Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial

*Sanjit S Jolly, Salim Yusuf, John Cairns, Kari Niemelä, Denis Xavier, Petr Widimsky, Andrzej Budaj, Matti Niemelä, Vicent Valentin, Basil S Lewis, Alvaro Avezum, Philippe Gabriel Steg, Sunil V Rao, Peggy Gao, Rizwan Afzal, Campbell D Joyner, Susan Chrolavicius, Shamir R Mehta, for the RIVAL trial group**

Summary

Background Small trials have suggested that radial access for percutaneous coronary intervention (PCI) reduces vascular complications and bleeding compared with femoral access. We aimed to assess whether radial access was superior to femoral access in patients with acute coronary syndromes (ACS) who were undergoing coronary angiography with possible intervention.

Methods The RadIal Vs femorAL access for coronary intervention (RIVAL) trial was a randomised, parallel group, multicentre trial. Patients with ACS were randomly assigned (1:1) by a 24 h computerised central automated voice response system to radial or femoral artery access. The primary outcome was a composite of death, myocardial infarction, stroke, or non-coronary artery bypass graft (non-CABG)-related major bleeding at 30 days. Key secondary outcomes were death, myocardial infarction, or stroke; and non-CABG-related major bleeding at 30 days. A masked central committee adjudicated the primary outcome, components of the primary outcome, and stent thrombosis. All other outcomes were as reported by the investigators. Patients and investigators were not masked to treatment allocation. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, NCT01014273.

Findings Between June 6, 2006, and Nov 3, 2010, 7021 patients were enrolled from 158 hospitals in 32 countries. 3507 patients were randomly assigned to radial access and 3514 to femoral access. The primary outcome occurred in 128 (3·7%) of 3507 patients in the radial access group compared with 139 (4·0%) of 3514 in the femoral access group (hazard ratio [HR] 0·92, 95% CI 0·72–1·17; p=0·50). Of the six prespecified subgroups, there was a significant interaction for the primary outcome with benefit for radial access in highest tertile volume radial centres (HR 0·49, 95% CI 0·28–0·87; p=0·015) and in patients with ST-segment elevation myocardial infarction (0·60, 0·38–0·94; p=0·026). The rate of death, myocardial infarction, or stroke at 30 days was 112 (3·2%) of 3507 patients in the radial group compared with 114 (3·2%) of 3514 in the femoral group (HR 0·98, 95% CI 0·76–1·28; p=0·90). The rate of non-CABG-related major bleeding at 30 days was 24 (0·7%) of 3507 patients in the radial group compared with 33 (0·9%) of 3514 patients in the femoral group (HR 0·73, 95% CI 0·43–1·23; p=0·23). At 30 days, 42 of 3507 patients in the radial group had large haematoma compared with 106 of 3514 in the femoral group (HR 0·40, 95% CI 0·28–0·57; p<0·0001). Pseudoaneurysm needing closure occurred in seven of 3507 patients in the radial group compared with 23 of 3514 in the femoral group (HR 0·30, 95% CI 0·13–0·71; p=0·006).

Interpretation Radial and femoral approaches are both safe and effective for PCI. However, the lower rate of local vascular complications may be a reason to use the radial approach.

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*Members listed at end of paper

McMaster University and the Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada (S S Jolly MD, Prof S Yusuf MBBS, P Gao MSc, R Afzal MSc, S Chrolavicius BScN, S R Mehta MD); **University of British Columbia, Vancouver, BC, Canada** (Prof J Cairns MD); **Tampere University Hospital and Tampere Heart Centre, Tampere, Finland** (Prof K Niemelä MD); **St John's Medical College and Research Institute, Bangalore, India** (D Xavier MD); **Charles University, Hospital Kralovske Vinohrady, Prague, Czech Republic** (Prof P Widimsky MD); **Postgraduate Medical School, Department of Cardiology, Grochowski Hospital, Warsaw, Poland** (Prof A Budaj MD); **Oulu University Hospital, University of Oulu, Oulu, Finland** (M Niemelä MD); **Hospital Universitari Dr Peset, Valencia, Spain** (V Valentin MD); **Lady Davis Carmel Medical Center, Haifa, Israel** (Prof B S Lewis MD); **Dante Pazzanese Institute of Cardiology, São Paulo, Brazil** (A Avezum MD); **INSERM U698 "Recherche Clinique en Athérothrombose", Université Paris 7 and Assistance Publique—Hôpitaux de Paris, Paris, France** (Prof P G Steg MD); **Duke Clinical Research Institute, Duke University, Durham, NC,**

Introduction

In patients with acute coronary syndromes (ACS; ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation ACS [NSTE-ACS]), major bleeding is as common as recurrent myocardial infarction and occurs in about 5% of patients, depending on the definition used. A substantial proportion of the bleeding occurs at the vascular access site.[1–4] Findings from observational studies suggest that major bleeding is associated with increased risk of death and recurrent ischaemic events.[5,6] Vascular access via the radial artery—a superficial and readily compressible site—might result in less bleeding than access through the femoral artery. Also, observational studies have suggested a lower risk of death and myocardial infarction with radial than with femoral access, but these analyses are limited because of potential confounding factors.[7–9] A meta-analysis of small randomised trials suggested that radial access might reduce major bleeding and was associated with weak evidence of a reduction in the composite of death, myocardial infarction, or stroke but also with weak evidence of an increased rate of percutaneous coronary intervention (PCI) failure.[10] The individual trials were

USA (S V Rao MD)**; and Sunnybrook Health Sciences, Toronto, ON, Canada** (Prof C D Joyner MD)

Correspondence to:
Dr Sanjit S Jolly, Room C3-118, DBCVSRI Building, Hamilton General Hospital, 237 Barton St East, Hamilton, ON L8L 2X2, Canada
sanjit.jollly@phri.ca

small, often single-centred, and underpowered to detect differences in important clinical events.

Accordingly, we did a large, multicentre, randomised trial among patients with ACS who were undergoing coronary angiography with possible intervention, to assess whether radial access was superior to femoral access.

Methods

Study design and patients

The RadIal Vs femorAL access for coronary intervention (RIVAL) trial was a randomised, parallel group, multicentre trial. The design of the RIVAL trial has been previously published.[11] The RIVAL trial first enrolled patients within an investigator-initiated randomised substudy of the Clopidogrel and aspirin optimal dose Usage to Reduce Recurrent EveNTS—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial.[12] The CURRENT-OASIS 7 trial was a randomised trial (n=25 086) with a factorial design that compared double dose clopidogrel (600 mg followed by 150 mg for 7 days then 75 mg once daily) versus standard dose clopidogrel (300 mg followed by 75 mg daily) and high-dose (300–325 mg) versus low-dose aspirin (75–100 mg) in patients with acute coronary syndromes.[13,14] After the CURRENT-OASIS 7 trial was completed, additional patients were enrolled in the RIVAL trial.

Patients were included if they had ACS with or without ST segment elevation, an invasive approach was planned, the interventional cardiologist was willing to proceed

