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Transradial Versus Transfemoral Intervention for Acute Myocardial Infarction

A Propensity Score-Adjusted and -Matched Analysis From the REAL (REgistro regionale AngiopLastiche dell'Emilia-Romagna) Multicenter Registry

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Objectives This study sought to assess whether transradial intervention, by minimizing access-site bleeding and vascular events, improves outcomes in patients with ST-segment elevation myocardial infarction compared with the transfemoral approach.

Background Bleeding and consequent blood product transfusions have been causally associated with a higher mortality rate in patients with myocardial infarction undergoing coronary angioplasty.

Methods We identified all adults undergoing percutaneous intervention for acute myocardial infarction in Emilia-Romagna, a region in the north of Italy of 4 million residents, between January 1, 2003, and July 30, 2009, at 12 referral hospitals using a region-mandated database of percutaneous coronary intervention procedures. Differences in the risk of death at 2 years between patients undergoing transfemoral versus transradial intervention, assessed on an intention-to-treat basis, were determined from vital statistics records and compared based on propensity score adjustment and matching.

Results A total of 11,068 patients were treated for acute myocardial infarction (8,000 via transfemoral and 3,068 via transradial route). According to analysis of matched pairs, the 2-year, risk-adjusted mortality rates were lower for the transradial than for the transfemoral group (8.8% vs. 11.4%; $p = 0.0250$). The rate of vascular complications requiring surgery or need for blood transfusion were also significantly decreased in the transradial group (1.1% vs. 2.5%, $p = 0.0052$).

Conclusions In patients undergoing angioplasty for acute myocardial infarction, transradial treatment is associated with decreased 2-year mortality rates and a reduction in the need for vascular surgery and/or blood transfusion compared with transfemoral intervention. (J Am Coll Cardiol Intv 2012;5:23–35) © 2012 by the American College of Cardiology Foundation

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Percutaneous coronary intervention (PCI) for acute myocardial infarction reduces the rates of death and recurrent ischemia compared with medical therapy (1).

Transfemoral access (TFA) is the preferred and most widely used percutaneous access site in most cardiac catheterization laboratories worldwide. Being a relatively deep and terminal vessel, however, the femoral artery may expose the patient to rare ischemic but frequent bleeding and vascular complications (2,3), especially in the setting of myocardial infarction where potent antithrombotic drugs are frequently used (4,5).

In registries, bleeding has been consistently associated with worse outcomes in patients undergoing coronary angioplasty (5–9). Similarly, 2 distinct pharmacological strategies that were able to reduce hemorrhagic events have concomitantly lowered cardiac mortality in randomized trials of patients affected by myocardial infarction (10,11), a finding that was not explained by the effect of treatment on ischemic endpoints, such as myocardial infarction, stroke, or recurrent angina (10,11). Therefore, a new paradigm has emerged, according to which bleeding prevention itself may improve survival in patients with acute myocardial infarction undergoing invasive coronary management (12,13).

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CI = confidence interval
HR = hazard ratio
IQR = interquartile range
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TFA = transfemoral access
TRA = transradial access
TRI = transradial intervention

After the Campeau et al. (14) report of successful coronary angiography by transradial access (TRA), the radial artery has been increasingly employed as an alternative access site to the femoral artery for both diagnostic and interventional procedures. Although technically more demanding, transradial intervention (TRI) offers the advantage of minimal access-site vascular complications (15). Yet, in the emergent setting of acute myocardial infarction, where a timely procedure is of paramount importance, and coronary anatomy is unknown, TRI is rarely employed (16).

We conducted a study on an unselected, population-based cohort of patients with myocardial infarction who were treated with percutaneous mechanical intervention via either the transfemoral or the transradial approach. We sought to determine whether TRI, by minimizing access-site bleeding and vascular complications, was associated with improved short- to medium-term outcomes compared with the traditional transfemoral approach.

Because the access site was not randomly assigned, we used propensity score matching to minimize bias.

Methods

Study population. The REAL registry (REgistro regionale AngiopLastiche dell'Emilia-Romagna) is a large, prospective, Internet–based registry designed to collect clinical and angiographic data on all consecutive PCIs performed in a region in northern Italy with 4 million residents. Thirteen public and private centers of interventional cardiology participated in data collection. Procedural data are retrieved directly and continuously from the resident databases of each laboratory, which share a common pre-specified dataset. These data are open for evaluation, and periodic audits are performed by the Regional Health Care Administration. Between January 2003 and June 2009, 11,355 patients that reside in the region underwent PCI for ST-segment elevation myocardial infarction (STEMI). For 273 patients (2.4%), the access site was not retrievable, whereas 14 patients (0.1%) underwent transbrachial intervention and were excluded. The present study population, therefore, consists of 11,068 resident patients, with a median follow-up of 992 days, who underwent transfemoral or TRI for acute myocardial infarction.

Study subjects were assigned to either the transfemoral or the transradial group according to the first attempted arterial access site, based on the intention-to-treat principle. Therefore, patients in whom the first attempted percutaneous access site was not successful, those who required an alternative access site before or during intervention, or those who underwent transfemoral intra-aortic pump implantation before, during, or after PCI were categorized based on the first attempted percutaneous access site. To ensure a correct application of the intention-to-treat principle, hospital records of all cases with intended or actual multiple arterial access sites were reviewed for additional information by site investigators.

Interventional strategy and device use, including stent type, were left to the discretion of the attending physicians. Periprocedural glycoprotein IIb/IIIa inhibitors and antithrombotic medications were used according to the operator's decision and current guidelines.

Antiplatelet treatment was prescribed according to current standards of treatment, including lifelong aspirin for all patients and at least 1 month of ticlopidine (250 mg twice a day) or clopidogrel (75 mg/day) treatment for patients who underwent stenting.

The REAL registry is based on current clinical practice; therefore, regulatory authorities required only an ordinary written informed consent to perform coronary intervention, which was obtained from all patients. The protocol of the study is in accordance with the Declaration of Helsinki.

Study outcomes. Follow-up information was obtained directly and independently from the Emilia-Romagna Regional Health Agency via an analysis of the hospital's discharge records and the mortality registries. This ensures a complete follow-up for 100% of the patients resident in the region, including all out-of-hospital deaths (this is the reason for the priori exclusion of patients who live outside the region).

The primary outcome was death from any cause within 2 years after the index procedure.

Secondary outcomes included recurrent myocardial infarction and stroke during follow-up, whereas the main safety outcome was the rate of major bleeding and vascular events within 30 days, which were defined as any bleedings requiring red blood cell transfusion and/or the need for access-site surgical repair.

