis confirmed the role of a systematic radial approach as an independent 30-day outcome predictor.

Consistent with an improved clinical outcome, patients in the radial arm also showed a shorter intensive coronary care unit stay, translating into reduced overall hospital stay.

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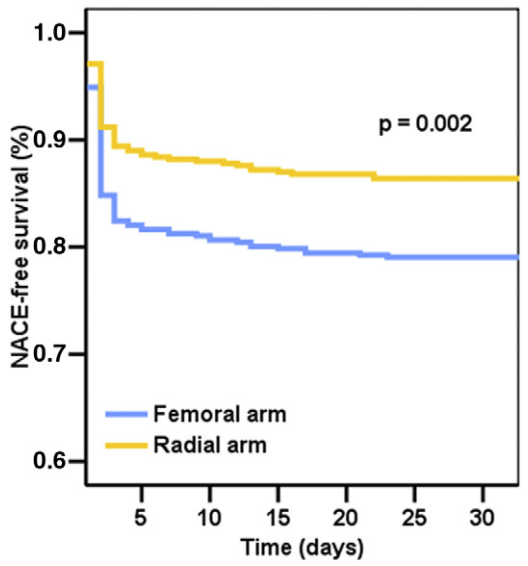

Figure 2 Time-to-Event Curves for NACE

Net adverse cardiac event (NACE) is the composite of cardiac death, myocardial infarction, target lesion revascularization, stroke, and bleeding.

Because prolonged bed rest itself seems to be a predictor of worse prognosis in coronary artery disease (35), the possibility of a more rapid mobilization as a result of the decrease in access site complications might have also played a role in the outcome difference.

Finally, the few exclusion criteria adopted in this trial and the enrollment of quite complex patients together with subjects at lower risk also confirm the feasibility of the radial approach in the emergency setting, with an access failure rate of 6% and negligible time delay by expert operators. This access crossover rate is comparable to the 5.3% rate reported in the RIVAL study (18) and the 3.8% rate reported by expert operators choosing the radial approach as initial access for primary PCI in patients without cardiogenic shock (36). Nonetheless, specific transradial expertise to guarantee procedural time and a success rate comparable to those with the femoral approach are strongly recommended before using this technique in the emergency setting. The exclusion of those who are not ideal candidates for radial approach (e.g., abnormal Allen's test) and the ability to handle specific vascular access difficulties (e.g., unfavorable anatomic variants) are necessary to avoid harmful treatment delays in treating STEACS patients (37,38). Indeed, there is some evidence that the more expert the operator is with radial access, the more patients will benefit from the use of radial approach (36,39).

Study limitations. The main limitation of this study is the almost exclusive use of heparin and glycoprotein IIb/IIIa inhibitors, with only 8% of patients receiving bivalirudin. Although it could have negatively affected the rate of bleeding events recorded in the study, the post hoc analysis of the HORIZON-AMI confirmed the advantage of the transradial approach with regard to hemorrhagic complications also in patients treated with bivalirudin (28). This may also explain the relatively high rate of NACEs in the femoral group in our trial compared with other similar randomized studies.

A second limitation is the fact that all operators were skilled in the radial approach thus making the external validity of these results lower for centers where operators mainly perform transfemoral procedures, underscoring the need for suitable training and learning curve for the radial approach to achieve optimal clinical results.

Another limitation is the sample size computation, which was based on analysis of published data as well as consensus among steering committee members, because the concept of NACEs is a new one in the field of STEACS, and NACE rates vary substantially depending on definitions.

Finally, notwithstanding the comparable baseline clinical and procedural characteristics as well as in-hospital management and complication rates between the 2 study groups, the possible role of unknown confounding factors on outcome could not be excluded. Indeed, most cardiac deaths were recorded in the early acute phase of STEACS (within 48 h), making the role of bleeding in the outcome not always clearly assessable (Online Appendix 1). Thus, further studies to confirm the benefit of the radial approach on survival in STEACS patients are warranted.

Conclusions

The RIFLE-STEACS results clearly demonstrate the advantage in terms of outcome of the radial over the femoral approach in STEACS patients. This net difference together with the high success rate should represent the primary reason to use the radial approach for the treatment of acute patients.

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Key Words: acute ST-segment elevation myocardial infarction ■ coronary angioplasty ■ randomized controlled trial ■ transradial access.

APPENDIX

For supplemental material, please see the online version of this article.