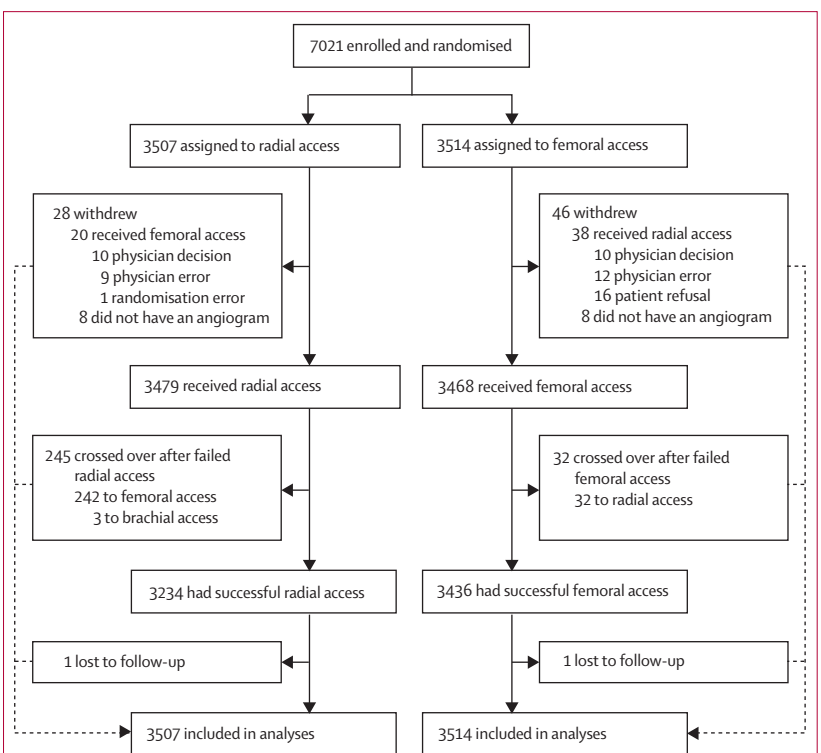

Figure 1: **Trial profile**

	Radial (n=3507)	Femoral (n=3514)
Demographics		
Age (years)	62 (12)	62 (12)
Age >75 years	506 (14·4%)	529 (15·1%)
Men	2599 (74·1%)	2561 (72·9%)
Diagnosis at admission		
Unstable angina	1554 (44·3%)	1606 (45·7%)
NTSTEMI	998 (28·5%)	905 (25·8%)
STEMI	955 (27·2%)	1003 (28·5%)
Ethnic origin		
European	2558 (72·9%)	2575 (73·3%)
Black	18 (0·5%)	32 (0·9%)
South Asian	483 (13·8%)	475 (13·5%)
East Asian	149 (4·2%)	137 (3·9%)
Other	299 (8·5%)	293 (8·3%)
History		
Present smoker	1083 (30·9%)	1097 (31·2%)
Hypertension	2118 (60·4%)	2076 (59·1%)
Diabetes mellitus	781 (22·3%)	722 (20·5%)
Myocardial infarction	658 (18·8%)	622 (17·7%)
PCI	431 (12·3%)	408 (11·6%)
Coronary artery bypass graft surgery	79 (2·3%)	75 (2·1%)
Peripheral vascular disease	91 (2·6%)	82 (2·3%)
Baseline characteristics		
ECG findings at study entry for NSTE-ACS*		
ST-segment depression	927 (36·3%)	930 (37·0%)
T-wave inversion	785 (30·8%)	751 (29·9%)
Elevated biomarker (among NSTE-ACS)	1586 (62·1%)	1613 (64·2%)
Antithrombotic treatment in hospital		
Aspirin	3479 (99·2%)	3489 (99·3%)
Clopidogrel	3368 (96·0%)	3358 (95·6%)
Clopidogrel loading dose ≤300 mg before PCI†	893 (38·6%)	963 (41·0%)
Clopidogrel loading dose >300 mg before PCI†	1208 (52·3%)	1165 (49·6%)
Low-molecular-weight heparin	1806 (51·5%)	1819 (51·8%)
Intravenous unfractionated heparin	1168 (33·3%)	1110 (31·6%)
Fondaparinux	383 (10·9%)	381 (10·8%)
Bivalirudin	76 (2·2%)	109 (3·1%)
Glycoprotein IIb/IIIa inhibitor	887 (25·3%)	844 (24·0%)
Glycoprotein IIb/IIIa inhibitor in patients with STEMI‡	329 (34·5%)	312 (31·1%)
Other in-hospital medications		
Proton-pump inhibitors	1050 (29·9%)	1097 (31·2%)
β blockers	3104 (88·5%)	3130 (89·1%)
Angiotensin-converting-enzyme inhibitors	2546 (72·6%)	2539 (72·3%)
Angiotensin-II-receptor blockers	377 (10·7%)	386 (11·0%)
Statins	3309 (94·4%)	3289 (93·6%)
Calcium-channel blockers	655 (18·7%)	623 (17·7%)

Data are mean (SD) or number (%). STEMI=ST-segment elevation myocardial infarction. NSTEMI=non-STEMI. PCI=percutaneous coronary intervention. NSTE-ACS= non-ST-segment elevation acute coronary syndromes. *n=2552 in the radial group and n=2511 in the femoral group. †n=2311 in the radial group and n=2349 in the femoral group. ‡n=955 in the radial group and n=1003 in the femoral group.

Table 1: **Demographics and baseline characteristics**

with either radial or femoral access (and had expertise for both, including at least 50 radial procedures for coronary angiography or intervention within the previous year), and dual circulation of the hand was intact as assessed by an Allen's test. Patients were ineligible for RIVAL if they presented with cardiogenic shock, severe peripheral vascular disease precluding a femoral approach, or previous coronary bypass surgery with use of more than one internal mammary artery. Webappendix p 1 contains detailed eligibility criteria, which have been previously published.[11]

See Online for webappendix

The study was approved by all appropriate national regulatory authorities and the ethics committees of participating centres. All patients provided written informed consent to participate before enrolment. The trial was coordinated by the Population Health Research Institute at McMaster University and Hamilton Health Sciences in Hamilton, ON, Canada. An independent data monitoring committee periodically reviewed unmasked data. An international steering committee was responsible for the conduct of the trial.

	Radial (n=3507)	Femoral (n=3514)
Invasive procedures after randomisation during initial stay in hospital		
Coronary angiography	3499 (99·8%)	3506 (99·8%)
PCI	2311 (65·9%)	2349 (66·8%)
Stent*†	2187 (94·6%)	2233 (95·1%)
Bare-metal stent	1428 (65·3%)	1544 (69·1%)
≥1 drug-eluting stent	835 (38·2%)	722 (34·6%)
Coronary artery bypass grafting	308 (8·8%)	291 (8·3%)
STEMI initial reperfusion therapy‡		
Primary PCI	702 (73·5%)	749 (74·7%)
Fibrinolytic therapy	121 (12·7%)	112 (11·2%)
Facilitated PCI	31 (3·2%)	31 (3·1%)
Neither primary PCI nor fibrinolytic	101 (10·6%)	111 (11·1%)
Operator's annual volume		
PCI per year	300 (190–400)	300 (190–400)
Percent radial PCI	40 (25–70)	40 (25–70)
Total number radial (diagnostic and PCI) procedures per year	352 (180–599)	345 (180–575)
Total number femoral (diagnostic and PCI) procedures per year	386 (181–647)	390 (190–655)
Procedural characteristics		
Arterial sheath size§		
≤5 French¶	505 (14·4%)	237 (6·8%)
6 French‖	2708 (77·4%)	2811 (80·2%)
≥7 French¶	35 (1·0%)	212 (6·0%)
Number of diagnostic catheters used**		
1¶	1073 (30·7%)	521 (14·9%)
2¶	1705 (48·7%)	2172 (62·0%)
≥3	703 (20·1%)	797 (22·7%)
Number of PCI guide catheters used†		
1	1890 (81·8%)	1970 (83·9%)
2	307 (13·3%)	291 (12·4%)
≥3	106 (4·6%)	82 (3·5%)
Intra-aortic balloon pump	31 (0·9%)	37 (1·1%)

Data are number (%) or median (IQR). PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. *Bare-metal stent p=0·006; drug-eluting stent p=0·013. †As a proportion of patients having PCI. ‡n=955 in the radial group and n=1003 in the femoral group. §n=3248 in the radial group and n=3260 in the femoral group; sheath size was not recorded on the case-report forms of the first 497 patients. ¶p<0·0001. ‖p=0·004. **n=3481 in the radial group and n=3490 in the femoral group; data on the number of diagnostic catheters were missing for 34 patients who had coronary angiography.

Table 2: **Invasive procedures after randomisation, operator volumes, and procedural characteristics**

	Radial (n=3507)	Femoral (n=3514)	Hazard ratio (95% CI)	p value
Primary outcome				
Death, MI, stroke, or non-CABG bleeding at 30 days	128 (3·7%)	139 (4·0%)	0·92 (0·72–1·17)	0·50
Secondary outcomes at 30 days				
Death, MI, or stroke	112 (3·2%)	114 (3·2%)	0·98 (0·76–1·28)	0·90
Non-CABG major bleeding	24 (0·7%)	33 (0·9%)	0·73 (0·43–1·23)	0·23
Death	44 (1·3%)	51 (1·5%)	0·86 (0·58–1·29)	0·47
MI	60 (1·7%)	65 (1·9%)	0·92 (0·65–1·31)	0·65
Stroke	20 (0·6%)	14 (0·4%)	1·43 (0·72–2·83)	0·30
Secondary outcomes at 48 h				
Death, MI, stroke, or non-CABG bleeding	50 (1·4%)	65 (1·8%)	0·77 (0·53–1·11)	0·17
Non-CABG major bleeding	11 (0·3%)	18 (0·5%)	0·61 (0·29–1·30)	0·20
Death	9 (0·3%)	15 (0·4%)	0·60 (0·26–1·37)	0·23
MI	29 (0·8%)	31 (0·9%)	0·94 (0·56–1·56)	0·80
Stroke	7 (0·2%)	6 (0·2%)	1·17 (0·39–3·48)	0·78
Other secondary outcomes				
PCI success*	2204 (95·4%)	2235 (95·2%)	1·01 (0·95–1·07)	0·83
Access site crossover	265 (7·6%)	70 (2·0%)	3·82 (2·93–4·97)	<0·0001
Major vascular complications	49 (1·4%)	131 (3·7%)	0·37 (0·27–0·52)	<0·0001
Minor bleeding	100 (2·9%)	118 (3·4%)	0·84 (0·65–1·10)	0·21
Safety outcomes				
Non-CABG TIMI major bleeding	19 (0·5%)	19 (0·5%)	1·00 (0·53–1·89)	1·00
CABG-related bleeding	48 (1·4%)	48 (1·4%)	1·00 (0·67–1·49)	1·00
Non-CABG-related blood transfusions	39 (1·1%)	45 (1·3%)	0·87 (0·56–1·33)	0·51
All blood transfusions	99 (2·8%)	98 (2·8%)	1·01 (0·76–1·33)	0·95
Post-hoc exploratory outcomes				
ACUITY major bleeding†	66 (1·9%)	157 (4·5%)	0·43 (0·32–0·57)	<0·0001
Death, MI, or stroke, or ACUITY major bleed†	167 (4·8%)	256 (7·3%)	0·65 (0·53–0·78)	<0·0001
Non-CABG major bleeding and major vascular complications	67 (1·9%)	157 (4·5%)	0·43 (0·32–0·57)	<0·0001
Death, MI, stroke, non-CABG major bleeding, or major vascular complications	167 (4·8%)	260 (7·4%)	0·63 (0·52–0·77)	<0·0001