Statistical analysis. Because the patients were not randomly assigned to undergo TRI, a propensity score analysis was performed by using a logistic regression model for TRI versus transfemoral intervention to adjust for differences in baseline characteristics.

This analysis was conducted according to a nonparsimonious approach, and it included a number of clinical, angiographic, and procedural variables, which are listed in Table 1, plus year and site of treatment. We performed a 1-to-1 matched analysis without replacement on the basis of the estimated propensity score of each patient. The log odds of the probability that a patient received TRI on an intention-to-treat basis (the "logit") was modeled as a function of the confounders that we identified and included in our dataset. Using the estimated logits, we first randomly selected a patient in the group receiving TRI and then matched that patient with the patient in the group undergoing transfemoral PCI with the closest estimated logit value. Patients in the group receiving transfemoral PCI who had an estimated logit within 0.25 SD of the selected patients in the group undergoing TRI were eligible for matching. We selected 0.25 because this value has been shown to eliminate more than 90% of the bias in observed confounders (17). If more than 1 patient in the group receiving transfemoral PCI met this criterion, we randomly selected 1 patient for matching. We analyzed the data according to 2 different propensity score models: 1 for any STEMI, and 1 restricted to individuals who were free from cardiogenic shock at the time of presentation. The decision to exclude patients with cardiogenic shock in the second propensity score model was based on the observation that severe hemodynamic instability at presentation emerged as the single most influential covariate for the propensity to undergo TRI in our real-world registry. To assess the success of the matching procedure, the estimates of the percentage reduction in bias from propensity score matching was measured by calculating an initial bias (as the difference in covariate mean values between groups before matching, b_i) and the post-matching bias (as the difference in covariate mean values after matching, b_m) and then calculating the percentage reduction in bias as: $100(1 - b_m/b_i)$ (18).

After all the propensity score matches were performed, we compared the baseline covariates between the 2 intervention groups. Continuous variables were compared using the paired *t* test or the Wilcoxon signed rank test, as appropriate, and categorical variables were compared using McNemar test. The statistical significance and the effect of treatment on outcomes were estimated using appropriate statistical methods for matched data (18,19). In the propensity score–matched cohort, the risks of each outcome were compared using Cox regression models, with robust standard errors that accounted for the clustering of matched pairs. Survival curves were also constructed with Kaplan-Meier estimates and compared by the Klein-Moeschberger test (20).

Because it has been suggested that combining multiple techniques with propensity score models may yield to a better estimator of treatment effect than deriving the treatment effect with any of the 3 available methods (i.e., matching, stratification, or regression adjustment) alone (18), the propensity score that was generated in the whole patient population (i.e., without the exclusion of patients with cardiogenic shock) was then incorporated into subsequent proportional-hazards models as a covariate. To avoid overadjustment, the multivariable Cox regression analysis was performed using only the 2 variables "propensity score" and "treatment."

To investigate the associations between the occurrence of major bleeding and vascular events within 30 days with the incidence of 2-year mortality, an additional multivariable Cox model was fitted with the adverse event as a time-updated binary covariate and with adjustment achieved based on the propensity score. Finally, the contribution of a major bleeding or vascular event within 30 days to 2-year mortality, the so-called attributable risk was calculated using the following formula: $AR = PF\ (adjHR - 1)/[PF(adjHR - 1) + 1]$, where PF is the prevalence of the adverse events within the studied population, AR is the attributable risk, and adjHR is the adjusted hazard ratio obtained with the multivariable time-updated Cox model. All reported p values are 2-sided, and p values of <0.05 were considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute, Cary, North Carolina) was used for statistical analyses. All analyses have been performed by an independent statistician (P.G.) working full time for the Emilia-Romagna region.

Results

Between January 1, 2003, and June 30, 2009, there were 12,407 adult patients who underwent PCI for STEMI in Emilia Romagna. We excluded 1,052 patients who were not residents of Emilia Romagna, 273 patients whose primary intended access site was not identifiable, and 14 patients in whom the primary intended access site was the brachial artery. The resulting cohort of 11,068 underwent PCI by 53 operators at 12 hospitals. Of these patients, 8,000 (median follow-up: 1,204 days) underwent transfemoral and 3,068

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Table 1. Characteristics of the Patients Before Propensity Score Matching

Characteristic	Transradial (n = 3,068)	Transfemoral (n = 8,000)	p Value
Age, yrs	65.2 ± 12.5	66.6 ± 13.2	<0.0001
Male	76.7	69.8	<0.0001
Diabetes	32 (24.4)	37 (28.0)	0.0914
Body mass index, kg/m^2	27.3 ± 4.3	26.8 ± 4.1	0.0001
Hypertension	59.6	60.3	0.5212
Hyperlipidemia	49.2	44.2	<0.0001
Current cigarette use	34.4	31.9	0.0139
Systolic blood pressure, mm Hg	125.5 ± 24.8	124.4 ± 29.1	0.0783
Heart rate, beats/min	76.0 ± 23.9	77.3 ± 20.5	0.0106
Prior myocardial infarction	10.5	14.7	<0.0001
Prior percutaneous coronary intervention	8.1	8.8	0.229
Prior coronary bypass surgery	1.6	2.8	0.0006
Left ventricular ejection fraction <35%	8.5	13.6	<0.0001
Chronic lung disease	6.4	6.9	0.369
History of heart rhythm disturbances	3.0	4.4	0.0011
Chronic kidney disease	5.3	5.9	0.225
Dialysis	0.1	0.6	0.0010
History of neoplasm	6.6	7.1	0.375
History of heart failure	6.2	19.6	<0.0001
History of anemia	1.0	1.3	0.180
Previous bleeding	1.5	2.1	0.0438
Prior red blood cell transfusion	1.6	2.0	0.152
Red blood cell transfusion in the previous 365 days	0.1	0.6	0.0010
Cardiogenic shock	3.8	13.4	<0.0001
Intra-aortic balloon pump	1.8	9.0	<0.0001
Invasive mechanical ventilation	1.4	4.9	<0.0001
Use of glycoprotein IIb/IIIa inhibitor	83.1	81.8	0.112
Warfarin therapy	3.5	3.5	0.948
Multivessel disease	68.8	72.7	0.0004
Infarct-related artery			
Left main stem	0.4	0.9	0.0004
Left anterior descending artery	45.6	48.6	0.0060
Left circumflex artery	16.3	13.1	<0.0001
Right coronary artery	36.9	36.1	0.449
Bypass vein graft	0.7	1.2	0.0238
Baseline TIMI flow grade 0–1	62.6	69.1	<0.0001
Lesion length, mm	19.9 ± 10.1	20.0 ± 10.0	0.782
Reference vessel diameter, mm	3.0 ± 0.5	3.0 ± 0.5	0.851
Total stent length, mm	23.2 ± 11.0	23.5 ± 11.5	0.244
Ostial disease as culprit lesion	5.6	8.3	<0.0001
Bifurcation disease as culprit	23.0	16.1	<0.0001
Type C lesion as culprit	40.5	45.6	<0.0001
Balloon angioplasty only	9.8	11.1	0.0510
Stent implantation without prior dilation	29.2	22.7	<0.0001
Bare-metal stent implantation in the culprit lesion	75.1	75.5	0.640
Drug-eluting stent implantation in the culprit lesion	15.1	13.4	0.0200
Angiographic success	96.5	95.1	0.0015

