MRC/UVRI Uganda Research Unit on AIDS, PO Box 49, Entebbe, Uganda (AE, SC, PK); London School of Hygiene & Tropical Medicine, London, UK (AE, SC, DM, PK); Uganda Virus Research Institute, Entebbe, Uganda (BN, BB, PK, EKM); Department of Medical Microbiology (BB, MJ) and Infectious Diseases Institute (AK), Makerere University College of Health Sciences, Kampala, Uganda; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (GP); Department of Parasitology, Leiden University Medical Centre, Leiden, The Netherlands (MY); Department of Pathology, University of Cambridge, Cambridge, UK (DD, AM); Makerere University Directorate of Research and Graduate Studies, Kampala, Uganda (EKR); and Kyambogo University, Kampala, Uganda (EKR)
alison.elliott@mrcuganda.org

We have received funding from the Wellcome Trust and European Union.
We declare no competing interests.

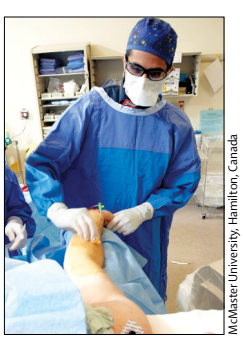
1 Wellcome Trust. Developing Excellence in Leadership, Training and Science Initiative. http://www.wellcome.ac.uk/Funding/Biomedical-science/Funding-schemes/Strategic-awards-and-initiatives/WTP057105.htm (accessed May 29, 2015).
2 European Commission. Horizon 2020. https://ec.europa.eu/programmes/horizon2020/ (accessed May 29, 2015).
3 European and Developing Countries Clinical Trials Partnership. http://www.edctp.org/ (accessed May 29, 2015).
4 Nachega JB, Uthman OA, Ho YS, et al. Current status and future prospects of epidemiology and public health training and research in the WHO African region. *Int J Epidemiol* 2012; **41:** 1829–46.
5 Ndebele P, Wassenaar D, Benatar S, et al. Research ethics capacity building in sub-Saharan Africa: a review of NIH Fogarty-funded programs 2000–2012. *J Empir Res Hum Res Ethics* 2014; **9:** 24–40.
6 Boutayeb A. The double burden of communicable and non-communicable diseases in developing countries. *Trans R Soc Trop Med Hyg* 2006; **100:** 191–99.
7 Ramsay M. Africa: continent of genome contrasts with implications for biomedical research and health. *FEBS Lett* 2012; **586:** 2813–19.
8 Nakanjako D, Ssewanyana I, Nabatanzi R, et al. Impaired T-cell proliferation among HAART-treated adults with suboptimal CD4 recovery in an African cohort. *BMC immunology* 2013; **14:** 26.
9 Nakimuli A, Chazara O, Byamugisha J, et al. Pregnancy, parturition and preeclampsia in women of African ancestry. *Am J Obstet Gynecol* 2014; **210:** 510–20.e1.
10 Nakimuli A, Chazara O, Farrell L, et al. A KIR B centromeric region present in Africans but not Europeans protects pregnant women from pre-eclampsia. *Proc Natl Acad Sci USA* 2015; **112:** 845–50.
11 Mpairwe H, Webb EL, Muhangi L, et al. Anthelminthic treatment during pregnancy is associated with increased risk of infantile eczema: randomised-controlled trial results. *Pediatr Allergy Immunol* 2011; **22:** 305–12.
12 Mpairwe H, Ndibazza J, Webb EL, et al. Maternal hookworm modifies the risk factors for eczema in childhood: birth cohort in Uganda. *Pediatr Allergy Immunol* 2014; **25:** 481–88.

Coronary intervention: radial artery access comes of age

It has taken a quarter of a century for the level of evidence supporting radial artery access, rather than femoral access, for cardiac intervention to reach that of common pharmaceutical interventions, such as antiplatelet therapy in acute coronary syndrome.[1,2] Historically, small trials and meta-analyses seemed to suggest that radial compared with femoral access reduced bleeding complications related to access site.[3] However, early uptake of the radial technique (ie, during 1993–2003) among interventional cardiologists was slow for several reasons. First, the radial technique is slightly more challenging than a femoral approach and needs experience to perfect. Second, the early trials supporting its use were relatively small, and not sufficiently compelling to affect guidelines and prompt a change in practice. Finally, and perhaps most importantly, there has been under-recognition of the importance of bleeding as an undesirable outcome after coronary intervention. However, over the past 15 years, a substantial body of evidence has accumulated showing not only that bleeding is a major concern, but that it is also associated with increased mortality, a relation that might be causal.[4] Pharmacological treatments that reduce bleeding have been associated with reductions in mortality.[5,6] If this relation is real, it should not matter how bleeding is reduced: a procedural technique that reduces bleeding should also reduce mortality.