Data are number (%). MI=myocardial infarction. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. ACUITY=Acute Catheterization and Urgent Intervention strategy. *As a proportion of patients who had PCI: n=2311 in the radial group and n=2349 in the femoral group. †Large haematomas diagnosed as per investigator's clinical decision.

Table 3: **Primary, secondary, safety, and exploratory outcomes**

Randomisation and masking

Patients were randomly assigned (1:1) to radial or femoral access by a 24 h computerised central automated voice response system located at the Population Health Research Institute. Randomisation was done in permuted blocks of variable sizes (two, four, and six), stratified by centre. A masked central committee adjudicated the primary outcome, components of the primary outcome, and stent thrombosis. All other outcomes were as reported by investigators. Patients and investigators were not masked to treatment allocation.

Procedures

Before coronary angiography, patients were assigned to either transradial access or transfemoral access for coronary angiography and same-sitting PCI if clinically indicated. The antithrombotic regimen (including glycoprotein IIb/IIIa inhibitors) used for PCI was at the discretion of the treating physician, as was the use of femoral vascular closure devices.

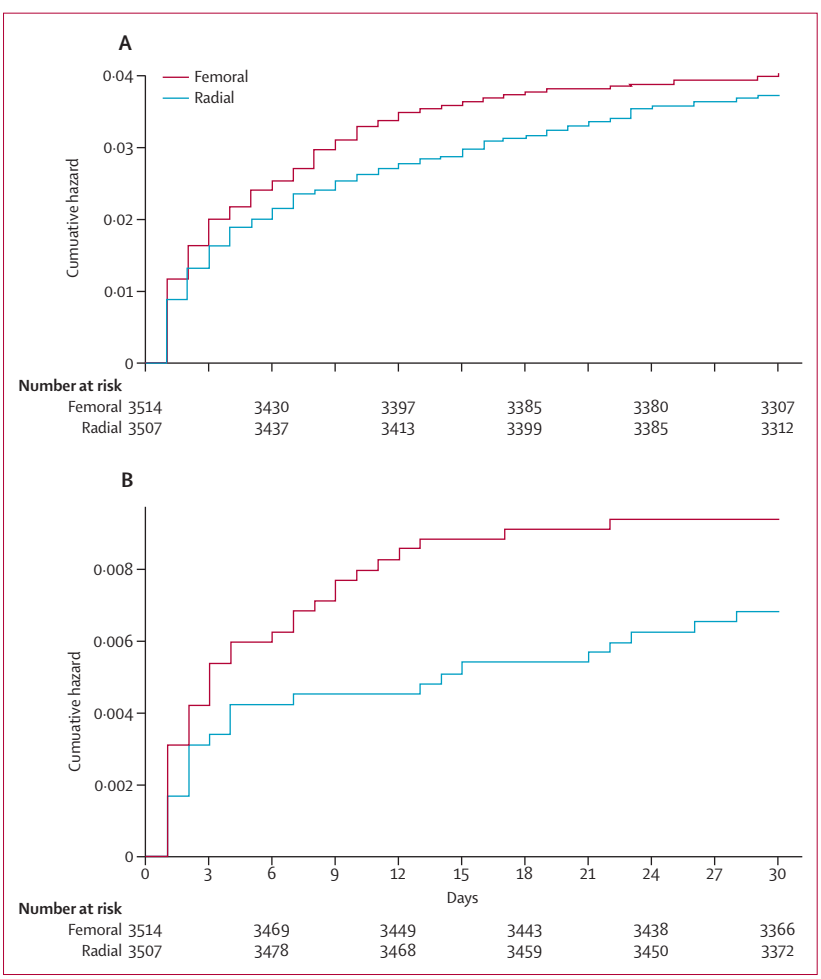

Figure 2: **Kaplan-Meier event curves for the primary outcome and a key secondary outcome**
(A) Composite primary outcome of death, myocardial infarction, stroke, or non-coronary artery bypass graft related major bleeding. (B) Secondary outcome of non-coronary artery bypass graft related major bleeding.

The primary efficacy outcome was the occurrence of death, myocardial infarction, stroke, or non-coronary artery bypass graft (non-CABG)-related major bleeding within 30 days. Key secondary outcomes were death, myocardial infarction, or stroke; and non-CABG-related major bleeding at 30 days. Other secondary outcomes included components of the primary outcome, major vascular access site complications at 48 h and 30 days, and PCI procedural success.

Detailed outcome definitions have been published[11] and are available in webappendix pp 2–3. In brief, major bleeding was defined as bleeding that was: (1) fatal; (2) resulted in transfusion of two or more units of red blood cells or equivalent whole blood; (3) caused substantial hypotension with the need for inotropes; (4) needed surgical intervention (a requirement for surgical access site repair constitutes major bleeding only if there has been substantial hypotension or transfusion of at least two units of blood); (5) caused severely disabling sequelae; (6) was intracranial and symptomatic or intraocular and led to significant visual loss; or (7) led to a drop in haemoglobin of at least 50 g/L. Acute Catheterization and Urgent Intervention strategy (ACUITY) non-CABG-related major bleeding was defined as RIVAL major bleeding, large haematomas, and pseudoaneurysms requiring intervention. Minor bleeding was defined as bleeding events that did not meet the criteria for a major bleed and required transfusion of one unit of blood or modification of the drug regimen (ie, cessation of antiplatelet or antithrombotic therapy). Major vascular access site complications were routinely recorded during hospital stay and at 30 days in all patients and included pseudoaneurysms needing closure, large haematoma (as judged by investigator), arteriovenous fistula, or an ischaemic limb needing surgery. These complications were classed as a major bleeding event or a minor bleeding event only if they also met the above definitions of major or minor bleeding.

Statistical analyses

Because of a lower than expected overall event rate for the primary outcome, in July, 2009, the sample size was increased from 4000 to 7000 by the RIVAL steering committee. We calculated that a sample size of 7000 would provide 80% power to detect a 25% relative risk reduction with a control event rate of 6% and a 30% relative risk reduction with a control event rate of 4·5%.[11]

All patients were included in the final intention-to-treat analyses, regardless of whether they crossed over to another access site or did not undergo PCI. A significance level of 0·05 with two-sided test was used, and all analyses were done in SAS (version 9.1). The relative efficacy of radial versus femoral access for the primary outcome was assessed by comparison of the survival curves (estimated with the Kaplan-Meier method) for the two approaches by the log-rank statistic.