Values are mean ± SD or n (%). Percentages may not total 100 because of rounding.
TIMI = Thrombolysis In Myocardial Infarction.

(median follow-up: 605 days) were primarily treated with TRI. The rate of TRI greatly increased over time, from <2% in 2003 to >60% in 2009 (Fig. 1). The rate of cross-over from primarily indented TRA to TFA increased from 0% in 2003, up to 7.5% in 2006, and then stabilized at around 3.5% through 2008 and 2009.

Unadjusted outcomes. Before propensity score matching, patients who underwent transfemoral intervention and those intended to undergo transradial approach differed significantly in clinical and procedural characteristics (Table 1). Male patients of a younger age with no previous history of coronary artery bypass grafting, with stable hemodynamic conditions, higher body mass index, yet with a less frequent history of previous blood cell transfusion were more likely to be treated transfemorally. The unadjusted rates of death within 2 years was lower (9.3% vs. 16.7%, $p < 0.001$) among patients undergoing TRI, which was largely driven by a mortality difference observed in the first 30 days after treatment (3.6% vs. 8.7%, $p < 0.001$). The composite of death or myocardial infarction and the rate of death, myocardial infarction, or stroke were also lower in the transradial group.

Similarly, the rate of major bleeding or vascular events was significantly reduced in the transradial as compared with the transfemoral group at 30 days (1.1% vs. 2.6%) and at 2 years (4.9% vs. 6.9%, $p < 0.001$), but not between 1 and 24 months (3.9% vs. 4.5%, $p = 0.230$).

The lower rates for both mortality (7.9% vs. 10.9%, $p < 0.001$) and major bleeding and vascular events (1.0% vs. 2.3%, $p < 0.001$) remained consistently in favor of the transradial group after exclusion of patients with cardiogenic shock.

Outcomes for the matched cohorts. After propensity score matching was performed for the entire population, there were 1,501 matched pairs of patients (Table 2). The area under the receiver-operating characteristic curve for this model was 0.906. Median percent reduction in bias was as high as 76.5% (interquartile range [IQR]: 61.5% to 88.6%), with no improvement noted for 4 covariates only (i.e., hypertension, lesion length, warfarin treatment, and bare-metal stenting in the infarct-related artery) which all appeared evenly distributed between groups before matching techniques were implemented and remained as such thereafter. This result supports the assumption of balance between treatment groups in observed confounders. A separate propensity score match was also performed after the exclusion of patients who had cardiogenic shock during index hospitalization (1,382 matched pairs; area under the curve: 0.904). Median percent reduction in bias was as high as 77.8% (IQR: 65.5% to 91.9%).

In these matched cohorts, there was no longer any significant difference between the transradial and the transfemoral group for any covariate, according to the use of statistical methods appropriate for matched data (Table 2).

With respect to the primary outcome, TRI, compared with transfemoral intervention, was associated with a significantly lower mortality at 2 years (8.8% vs. 11.4%, hazard ratio [HR]: 1.303; 95% confidence interval [CI]: 1.034 to 1.642; $p = 0.0250$) (Fig. 2A, Table 3).

The rates of myocardial infarction (Fig. 2B) or stroke (Fig. 2C) did not differ at 2 years in patients who underwent TRI as compared with the transfemoral group, yet both composite of death or myocardial infarction, and death, myocardial infarction, or stroke (Fig. 2D) were lower in the transradial group at 2 years, entirely driven by the observed difference in mortality between groups (Table 3).

At subgroup analysis, the mortality benefit favoring the transradial access site appeared consistent across key preselected covariates (Fig. 2E).

In the matched cohort of patients without cardiogenic shock, mortality and the composite of death, myocardial infarction, or stroke was also consistently reduced in the transradial group (Table 3, Fig. 3).

After propensity score matching, the rate of major bleeding and vascular events was significantly reduced at

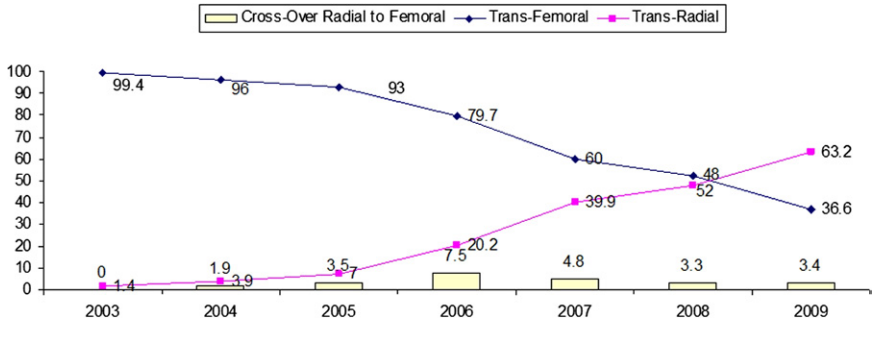

Figure 1. Temporal Trends of Transradial and Transfemoral Intervention During the Study Period

Proportions do not always add up to 100% due to incomplete data reporting and use of the brachial access site.