The six prespecified pre-randomisation subgroups were age (<75 and ≥75 years), sex, body-mass index

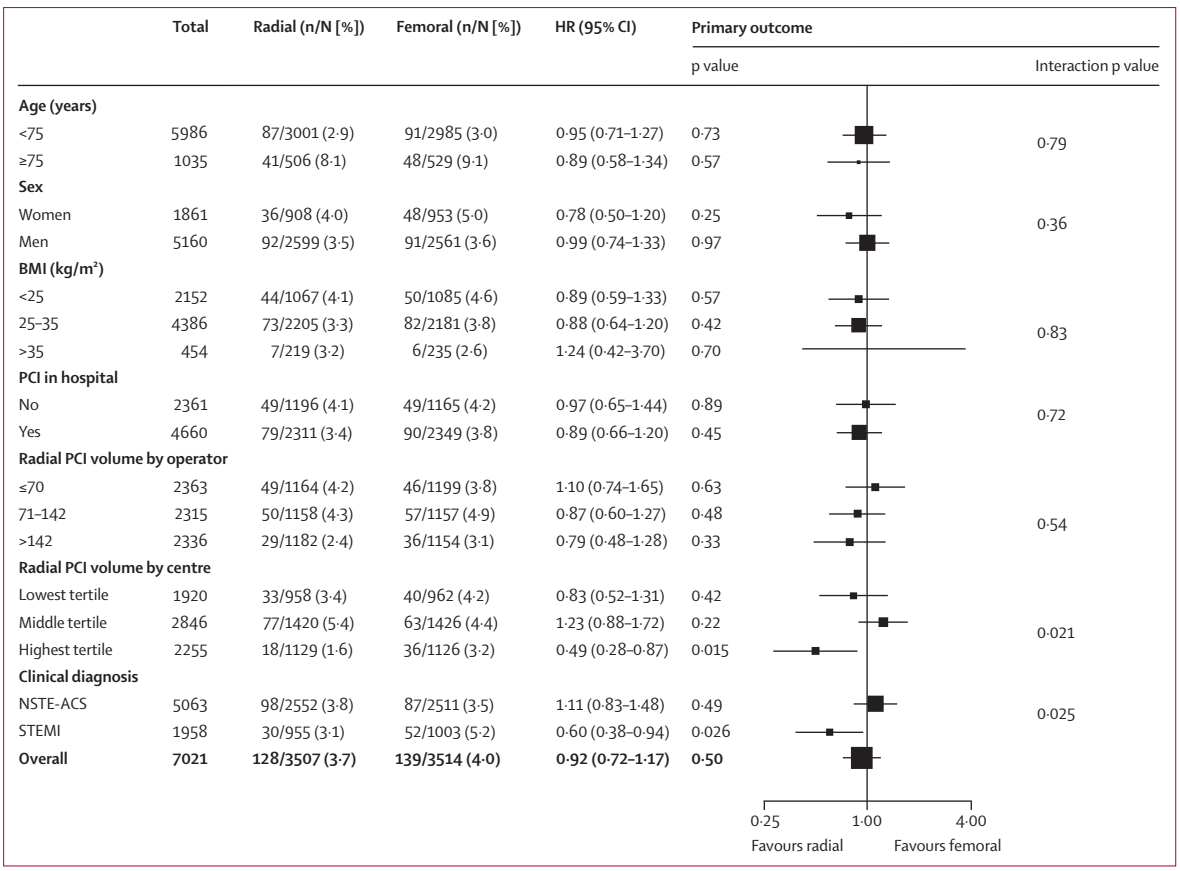

Figure 3: **Forest plot of prespecified subgroup analyses of the composite primary outcome**
HR=hazard ratio. BMI=body-mass index. PCI=percutaneous coronary intervention. NSTE-ACS=non-ST-segment elevation myocardial infarction. STEMI=ST-segment elevation myocardial infarction.

(<25, ≥25 to ≤35, and >35 kg/m²), STEMI versus NSTE-ACS, and by tertiles of each operator's annual radial PCI volume (low [≤70 radial PCI per year per operator], intermediate [71–142 radial PCI per year per operator], and high [>142 radial PCI per year per operator]), and each centre's median operator's radial PCI volume (low [≤60 radial PCI per year per operator], intermediate [61–146 radial PCI per year per operator], and high [>146 radial PCI per year per operator]). The rationale to assess centre volume characteristics is that randomisation was stratified by centre and there was the potential for an individual operator to do only one study procedure, making inferences at the operator level less reliable.[15,16] The significance level for interaction was set at 0·05. A prespecified analysis examined the results in patients who underwent PCI versus no PCI.

We did an updated meta-analysis with the same method as in our previous meta-analysis (web-appendix p 4).[10] We searched Medline and Embase and also hand searched conference abstracts from the American Heart Association, American College of Cardiology, Transcatheter Therapeutics, and European Society of Cardiology from April, 2008, to December, 2010.[10] We assessed the following outcomes: non-CABG major bleeding (RIVAL definition); blood transfusion; major vascular access site complications; death, myocardial infarction, or stroke; death; myocardial infarction; and stroke.

This trial is registered with ClinicalTrials.gov, NCT01014273.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SSJ, SY, SRM, JC, PG, and RA had full access to all the data in the study and the steering committee had final responsibility for the decision to submit for publication.

Results

Between June 6, 2006, and Nov 3, 2010, 7021 patients were enrolled from 158 hospitals in 32 countries. 142 of 597 CURRENT-OASIS 7 sites participated in RIVAL and these sites enrolled 3831 (45%) of 8515 of patients from CURRENT-OASIS 7 into RIVAL. 3190 additional patients were enrolled after CURRENT-OASIS 7 was completed. 3507 of 7021 patients were randomly assigned to radial access and 3514 to femoral access (figure 1). 7005 (99·8%)

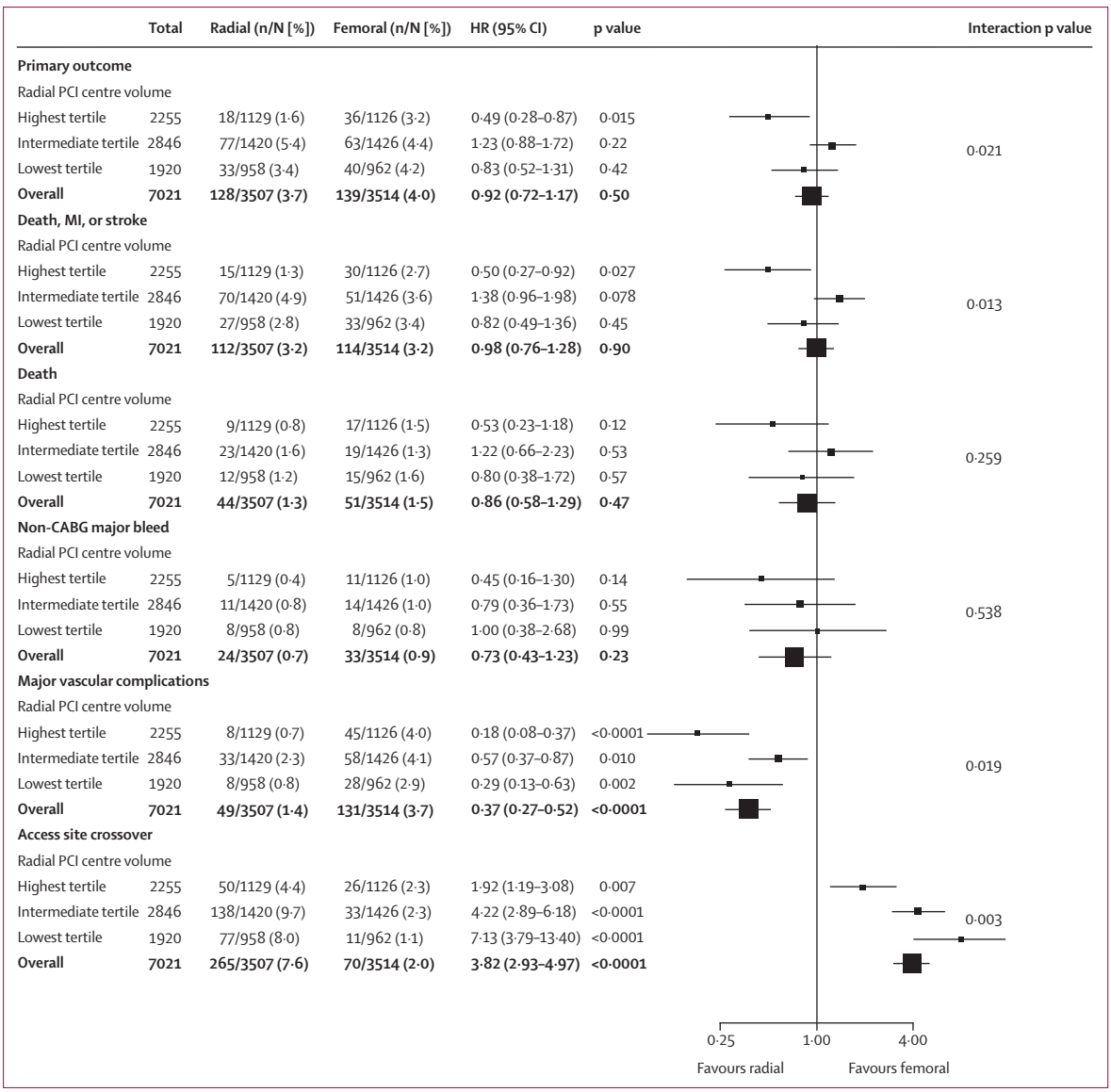

Figure 4: **Forest plot of outcomes by centre's radial PCI volume**
HR=hazard ratio. PCI=percutaneous coronary intervention. MI=myocardial infarction. CABG=coronary artery bypass graft.

of 7021 patients underwent diagnostic coronary angiography. 4660 (66·4%) of 7021 patients had PCI and 599 (8·5%) had coronary bypass surgery. Follow-up was complete in all but two patients (figure 1). The overall rates of access site crossover were 7·6% in the radial group versus 2·0% in the femoral group. However, when excluding non-adherence (figure 1), crossover related to failure of initial strategy was 7·0% in the radial group and 0·9% in the femoral group. Reasons for crossover are available in the 3190 patients who were randomised after CURRENT-OASIS 7, and in the radial group these reasons were radial spasm in 80 (5·0%), radial artery loop in 20 (1·3%), and subclavian tortuosity in 31 (1·9%) of 1594 patients. The reasons for crossover in the femoral group were femoral iliac tortuosity in ten (0·6%) and peripheral vascular disease in nine (0·6%) of 1596 patients. The baseline characteristics for the two groups were well balanced (table 1). Of the 7021 patients included, 5063 had NSTE-ACS and 1958 (28·5% of the radial group and 27·2% of the femoral group) had STEMI at presentation. 25% of patients received glycoprotein IIb/IIIa inhibitors. 2·2% of patients in the radial group and 3·1% of those in the femoral group were receiving bivalirudin.

A 5 French sheath was used more often in patients in the radial group than the femoral group (p<0·0001), as was a single diagnostic coronary angiography catheter (p<0·0001; table 2). The number of PCI guide catheters used was

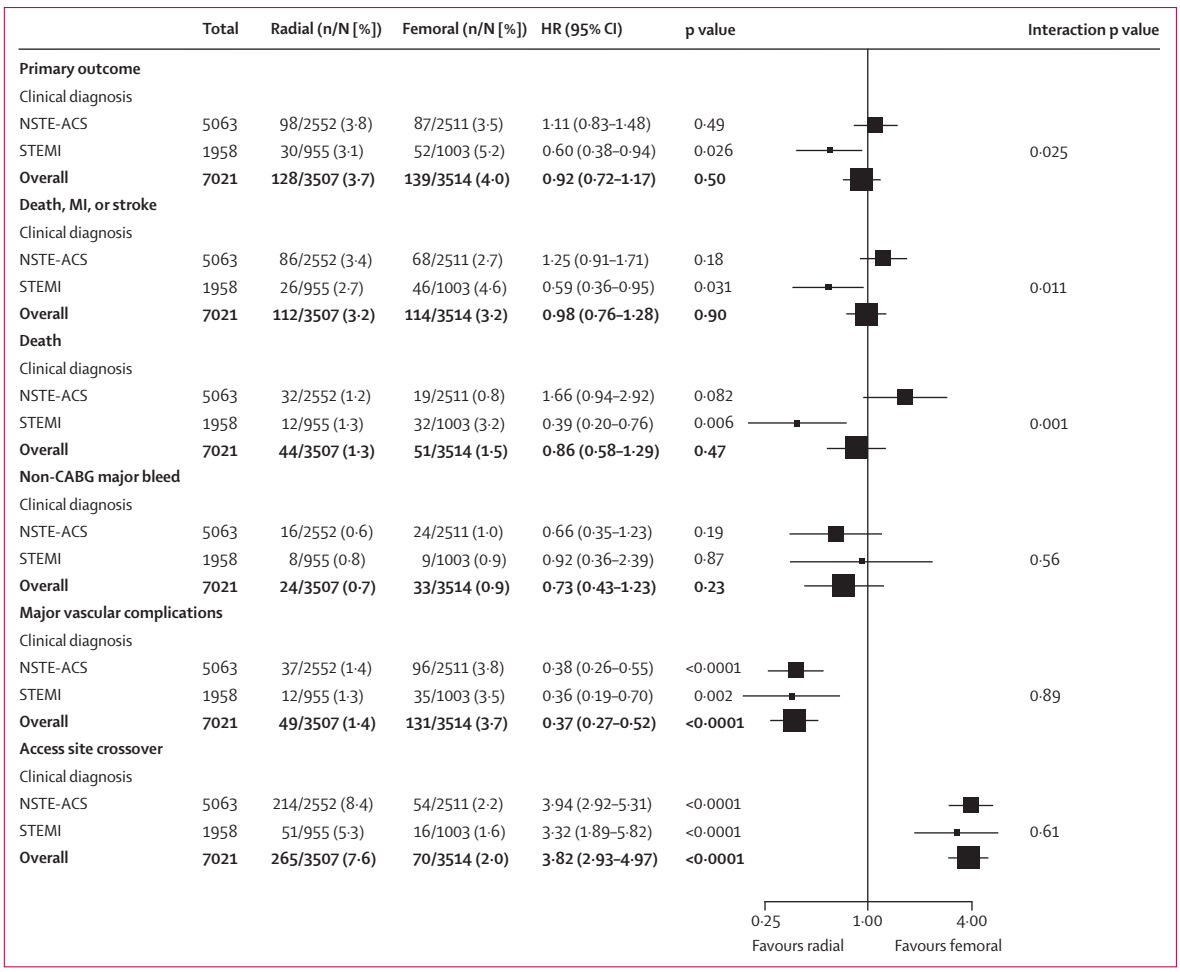

Figure 5: **Forest plot of outcomes by STEMI versus NSTE-ACS**
HR=hazard ratio. NSTE-ACS=non-ST-segment elevation myocardial infarction acute coronary syndromes. STEMI=ST-segment elevation myocardial infarction. MI=myocardial infarction. CABG=coronary artery bypass graft.

similar between the two groups (p=0·059). Stents were used in most patients who underwent PCI (95%) in both groups. The ratio of drug-eluting (p=0·013) and bare-metal (p=0·006) stents was higher in the radial than in the femoral group, but clinical differences were small. Median fluoroscopy time was higher in the radial group than the femoral group (7·8 min *vs* 6·5 min; p<0·0001).

The primary outcome of death, myocardial infarction, stroke, or non-CABG-related major bleeding at 30 days occurred in 3·7% of patients in the radial access group and 4·0% in the femoral access group (p=0·50; table 3; figure 2). The difference between groups in the secondary outcomes of death, myocardial infarction, or stroke at 30 days (p=0·90), and non-CABG related major bleeding (p=0·23; table 3; figure 2) were not significant. In a post-hoc analysis, when we used a bleeding definition from the ACUITY trial,[2] the rate was significantly less with radial than with femoral access (p<0·0001). There was a significant reduction in the secondary endpoint of vascular access site complications with radial compared with femoral access (p<0·0001). Symptomatic radial occlusion needing medical attention and ultrasound confirmation occurred in six patients (0·2%) in the radial group, but none of these patients needed surgical intervention.

Access site major bleeding occurred in six (0·2%) patients in the radial group compared with 12 (0·3%) in the femoral group (hazard ratio [HR] 0·50, 95% CI 0·13–1·33). However, in a post-hoc analysis that assessed the actual location of the access site major bleed, there were no reported cases of access site major bleeds at the radial access site versus 18 at femoral access site (because of crossover, intra-aortic balloon pump insertion, or subsequent procedures; webappendix p 5). Of 57 non-CABG-related major bleeds, 40 occurred remotely from the access site and the rates of such bleeding were not significantly different between the two groups (0·5% radial *vs* 0·6% femoral; p=0·75). The most common origin of non-CABG bleeding was gastrointestinal (21 of 57; 37%), followed by cardiac tamponade (six of 57; 11%), and intracranial haemorrhage

	Radial (n=3507)	Femoral (n=3514)	HR (95% CI)	p value
Major vascular complications at 30 days				
Large haematoma	42 (1·2%)	106 (3·0%)	0·40 (0·28–0·57)	<0·0001
Pseudoaneurysm needing closure	7 (0·2%)	23 (0·6%)	0·30 (0·13–0·71)	0·006
Arteriovenous fistula	0 (0%)	5 (0·1%)	..	..
Ischaemic limb needing surgery	1 (0%)*	0 (0%)	..	..
PCI complications†				
Abrupt closure	12 (0·5%)	11 (0·5%)	1·11 (0·49–2·51)	0·81
No reflow	21 (0·9%)	31 (1·3%)	0·69 (0·40–1·20)	0·19
Dissection with reduced flow	30 (1·3%)	25 (1·1%)	1·22 (0·72–2·07)	0·46
Coronary perforation	5 (0·2%)	4 (0·2%)	1·27 (0·34–4·73)	0·72
Catheter thrombus	2 (0·1%)	2 (0·1%)	1·01 (0·14–7·21)	0·99
Stent thrombosis‡	16 (0·7%)	26 (1·2%)	0·63 (0·34–1·17)	0·14
Definite	8 (0·4%)	16 (0·7%)	0·51 (0·22–1·19)	0·12
Probable	8 (0·4%)	11 (0·5%)	0·74 (0·30–1·84)	0·52
PCI procedural time (min)	35 (22–50)	34 (22–50)	..	0·62
Fluoroscopy time (min)§	9·3 (5·8–15·0)	8·0 (4·5–13·0)	..	<0·0001
PCI contrast volume (mL)	181 (140–240)	180 (145–240)	..	0·87
Length of stay in hospital (days)	4 (3–7)	4 (3–7)	..	0·18
Persistent pain at access site for >2 weeks	87/3378 (2·6%)	104/3392 (3·1%)	0·84 (0·63–1·12)¶	0·22
Patient prefers radial next procedure	2962/3282 (90·2%)	1629/3210 (50·7%)	8·99 (7·86–10·28)¶	<0·0001