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Table 2. Characteristics of the Propensity Score–Matched Patients

Characteristic	Overall Patient Population			Patients Without Cardiogenic Shock		
	Transradial (n = 1,501)	Transfemoral (n = 1,501)	p Value	Transradial (n = 1,382)	Transfemoral (n = 1,382)	p Value
Age, yrs	66.1 ± 12.4	65.7 ± 13.1	0.426	65.6 ± 12.6	65.5 ± 12.9	0.936
Male	74.7	74.6	0.933	75.3	74.8	0.757
Diabetes	20.1	20.8	0.618	19.6	19.5	0.961
Body mass index, kg/m^2	27.3 ± 4.3	26.8 ± 4.0	0.288	27.3 ± 4.3	26.9 ± 4.0	0.186
Hypertension	61.0	60.4	0.707	60.2	61.4	0.507
Hyperlipidemia	48.3	47.9	0.827	48.1	47.3	0.667
Current cigarette use	33.3	33.8	0.968	34.4	34.8	0.935
Systolic blood pressure, mm Hg	126.4 ± 25.6	126.0 ± 28.3	0.855	128.7 ± 24.6	128.6 ± 26.3	0.497
Heart rate, beats/min	75.4 ± 16.4	75.7 ± 26.8	0.904	74.9 ± 16.0	74.9 ± 17.9	0.781
Time from symptoms onset to hospital presentation, min	208 ± 96	210 ± 89	0.798	198 ± 88	197 ± 89	0.984
Time from hospital presentation to angioplasty, min	88 ± 65	86 ± 64	0.687	81 ± 59	80 ± 58	0.887
Prior myocardial infarction	11.9	11.9	0.954	11.6	12.2	0.639
Prior percutaneous coronary intervention	8.1	8.5	0.740	8.0	8.7	0.498
Prior coronary bypass surgery	1.9	1.7	0.680	1.7	1.9	0.777
Left ventricular ejection fraction <35%	8.9	9.8	0.732	8.0	7.8	0.902
Chronic lung disease	7.5	6.5	0.322	6.9	7.1	0.879
History of heart rhythm disturbances	3.1	3.5	0.540	3.0	3.0	0.913
Chronic kidney disease	5.1	5.3	0.744	5.1	5.2	0.864
Dialysis	0.2	0.1	0.317	0.1	0.1	0.564
History of neoplasm	7.2	6.9	0.774	6.4	7.5	0.236
History of heart failure	6.9	7.0	0.942	5.9	6.6	0.420
History of anemia	1.0	1.2	0.590	1.0	1.0	1.000
Previous bleeding	1.7	1.6	0.777	1.6	1.5	0.879
Prior red blood cell transfusion	1.5	1.3	0.647	1.6	1.3	0.527
Red blood cell transfusion in the previous 365 days	0.2	0.1	0.317	0.1	0.1	0.5564
Cardiogenic shock	4.9	5.5	0.414	0	0	—
Intra-aortic balloon pump	2.9	2.7	0.825	1.3	1.2	0.865
Invasive mechanical ventilation	1.5	1.9	0.484	0.7	0.4	0.439
Use of glycoprotein IIb/IIIa inhibitor	79.7	79.6	0.964	80.5	81.6	0.465
Warfarin therapy	3.5	3.6	0.922	3.2	3.0	0.827
Multivessel disease	73.4	71.9	0.867	72.0	71.5	0.507
Multivessel intervention	3.4	3.1	0.606	3.2	3.0	0.741
Infarct-related artery						
Left main stem	0.6	0.5	0.808	0.4	0.2	0.480
Left anterior descending artery	46.7	47.6	0.629	46.8	47.3	0.826
Left circumflex artery	15.3	15.4	0.960	15.8	14.9	0.532
Right coronary artery	36.6	35.6	0.594	36.4	36.8	0.816
Bypass vein graft	0.8	0.9	0.842	0.7	0.8	0.655
Baseline TIMI flow grade 0–1	65.8	65.8	0.969	65.1	64.7	0.845
Lesion length, mm	19.9 ± 10.1	19.7 ± 9.4	0.565	19.6 ± 9.9	19.6 ± 9.7	0.866
Reference vessel diameter, mm	3.0 ± 0.5	3.0 ± 0.5	0.689	3.0 ± 0.5	3.0 ± 0.5	0.840
Total stent length, mm	22.8 ± 10.9	23.0 ± 10.6	0.334	22.7 ± 10.8	23.0 ± 10.7	0.330
Ostial disease as culprit lesion	6.5	6.6	0.882	5.7	5.6	0.931
Bifurcation disease as culprit	21.2	29.6	0.688	21.2	20.7	0.742
Type C lesion as culprit	40.1	41.7	0.633	40.3	41.5	0.198
Balloon angioplasty only	7.6	8.1	0.633	7.2	8.1	0.398
Stent implantation without prior dilation	26.9	26.6	0.871	26.8	26.9	0.931
Bare-metal stent implantation in the culprit lesion	75.4	75.3	0.966	75.7	74.9	0.626
Drug-eluting stent implantation in the culprit lesion	17.0	16.6	0.773	17.1	17.0	0.959
Angiographic success	97.9	97.5	0.622	98.1	98.4	0.555

Values are mean ± SD or %.
TIMI = Thrombolysis In Myocardial Infarction.

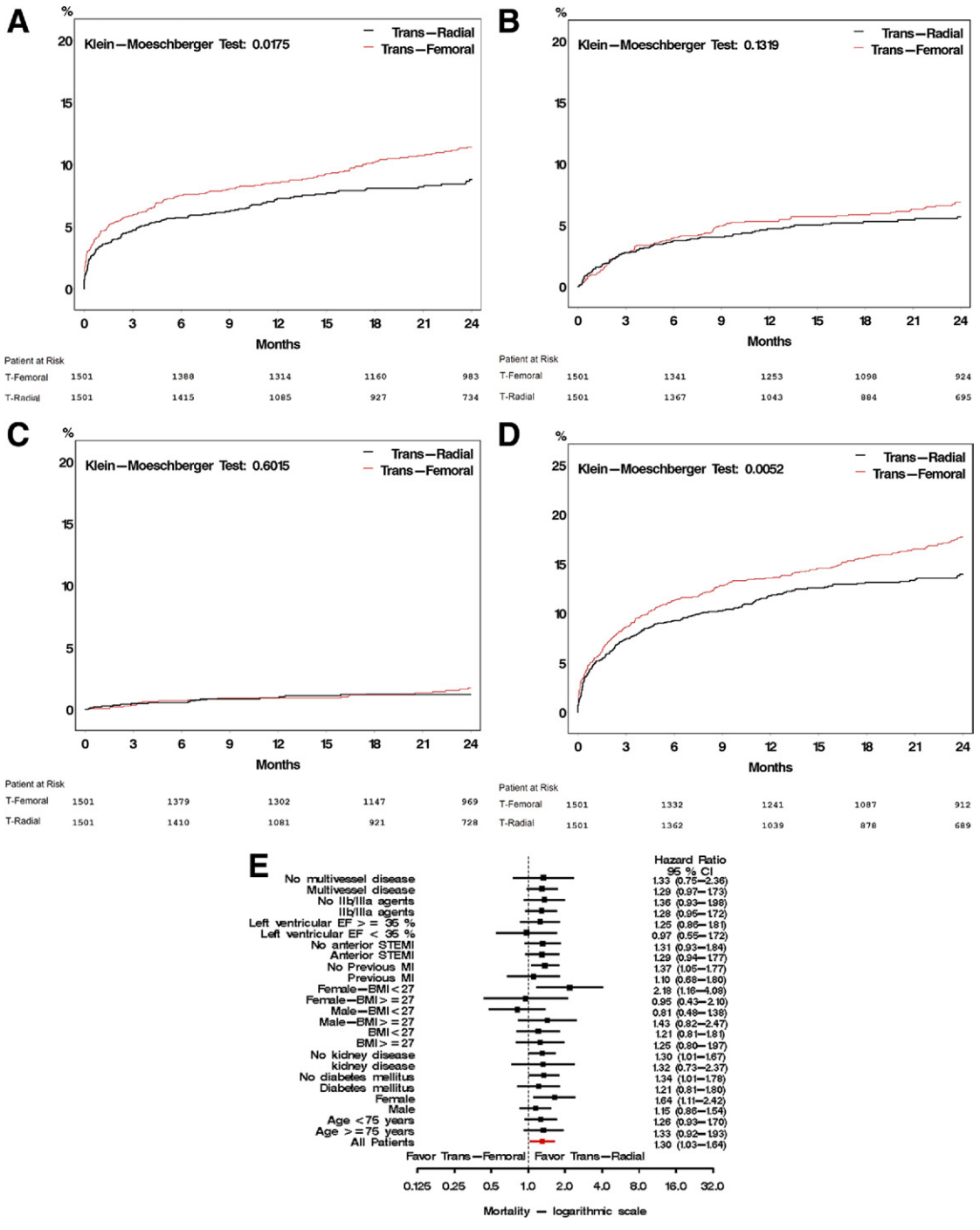

Figure 2. Kaplan-Meier Curves for Outcomes in the Propensity Score–Matched Cohort of Patients

Patients who underwent transradial or transfemoral intervention were matched for propensity scores. Propensity matching for the entire cohort created 1,501 matched pairs of patients. **(A)** Shown are the outcomes for overall survival; **(B)** outcomes for myocardial infarction; **(C)** outcomes for stroke; **(D)** outcomes for overall death, myocardial infarction, or stroke; and **(E)** shows the hazard ratios for overall survival at 2 years according to selected subgroups of study patients. Event-free survival rates were derived from paired Kaplan-Meier curves.

Table 3. Clinical Outcomes in the Propensity Score–Matched Population

Outcomes	Overall Patient Population				Patients Without Cardiogenic Shock			
	Kaplan-Meier Estimates				Kaplan-Meier Estimates			
	Transradial Group (n = 1,501)	Transfemoral Group (n = 1,501)	Hazard Ratios (95% CI)	p Value	Transradial Group (n = 1,382)	Transfemoral Group (n = 1,382)	Hazard Ratios (95% CI)	p Value
30 days								
All-cause death	3.4	4.6	1.363 (0.946–1.964)	0.097	1.8	2.9	1.611 (0.980–2.648)	0.0599
Myocardial infarction	1.4	1.0	0.672 (0.340–1.326)	0.252	1.4	1.0	0.743 (0.371–1.488)	0.402
All-cause death or myocardial infarction	4.7	5.4	1.165 (0.841–1.612)	0.358	3.1	3.8	1.241 (0.828–1.860)	0.295
Stroke	0.2	0.1	0.337 (0.035–3.244)	0.346	0.1	0.1	0.504 (0.046–5.567)	0.576
All-cause death, myocardial infarction, or stroke	4.9	5.5	1.130 (0.820–1.558)	0.454	3.3	3.9	1.207 (0.811–1.798)	0.353
Major bleeding and vascular events	1.1	2.5	2.288 (1.280–4.089)	0.0052	1.2	2.0	1,774 (0.971–3.243)	0.0625
Major bleeding and vascular events within index hospitalization	0.8	2.2	2.794 (1.439–5.427)	0.0015	0.9	1.9	2.193 (1.124–4.279)	0.0213
2 yrs								
All-cause death	8.8	11.4	1.303 (1.034–1.642)	0.0250	6.8	9.8	1.474 (1.121–1.938)	0.0055
Myocardial infarction	5.7	6.9	1.189 (0.874–1.618)	0.271	5.7	6.6	1.136 (0.828–1.558)	0.429
All-cause death or myocardial infarction	13.1	16.6	1.265 (1.042–1.536)	0.0174	11.3	14.9	1.319 (1.066–1.632)	0.0109
Stroke	1.2	1.7	1.280 (0.673–2.432)	0.452	1.0	2.1	1.940 (0.976–3.855)	0.0587
All-cause death, myocardial infarction, or stroke	13.9	17.7	1.268 (1.052–1.530)	0.0130	12.0	16.1	1.344 (1.092–1.654)	0.0052
Major bleeding and vascular events	4.8	5.8	1.251 (0.891–1.758)	0.196	4.8	5.5	1.168 (0.817–1.669)	0.395

Values are % unless otherwise indicated.
CI = confidence interval.

30 days by more than 50% in the transradial group (Table 3), a treatment effect that was consistent in the matched cohort of patients who did not suffer from cardiogenic shock (Table 3).