Data are number (%) or median (IQR), unless otherwise stated. HR=hazard ratio. PCI=percutaneous coronary intervention. *Related to iliac artery thrombosis secondary to intra-aortic balloon pump inserted via femoral site. †As a proportion of patients having PCI: n=2311 in the radial group and n=2349 in the femoral group. ‡As a proportion of individuals receiving a stent: n=2197 in the radial group and n=2243 in the femoral group. §Fluoroscopy times added to case report forms and available for 2850 patients in the radial group and 2890 patients in the femoral group. ¶Odds ratio (95% CI).

Table 4: **Procedural complications and outcomes and patient preference**

(five of 57; 9%). There were no reported cases of compartment syndrome in either group.

In exploratory analyses, when we analysed outcomes by the access site used to complete the procedure, the primary outcome did not differ between radial and femoral access (3·4% radial *vs* 4·1% femoral; HR 0·83, 95% CI 0·65–1·06; p=0·14). The rates of death, myocardial infarction, or stroke were also similar (3·1% radial *vs* 3·3% femoral; HR 0·92, 95% CI 0·71–1·19; p=0·52); however, the rate of non-CABG related major bleeding was lower with radial access (0·6% *vs* 1·0%, HR 0·53, 95% CI 0·30–0·92; p=0·025).

There were no significant interactions between the effects on the primary outcome of the access site groups and the prespecified subgroups of age, sex, and body-mass index (figure 3). There was no significant interaction by whether patients were recruited within the CURRENT-OASIS 7 study versus later (data not shown). However, there were significant interactions between the prespecified subgroups of radial PCI volume by centre and a diagnosis of STEMI versus NSTE-ACS for the primary outcome and some secondary outcomes (figure 3; figure 4; figure 5).

In the centres with radial PCI volumes in the upper tertile, there seemed to be a benefit of radial versus femoral access for the primary outcome, with no such benefit in middle or low tertiles (interaction p=0·021; figure 4). At centres undertaking a high proportion of radial procedures, there was a benefit with radial access over femoral access for access site crossover, major vascular complications, and the composite of death, myocardial infarction, or stroke (figure 4). We did a post-hoc analysis of the outcomes after dividing centres on the basis of their experience with femoral access, and did not find a significant interaction with radial versus femoral access for the primary outcome (interaction p=0·75).

Patients with STEMI benefitted more from radial access with regards the primary outcome than did those with NSTE-ACS (interaction p=0·025; figure 5). In patients with STEMI, there was a benefit with radial access for the composite of death, myocardial infarction, and stroke (interaction p=0·011), and death (interaction p=0·001; figure 5).

Of the 3514 patients randomly assigned to femoral access, 900 (25·6%) received a femoral vascular closure device. Angioseal (St Jude, Minneapolis, MN, USA) was the most commonly used device in these patients (628 patients; 70%); other devices, such as Starclose (Abbott Vascular, Redwood City, CA, USA; 81 patients; 9%) and Perclose (Abbott Vascular; 55 patients; 6%) were used infrequently; 136 patients received other closure devices. The rate of non-CABG related major bleeding in those who received a closure device was six (0·7%) of 900 versus 27 (1·0%) of 2614 in those randomised to femoral access. For patients treated with glycoprotein IIb/IIIa inhibitors, the results were consistent with the overall results for the

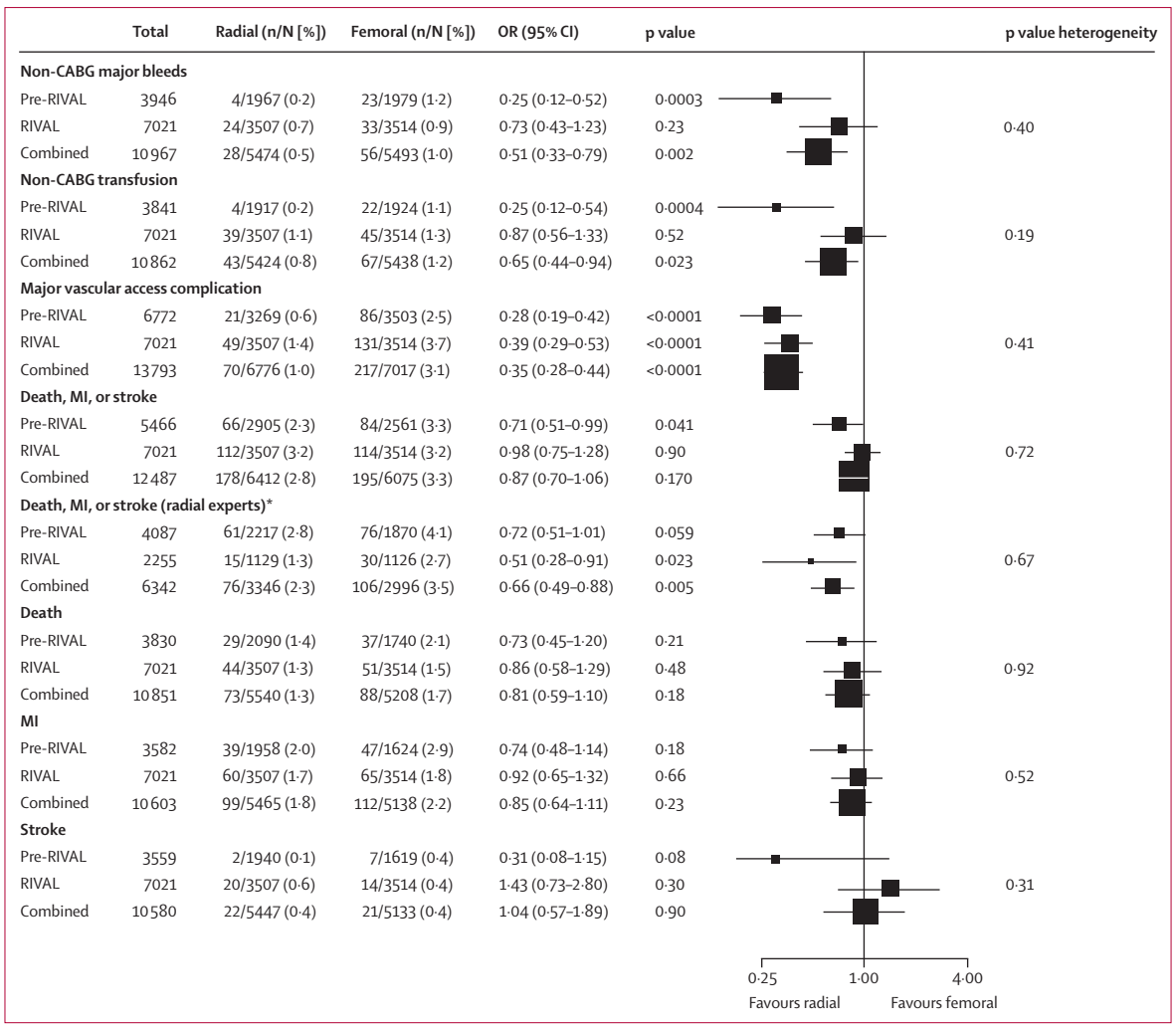

Figure 6: **Forest plot of the updated meta-analysis**
OR=odds ratio. CABG=coronary artery bypass graft. MI=myocardial infarction. *Defined as centres with radial as the preferred route or known expert centres for pre-RIVAL, and centres with the highest tertile radial intervention centre volume for RIVAL.

primary outcome (4·6% radial *vs* 4·7% femoral; HR 0·97, 95% CI 0·63–1·50; interaction p=0·76) and for non-CABG related major bleeding (1·5% *vs* 1·5%; HR 0·95, 95% CI 0·44–2·05; interaction p=0·33).