This difference in both the whole matched cohort of patients (Fig. 4A, Table 3) or in those matched without cardiogenic shock (Fig. 4B, Table 3) was entirely due to events which occurred during the index hospitalization,

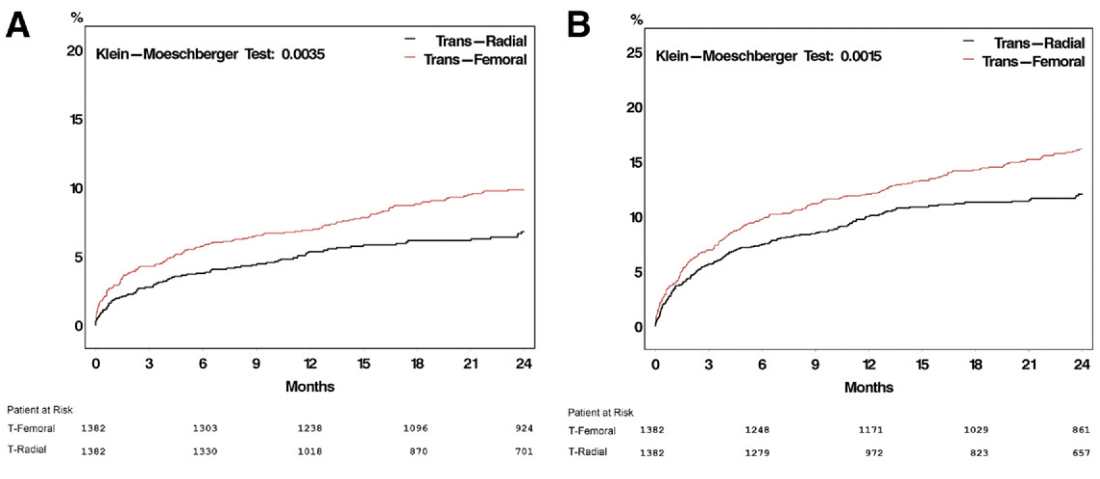

Figure 3. Kaplan-Meier Curves for Outcomes in a Propensity Score–Matched Cohort of Patients Without Cardiogenic Shock

Patients underwent transradial or transfemoral intervention and were matched for propensity scores. Propensity matching for patients without cardiogenic shock created 1,382 matched pairs of patients. **(A)** Shown are the outcomes for overall survival; **(B)** outcomes for overall death, myocardial infarction, or stroke. Event-free survival rates were derived from paired Kaplan-Meier curves.

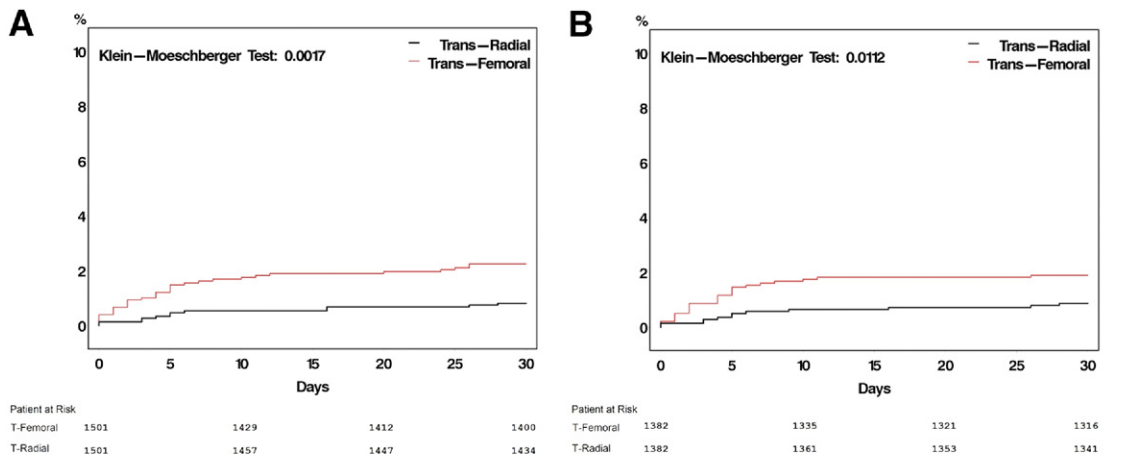

Figure 4. Kaplan-Meier Curves for Safety Events in a Cohort of Patients With or Without Cardiogenic Shock

Patients underwent transradial or transfemoral intervention and were matched for propensity scores. Propensity matching for patients, including or excluding those with cardiogenic shock, created 1,501 and 1,382 matched pairs of patients, respectively. **(A)** Shown are the outcomes for in-hospital major bleeding and vascular events within 30 days in 1,501 matched pairs of patients; **(B)** the outcomes for in-hospital major bleeding and vascular events within 30 days in 1,382 matched pairs of patients.

whereas bleeding and vascular events occurring after discharge from index hospitalization did not differ in either group (Table 3).

Propensity score-adjusted outcomes. The adjusted outcomes based on a propensity score analysis of the whole population showed a 30% mortality reduction (HR: 1.309; 95% CI: 1.070 to 1.602; p = 0.0089) at 2 years in favor of TRI (Fig. 5A, Table 4), reflecting an early significant mortality benefit within 30 days after treatment (HR: 1.380; 95% CI: 1.016 to 1.876; p = 0.0395), whereas the death rate between 1 and 24 months did not differ in the transradial as compared with the transfemoral group (HR: 1.289; 95% CI: 0.985 to 1.687; p = 0.0648). The composite endpoints of death or myocardial infarction (HR: 1.240; 95% CI: 1.050 to 1.465; p = 0.0114) (Fig. 5B) and death, myocardial infarction, or stroke (HR: 1.259; 95% CI: 1.069 to 1.481; p = 0.0057) (Fig. 5C) were also significantly reduced at 2 years in the transradial group (Table 4).

Similarly, the adjusted 30-day rate of major bleeding or vascular events remained lower in the transradial group (HR: 1.899; 95% CI: 1.116 to 3.229; p = 0.018) (Fig. 5D) with no difference thereafter up to 24 months (HR: 0.919; 95% CI: 0.640 to 1.320; p = 0.646) (Table 4).

At subgroup analysis, the adjusted mortality benefit at 2 years favoring the transradial access site appeared largely consistent across several analyzed covariates (Fig. 5E).

Length of hospitalization. In the overall patient population, the unadjusted length of hospitalization was significantly lower in the transradial (median [IQR]: 4 [6 to 8]) compared with the transfemoral group (median [IQR]: 7 [5 to 10]; p < 0.0001). Similarly, after propensity score matching, duration of hospitalization remained markedly shorter in the transradial group, both in the whole matched population (median [IQR]: 4 [6 to 8] vs. 6 [5 to 9]; p < 0.0001) and in those matched without cardiogenic shock (median [IQR]: 3 [4 to 6] vs. 5 [5 to 8]; p < 0.0001).

Contribution of major bleeding or vascular events to 2-year mortality. The occurrence within 30 days of major bleeding or vascular events was associated to an adjusted 7-fold increase of overall mortality at 2 years at a time-updated regression model (HR: 7.084; 95% CI: 3.482 to 14.410. p < 0.0001), with a significant interaction between bleeding or vascular complications and femoral access site (p = 0.047). Hence, we calculated that 11% of all deaths at 2 years were attributable to the occurrence within 30 days of major bleeding or vascular events.

Discussion

We compared the medium-term outcomes as well as the safety profile of TRI versus transfemoral intervention in patients with STEMI undergoing primary percutaneous intervention. Our observational region-wide study, based on a large and unselected cohort of patients, showed that TRI was associated with a decreased mortality compared with the traditional transfemoral approach. The observed difference in death was not apparently explained by the incidence of myocardial infarction or stroke, which did not differ between groups. By contrast, TRI was associ-

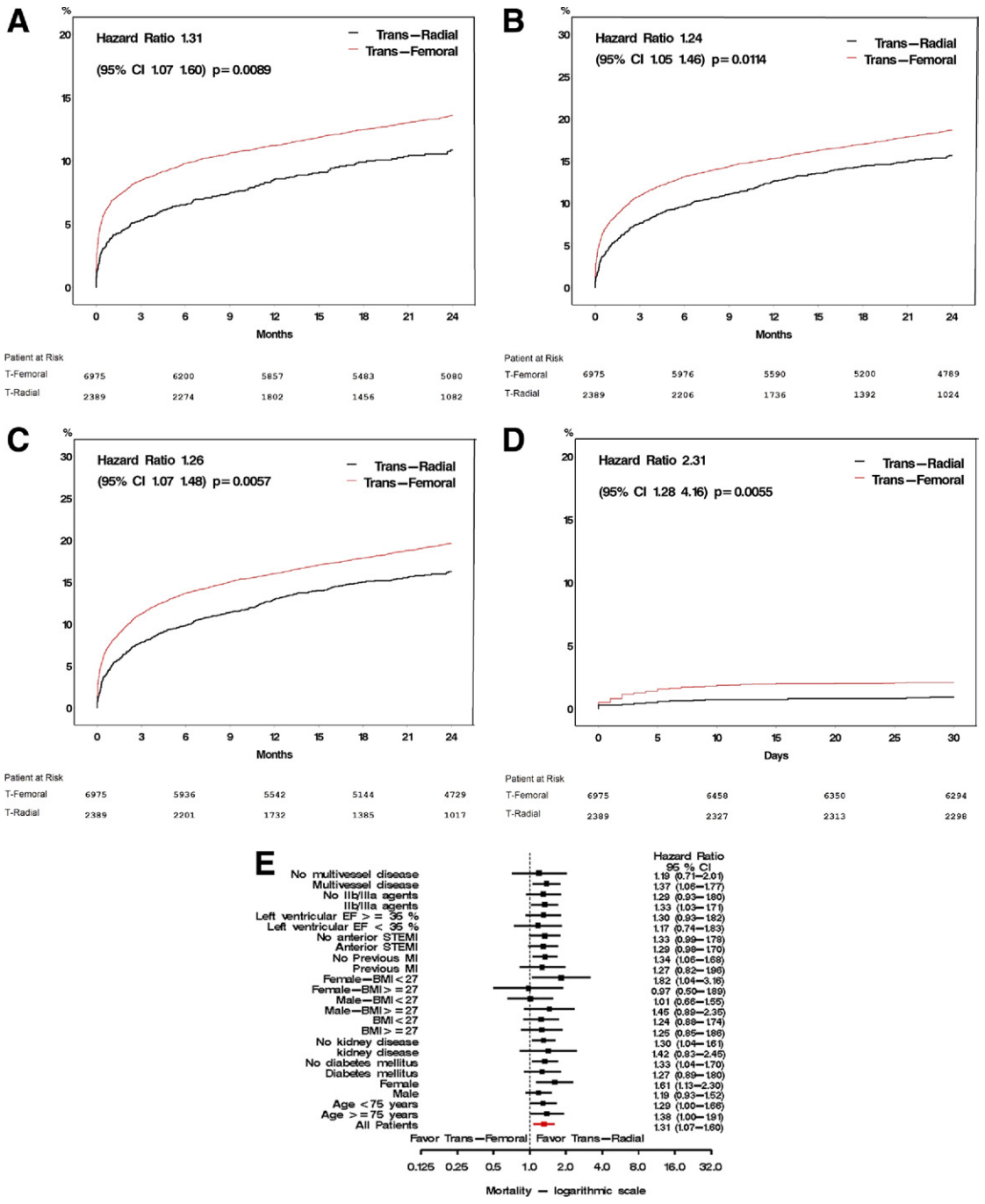

Figure 5. Propensity Score–Adjusted Kaplan-Meier Curves for Outcomes in the Overall Cohort

A total of 11,068 patients underwent transradial or transfemoral intervention. **(A)** Shown are the outcomes for overall survival; **(B)** outcomes for overall death or myocardial infarction; **(C)** outcomes for overall death, myocardial infarction, or stroke; **(D)** outcomes for major bleeding or vascular events; and **(E)** subgroup analyses are shown, with propensity-adjusted hazard ratios and 95% confidence intervals, for the primary endpoint of death for any cause among strata of patients treated either transradially or transfemorally.

ated with a significant and marked reduction of in-hospital major bleeding or vascular events. Bleeding and/or blood product transfusions have been causally associated with a higher mortality rate in patients with acute coronary syndromes (ACS) (7–12,21). The transradial approach may improve the survival rate by mini-

Table 4. Propensity Score–Adjusted HRs for Clinical Outcomes

Outcomes	Adjusted Hazard Ratios (95% Confidence Interval)*	p Values
30 days		
All-cause death	1.380 (1.016–1.876)	0.0395
Myocardial infarction	0.612 (0.332–1.122)	0.113
All-cause death or myocardial infarction	1.199 (0.913–1.574)	0.192
Stroke	0.560 (0.103–3.050)	0.503
All-cause death, myocardial infarction or stroke	1.177 (0.900–1.538)	0.234
Major bleeding and vascular events	1.899 (1.116–3.229)	0.0180
Major bleeding and vascular events within index hospitalization	2.306 (1.279–4.156)	0.0055
2 yrs		
All-cause death	1.309 (1.070–1.602)	0.0089
Myocardial infarction	1.135 (0.862–1.495)	0.366
All-cause death or myocardial infarction	1.240 (1.050–1.465)	0.0114
Stroke	1.855 (1.014–3.393)	0.0450
All-cause death, myocardial infarction, or stroke	1.259 (1.069–1.481)	0.0057
Major bleeding and vascular events	1.181 (0.877–1.590)	0.273
Major bleeding and vascular events within index hospitalization	2.277 (1.283–4.041)	0.0049

*Values >1 indicate lower event rate in the transradial group; complete data for the multivariable analysis were available in 9,364 patients.

mizing access-site–related complications and their negative prognostic consequences, including the relatively rare need for access-site surgery (22) and the much more incidental transfusion of blood products (2,22).