At 30 days, more patients in the femoral group than in the radial group had large haematoma (p<0·0001) and pseudoaneurysm needing closure (p=0·006; table 4). About 3% of patients in each group had persistent pain at the access site for over 2 weeks.

Our previous meta-analysis included 23 randomised trials (n=7020; only 4458 patients in 18 trials had outcomes available for major bleeding).[10] In our updated search in January, 2011, we identified 354 abstracts and five additional trials, including RIVAL (n=8404).[11,17–20] A sixth trial was available only in abstract form and had insufficient outcome data to do an analysis and so was excluded.[21] With the RIVAL definition for non-CABG-related major bleeding, there was a reduction in major bleeding with radial compared with femoral access (p=0·002; figure 6). There was no significant difference in the composite of death, myocardial infarction, or stroke, or the components of this outcome in the meta-analysis. However, when analyses were restricted to radial experts (preferred approach radial or known radial expert centre study with highest radial centre tertile in RIVAL), the composite of death, myocardial infarction, or stroke was lower in the radial group than the femoral group (p=0·005).

Discussion

In patients with ACS undergoing coronary angiography, radial access did not reduce the primary outcome of death, myocardial infarction, stroke, or non-CABG-related major bleeding compared with femoral access. However, radial access significantly reduced vascular access complications compared with femoral access, with similar PCI success rates, and was more commonly

Panel: **Research in context**

Systematic review

We searched Medline and Embase for randomised trials with the terms "radial", "femoral", and "access", with no language or date restrictions set. We also hand searched conference abstracts from the American Heart Association, American College of Cardiology, Transcatheter Therapeutics, and European Society of Cardiology from 2008 to 2010.[10] Previous systemic reviews were also hand searched for relevant trials. Randomised trials of radial versus femoral access with outcome data available were included. Data were abstracted independently by SJ and AS, and differences were resolved by consensus. We used the assumption-free method as described by Peto-Yusuf to combine odds ratio and 95% CI data from individual trials.

Interpretation

RIVAL is the largest randomised trial to compare radial and femoral access. Both the RIVAL trial and updated meta-analysis show that radial access reduces major vascular complications compared with femoral access. Percutaneous coronary intervention success rates seem to be similar. Both patients and clinicians might choose radial access because of its similar efficacy and reduced vascular complications.

preferred by patients for subsequent procedures. These results are consistent with a meta-analysis of all trials, including RIVAL (panel).

In the RIVAL trial, low rates of major bleeding overall were reported in patients treated with femoral access compared with previous studies,[2–4] possibly because of improvements in technology (smaller diameter sheaths) and more experience. Retroperitoneal bleeding leading to a major bleed occurred in only 0·1% of patients in the femoral access group. This low rate suggests that the operators in our trial were highly skilled in femoral access.

There are several possible explanations for not finding a statistically significant reduction in non-CABG-related major bleeding with radial access. First, for a vascular access site complication to qualify as a major bleed, it had to meet the rigorous definition of major bleeding. Second, only a third of all major bleeding events were classed as having been at a vascular access site; most originated from gastrointestinal, intracranial, pericardial, or other sites, and bleeds at these sites would not be expected to be altered by the method of angiography. Third, the femoral access site group had a much lower than anticipated risk of major bleeding (0·9%)—lower than that reported in most recent trials of ACS patients undergoing an early invasive strategy.[13,15,22] The rate of femoral access site bleeding might have been low because operators participating in RIVAL were experienced, high-volume interventional cardiologists, with a median PCI volume of 300 cases per year—substantially higher than the median for operators in the USA.[22]

Our updated meta-analysis of randomised trials shows a clear reduction in non-CABG-related major bleeding with radial access. In RIVAL, the effect size for non-CABG major bleeding was less than in the other trials in the meta-analysis, possibly because of differences in the distribution of bleeding sites between ACS patients having PCI and elective outpatients having PCI. In PCI trials (most of which enrol elective outpatients), 70% of non-CABG-related major bleeds arise from the access site, whereas in an ACS population (as enrolled in RIVAL) only 30% of non-CABG-related major bleeds arise from the access site.[16] With more potent antithrombotic treatments in STEMI and NSTE-ACS, gastrointestinal, intracranial, and other sites of bleeding become more common.[4]

A potentially important finding of our trial was that radial access seemed to be beneficial compared with femoral access in centres undertaking a high number of radial procedures. These centres had lower crossover rates, probably because of more expertise with radial access. The link between better outcomes and PCI procedural volume has been reported in multiple previous studies of primarily femoral procedures, so our identification of a similar relation with radial procedures is logical.[15,16] That the converse was not found is important; femoral access was not superior to radial access at high volume femoral centres. Experience and expertise might be particularly important with radial access.

Another potentially important finding was that, among patients with STEMI, radial access seemed to reduce the incidence of the primary outcome and the secondary outcomes of death, myocardial infarction, or stroke, and overall mortality. Although the rates of major bleeding were not less with radial access in patients with STEMI, the rates of major vascular complications were significantly reduced. Future randomised trials will be useful to confirm these findings.

RIVAL was underpowered to conclusively rule out moderate but important differences in the primary outcome. On the basis of the reported event rate of 4%, a sample of size of 17 000 patients would be needed to have 80% power to detect a 20% relative risk reduction in the primary outcome.

Radial versus femoral access for coronary angiography and intervention resulted in similar rates of the composite of death, myocardial infarction, stroke, or non-CABG-related major bleeding. Radial access reduced major vascular complications compared with femoral access, with similar PCI success rates. The effectiveness of radial access might be linked to expertise and volume.

Contributors

SSJ, SY, JC, KN, DX, PW, MN, VV, BSL, AA, PGS, SVR, PG, RA, CDJ, SC, and SRM designed the study, analysed and interpreted data, and revised and reviewed the manuscript. SSJ wrote first draft with SY, JC, and SRM. PG and RA did all statistical analysis. SSJ did the meta-analysis.

RIVAL trial group

Steering Committee—S Jolly (principal investigator), S R Mehta (co principal investigator), A Avezum, A Budaj, J Cairns, S Chrolavicius (project manager), R Diaz, V Dzavik, M G Franzosi, C Granger, C Joyner (events adjudication committee chair), M Keltai, F Lanas, B Lewis, K Niemelä, S Rao, P G Steg, V Valentin, P Widimsky, D Xavier, and S Yusuf (chair). *Events Adjudication Committee*—S Ameriso, M Atra, A Avezum, G Borislav, A Budaj, A Czepiel,

H DeRaedt, M Dorobantu, G Fodor, B Gross, H Guimaraes, J Healey, O Happola, J Hartikainen, D Himbert, Q Hua, C Joyner, P Kalvach, C-J Kim, J-H Kim, M Laine, A Lamy, S Lang, M Lawrence, B Lewis, A Maggioni, J Narendra, A Peeters, M Penicka, L Piegas, G Pizzolato, J Renkin, M Rokoss, N Runev, B Stockins, PG Steg, P Widimsky, J Zaborski, R Zimlichman, and Y Yang. *Data Monitoring Committee*—P Sleight (chair), J L Anderson, D L DeMets, J Hirsh, D R Holmes Jr, and D E Johnstone. *PHRI Project Office Staff*—S Chrolavicius (project manager), B Jedrzejowski (research coordinator), M Lawrence (event adjudication coordinator), C Cramp (past research coordinator), C Horsman (past research coordinator), A Robinson (past research coordinator), R Afzal (statistician), P Gao (statistician), L Xu (statistician), R Manojlovic, L Mastrangelo, E Pasadyn, L Blake, W Chen, S Di Diodato, A Lehmann, T Sovereign, L Wasala, C Agrippa, and M McClelland.