As a result of its long history of use, the wide availability of several dedicated preformed catheters, and the possibility to exploit relatively large-diameter catheters and sheaths, should these be necessary for complex PCI, TFI is currently considered the gold-standard access site worldwide.

Although several methodological refinements for puncture technique and sheath management have been identified in the literature (23,24), access-site complications remain frequent in clinical practice, especially in patients undergoing transfemoral coronary intervention for ACS (2,4,22). This consistent observation across studies may be explained by the complex interplay between several factors, including the high-risk patient profile per se, the emergency nature of intervention, and the frequent use of more potent antithrombotic treatments in this patient population (13).

Similarly, although several access-site closure devices for the femoral artery have been developed and tested in clinical trials, none of them so far have convincingly shown the ability to reduce major vascular complications compared with manual compression (25,26).

Compared with the femoral artery, the radial artery is much more superficial and has a much smaller caliber. which makes access-site homeostasis after sheath removal highly predictable even in the presence of systemic anticoagulation (15,27).

Several randomized controlled studies of relatively limited sample size have convincingly shown that TRI greatly reduces the incidence of access-site major and minor bleeding complications (15). Yet, none of these studies were powered to assess whether the use of the radial instead of the femoral route may translate into an improved short- to medium-term outcome. A meta-analysis of 18 randomized trials comparing TRA versus TFA that mainly focused on elective patients undergoing coronary angiography and/or ad hoc intervention showed a 73% reduction of access-site bleeding complications and a trend toward a 29% reduction of the ischemic composite endpoint of death, myocardial infarction, or stroke in the transradial group (27).

A systematic review of the literature involving 2,808 STEMI patients who were largely recruited via nonrandomized comparisons, showed that TRI was associated with a significant, almost 50% decrease of overall mortality. Mortality in the 516 patients in whom access sites were randomly allocated was also numerically almost 40% lower in the transradial group, but this difference failed to reach statistical significance (28).

In the RIVAL (RadIal Vs femorAL access for coronary intervention) study, patients randomized to the transradial arm in the highest tertile for radial PCI center volume showed a 50% reduction of death, myocardial infarction, or stroke compared with the transfemoral group, which came along with a 55% reduction of major bleeding complications (29). Interestingly, in the 1,958 STEMI study patients, a 41% significant reduction of the composite ischemic endpoint and a 61% reduction of mortality alone were noted in the transradial group, suggesting that this patient popula-

tion may benefit relatively more from a dedicated bleeding minimization strategy (29). An alternative hypothesis that merits further investigation is that only centers with high radial PCI volumes were confident in randomizing STEMI patients in the study; therefore, STEMI patients in the study may simply serve to identify operators particularly experienced for transradial PCI.

In patients with STEMI undergoing angioplasty, prompt restoration of coronary flow is critical to the survival advantage noted over medical treatment (30). Thus, it is frequently felt that the use of the transradial route to restore coronary flow is excessively time consuming in this setting where, in addition, coronary anatomy is unknown, and the need for large-lumen guiding catheters is highly unpredictable (16). The relatively slow rate of adopting TRI over time in our regional STEMI registry suggests that the transition from the transfemoral to the transradial route is a long-term process in this challenging patient population. Although 10 of the 12 regional sites launched a TRI program in 2004 and 2005, several hundreds of PCI cases treated over a 3-year time frame were deemed necessary to make TRI the more prevalent access site in the acute setting of STEMI treatment. Similarly, the cross-over from the radial to the femoral access site peaked at almost 8% in 2006 and subsequently declined to a much more acceptable 3% rate, despite a progressive TRI increase over time.

Our study, in keeping with recent evidence (29), suggests that the risks of transitioning toward the transradial route over the conventional transfemoral approach in STEMI patients, provided the process is undertaken in a step-wise approach as part of a global TRI program, may be largely outweighed by a lower mortality rate. Although a causal relationship between the observed improved short-term safety profile and the lower 2-year fatality rate cannot be proven by our study, this hypothesis is of major potential relevance for the whole medical community, and it is currently being tested in the MATRIX (Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX) study.

Finally, based on a substantial reduction in the length of hospitalization (28) as well as in access-site bleeding and vascular complications (15,27,28), the widespread adoption of TRI may dramatically impact the economic burden of ACS in Western countries (31).

Study limitations. Our findings should be interpreted in the context of our study design and its limitations. First, our data are observational. We used propensity score matching to make the patient groups comparable according to the measured confounders, and we successfully eliminated the observed differences. However, residual confounding cannot be excluded.

Second, there was a substantial use of glycoprotein IIb/IIIa inhibitors in our study population. The use of bivalirudin, as compared with glycoprotein IIb/IIIa inhibitors, has been shown to decrease bleeding events in patients with myocardial infarction, which translated into a long-term mortality benefit (11). Whether our observations are similarly valid also for patients receiving a less aggressive pharmacological treatment remains to be determined. Bleeding events were not prospectively collected in our registry; therefore, red blood cell transfusion and access-site surgical repair was used as a surrogate for major bleeding or vascular events.

It remains to be determined whether the reduction of myocardial infarction and stroke at 2-year follow-up favoring the transradial approach is a spurious finding or may reflect a true long-term advantage of a strategy that minimizes bleeding and vascular events.

Finally, the use of secondary prevention medications was not prospectively collected in our registry. Therefore, we cannot rule out the possibility that a less aggressive implementation of secondary prevention pharmacological measures in patients who experienced major in-hospital bleeding and vascular events may at least partially explain the observed association between TRI and improved cardiovascular outcomes (32).

Conclusions

In patients undergoing angioplasty for acute myocardial infarction, transradial treatment is associated with decreased 2-year mortality rates and a reduction in the need for vascular surgery and/or blood transfusion compared with transfemoral intervention. Large, randomized trials are ongoing and will be necessary to confirm this observation.

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Key Words: mortality ■ primary angioplasty ■ propensity-score matching ■ ST-segment elevation myocardial infarction ■ transradial intervention.

APPENDIX

For a list of investigators, please see the online version of this article.