RIVAL investigators

Argentina (94 patients enrolled)—M Berli, W P Casali, C R Castellanos, C M Cigalini, E C Conci, G Covelli, M A Hominal, C R Majul, L L Lobo Marquez, G J Pacheco, M Payaslian, D L Piskorz, J C Pomposiello, S M Salzberg, A Sanchez, D Santos, G Zapata. *Australia (55)*—M I Worthley, S G Worthley, R P Thompson. *Belgium (43)*—V Dangoisse, P E Massart, M Vincent. *Brazil (183)*—V Botelho, N T Duda, S A Hilgemberg, J A Mangione, M F Mauro, M S M O Paiva, G Reis, W F Saporito, J F K Saraiva, M V Seroqui, A Timerman, R T Tumelero. *Bulgaria (551)*—A Doganov, J Jorgova-Makedonska, I Manoukov, G Mazhdrakov, Penev. *Canada (1475)*—T I Anderson, P Beliveau, J Berlingieri, O F Bertrand, R H Boone, S W Brons, W J Cantor, Y K Chan, F Charbonneau, A N Cheema, J-P Dery, V Dzavik, A Y Fung, G Gosselin, F Hussain, M Kass, T Kot, M J B Kutryk, D C MacCallum, F Nigro, S Pallie, J T W Pang, D-C Phaneuf, K Robbins, M Rokoss, O Salehian, J Saw, S Shariff , C Van Kieu. *Chile (146)*—R L Betancourt, C P P Jofre, E E G Flores, M Lopetegui. *China (208)*—J Chen, G Ma, Y Han, T Li, B Xu, J Wang, D Wang, M Wei, S Zhang, H Xie. *Croatia (1)*—M Bergovec. *Czech Republic (187)*—O Bocek, J Cech, P Červinka, Z Coufal, L Groch, P Kala, A Linhart, R Ondrejcak, V Pechman, M Rezek, J Vojacek. *Finland (1124)*—K J Airaksinen, M Eskola, K Kervinen, M Niemelä, M Pietilä, S Vikman, A Ylitalo. *France (187)*—H Abergel, D Doyen, G Ducrocq, E Ferrari, G Grollier. *Germany (94)*—D Andresen, J vom Dahl, K Dominick, S Hoffmann, F Laubenthal, C Nienaber. *Hungary (31)*—S Bakk, B Nagybaczoni, P Polgár, Z Szigeti. *India (902)*—H Baxi, P A Jiwani, D R Kodem, S Kumar, P R Kumar, B R Malipeddi, S R Naik, K Parikh, B Pinto, M B Rao, P K Shetty, N Sinha. *Ireland (9)*—P Crean. *Israel (239)*—J Arbel, R Jaffe, M Halabi, N Khader, A Marmor, A Roguin, Y Turgeman. *Italy (129)*—B Cortese, U Limbruno, G Piovaccari, S Pirelli, M Rossi, A Santarelli, G Steffenino, L Tomasi, R Zanini. *Latvia (11)*—A Erglis, I Narbute. *Lithuania (80)*—R Unikas, A Janavicius; *Malaysia (1)*—C W Peng. *Mexico (17)*—J L Arenas, M Ledesma, J J Rivera, A Ruiz, M S L Velasco. *New Zealand (9)*—G P Devlin, S Harding. *Poland (583)*—P Achremczyk, M P Dalkowski, M Fudal, K Grzesik, Z Kalarus, D Kawecki, J Kopaczewski, V Kowalik, B Kuśnierz, P Maciejewski, P Miekus, P Panin, L Polonski, M Swierad, D Winek, A W Wlodarczak, J Wodniecki, B Wrzosek. *Romania (12)*—R Capalneanu. *Russia (1)*—S Berns. *Singapore (5)*—T H Koh. *Slovakia (20)*—P Kurray R Margozcy. *Spain (432)*—A Rincon de Arellano, T Canton, P Carrillo, J A Ferrer, I Gomez, A Iñiguez, I Lekuona, C Macaya, J Moreu, J M Nuñez, F Bosa Ojeda, A Fernández-Ortiz, R López-Palop, M Sabate, J Sanchis, A Subinas, R Trillo, M Vargas Torres, N Vazquez. *Sweden (50)*—A Hot-Bjelak, J Harnek, L Henareh, B Welin-Berger, G K Olivecrona. *UK (20)*—A Baumbach, A de Belder, S Kesavan, I Malik, M Pitt, D Hildick-Smith. *USA (122)*—M K Ariani, J Chambers, S K Fulton, S L Goldberg, J Magno, R Mazhari, J S Reiner, M Saririan, N Singh, S Thew.

Conflicts of interest

SSJ receives institutional research grants from Sanofi-Aventis, Bristol-Myers Squibb, and Medtronic, and consulting fees from Sanofi-Aventis, GlaxoSmithKline, and AstraZeneca. JC is a board member for Boerhinger Inglelheim. DX receives grants and travel or accommodation expenses from AstraZeneca, Boerhinger Ingelheim, Cadila Pharma, GlaxoSmithKline, Sanofi-Aventis, and Bristol-Myers Squibb. PW and VV have received payments for services from Population Health Research Institute. AB receives consultancy fees from Sanofi-Aventis, Eli Lilly, Novartis, AstraZenca, and Merck, and grants from Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, Bristol-Myers Squibb, and AstraZenca. BSL receives grant support from Population Health Research Institute. AA receives consultancy fees from GlaxoSmithKline and Boerhinger Ingelheim. PGS and CDJ receive payments for services from Hamilton Health Sciences. PGS also receives institutional research grants from Servier; consulting fees or honoraria from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Medtronic, Merck, Otsuka, Roche, Sanofi-Aventis, Servier, and The Medicines Company; and has stock options in Aterovax. SVR receives consultancy fees and travel and accommodation expenses from Terumo Medical. SRM receives institutional research grants from Sanofi-Aventis and Bristol-Myers Squibb, and consulting fees from Sanofi-Aventis, Eli Lilly, AstraZeneca, and Bristol-Myers Squibb. SY, KN, MN, SC, PG, and RA declare that they have no conflicts of interest.

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References

1 Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes. Variations in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2002; **23:** 1177–89.

2 Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355:** 2203–16.

3 Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354:** 1464–76.

4 Budaj A, Eikelboom JW, Mehta SR, et al. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. *Eur Heart J* 2009; **30:** 655–61.

5 Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005; **96:** 1200–06.

6 Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006; **114:** 774–82.

7 Chase AJ, Fretz EB, Warburton WP, et al. The association of arterial access site at angioplasty with transfusion and mortality: the M.O.R.T.A.L study (Mortality benefit of Reduced Transfusion After PCI via the Arm or Leg). *Heart* 2008; **94:** 1019–25.

8 Rao SV, Ou FS, Wang TY, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. *JACC Cardiovasc Interv* 2008; **1:** 379–86.

9 Montalescot G, Ongen Z, Guindy R, et al. Predictors of outcome in patients undergoing PCI. Results of the RIVIERA study. *Int J Cardiol* 2008; **129:** 379–87.

10 Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J* 2009; **157:** 132–40.

11 Jolly SS, Niemela K, Xavier D, et al. Design and rationale of the RadIal Vs. femorAL access for coronary intervention (RIVAL) trial: a randomized comparison of radial versus femoral access for coronary angiography or intervention in patients with acute coronary syndromes. *Am Heart J* 2011; **161:** 254–60. e1–4.

12 Mehta SR, Bassand JP, Chrolavicius S, et al. Design and rationale of CURRENT-OASIS 7: a randomized, 2 x 2 factorial trial evaluating optimal dosing strategies for clopidogrel and aspirin in patients with ST and non-ST-elevation acute coronary syndromes managed with an early invasive strategy. *Am Heart J* 2008; **156:** 1080–88 e1.

13 Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010; **363:** 930–42.

14 Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 2010; **376:** 1233–43.

15 Post PN, Kuijpers M, Ebels T, Zijlstra F. The relation between volume and outcome of coronary interventions: a systematic review and meta-analysis. *Eur Heart J* 2010; **31:** 1985–92.

16 Rao SV, Cohen MG, Kandzari DE, Bertrand OF, Gilchrist IC. The transradial approach to percutaneous coronary intervention: historical perspective, current concepts, and future directions. *J Am Coll Cardiol* 2010; **55:** 2187–95.

17 Brueck M, Bandorski D, Kramer W, Wieczorek M, Holtgen R, Tillmanns H. A randomized comparison of transradial versus transfemoral approach for coronary angiography and angioplasty. *JACC Cardiovasc Interv* 2009; **2:** 1047–54.

18 Ziakas A, Klinke P, Mildenberger R, et al. Comparison of the radial and the femoral approaches in percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 2003; **91:** 598–600.

19 Hou L, Wei YD, Li WM, Xu YW. Comparative study on transradial versus transfemoral approach for primary percutaneous coronary intervention in Chinese patients with acute myocardial infarction. *Saudi Med J* 2010; **31:** 158–62.

20 Yan ZX, Zhou YJ, Zhao YX, et al. Safety and feasibility of transradial approach for primary percutaneous coronary intervention in elderly patients with acute myocardial infarction. *Chin Med J (Engl)* 2008; **121:** 782–86.

21 Schaufele TG, Gruenbaum J-P, Breidenbach T, Lippe B, von Hodenberg E. Radial access versus conventional femoral puncture: outcome and resource effectiveness in a daily routine: the raptor trial. *Circulation* 2009; **120:** 2152–61. Abstract 41.

22 McGrath PD, Wennberg DE, Dickens JD Jr, et al. Relation between operator and hospital volume and outcomes following percutaneous coronary interventions in the era of the coronary stent. *JAMA* 2000; **284:** 3139–44.