The first large multicentre trial of radial access, RIVAL (n=7021),[7] involved high-volume percutaneous coronary intervention operators, many of whose practice was in transition from primarily femoral to radial access. In RIVAL, there was no difference in the primary outcome of death, myocardial infarction, stroke, or major bleeding between patient groups receiving radial and femoral access. There was, however, a more than 60% reduction in major vascular complications with radial access. Additionally, there did seem to be a reduction in the primary outcome in high-volume radial centres and in those patients with ST-elevation myocardial infarction.[8,9] Subsequently, practice guidelines for the first time provided a class IIa recommendation for radial access.[10,11]

In *The Lancet*, Marco Valgimigli and the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial investigators[12] should be congratulated for doing the largest trial to date (n=8404) comparing radial with femoral access for coronary intervention in patients with acute coronary syndrome. They did


McMaster University, Hamilton, Canada

Published Online
March 16, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60507-4

See Articles page 2465

not simply seek to replicate RIVAL, but instead built upon its findings and specifically tested the benefit of transradial versus transfemoral access in high-volume radial centres. Operators were required to have done most of their procedures transradially (>50%), and to have done at least 75 transradial percutaneous coronary interventions, in the previous year.

The trial used coprimary outcomes, with a two-sided p value of 0·025 needed to declare superiority for each of the two outcomes.[12] Based on this criterion, the first coprimary outcome of death, myocardial infarction, or stroke did not meet statistical significance, although numerically there were fewer events in the radial group (369 [8·8%] patients with radial access *vs* 429 [10·3%] patients with femoral access; rate ratio [RR] 0·85, 95% CI 0·74–0·99; p=0·0307). For the second coprimary outcome, net adverse clinical events, there was clear evidence of superiority of the radial technique, with a 17% reduction in death, myocardial infarction, stroke, or major bleeding (410 [9·8%] patients *vs* 486 [11·7%] patients; 0·83, 0·73–0·96; p=0·0092). There was also an apparent 28% reduction in mortality (66 [1·6%] patients vs 91 [2·2%] patients; 0·72, 0·53–0·99; p=0·045) with radial access. Finally, there was a significant interaction by radial centre volume, with the greatest benefit of radial access seen in the highest volume centres (ie, those doing at least 80% of their procedures via radial access).

How do we integrate the results of RIVAL and MATRIX? The difference in bleeding definitions used in the two trials probably accounts for the differences in bleeding reported. Furthermore, despite being similar sized trials, MATRIX had a three times higher event rate than RIVAL (ie, death, myocardial infarction, and stroke: 10·3% in MATRIX *vs* 3·2% in RIVAL in the control groups).[7] This difference was probably because patients in cardiogenic shock and even post-cardiac arrest were enrolled in MATRIX but not in RIVAL. As a result, MATRIX had power to detect more modest reductions (ie, a 15% relative risk reduction) in the primary outcome. Finally, MATRIX was done by radial experts, and thus validated the subgroup hypothesis from RIVAL that showed the greatest benefit in the highest volume centres.

One implication of these findings is that centres should strive to maximise their volumes of radial procedures, rather than reserving the procedure for patients in whom femoral access is not possible. By contrast with RIVAL, the consistency of findings for radial access between non-ST elevation coronary syndrome and ST-elevation myocardial infarction in MATRIX emphasises the importance of testing subgroup findings from previous trials, and suggests a benefit of radial access for the entire spectrum of patients with acute coronary syndrome.

The results of MATRIX, in the context of RIVAL and other smaller trials, suggest that, at the very least, access site bleeding will be substantially reduced and, at best, that there will be a corresponding reduction in mortality. Although the apparent reduction in mortality in MATRIX should be interpreted cautiously given that it was a secondary outcome, a meta-analysis including MATRIX shows consistency for the reduction in mortality.[12] In a health-care era in which patient-centred outcomes are being recognised to be increasingly important, even if mortality was not explicitly shown to have been reduced, based on the reduction in bleeding and patients' preferences, radial access should probably become the default approach in most centres.

Radial access has grown rapidly over the past 10 years, and now accounts for more than 50% of procedures in many countries. The rate of radial access in the USA has lagged behind that in other countries, but has increased from 1·2% in 2007 to 16·1% in 2012.[13] Unlike a pharmaceutical intervention, which simply requires physicians to know the appropriate dose and write a prescription, a procedural innovation needs training and for physicians to go through the discomfort of a learning curve. However, adoption of new techniques is essential in medicine. We cannot imagine a general surgeon continuing to practise open cholecystectomy without gaining the expertise needed for laparoscopic cholecystectomy. Similarly, interventional cardiologists will be expected to be proficient in transradial intervention.

Many large randomised trials now show the benefits of radial access. The next step is for guideline committees in both the USA and Europe to consider these data carefully and upgrade recommendations to make radial access the default approach for coronary angiography and intervention.

Sanjit S Jolly, Shamir R Mehta
McMaster University and the Population Health Research Institute, Hamilton General Hospital, Hamilton, ON L8L 2X2, Canada
sanjit.jollly@phri.ca

We declare no competing interests.

1 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361:** 1045–57.

2 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502.

3 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.

4 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.

5 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.

6 Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; **358:** 2218–30.

7 Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 2011; **377:** 1409–20.

8 Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol* 2012; **60:** 2490–99.

9 Jolly SS, Cairns J, Yusuf S, et al. Procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. *J Am Coll Cardiol* 2014; **63:** 954–63.

10 Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2012; **79:** 453–95.

11 Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.

12 Valgimigli M, Gagnor A, Calabró P, et al, for the MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015; published online March 16. http://dx.doi.org/10.1016/S0140-6736(15)60292-6.

13 Feldman DN, Swaminathan RV, Kaltenbach LA, et al. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the national cardiovascular data registry (2007–2012). *Circulation* 2013; **127:** 2295–306.

PARTNERs in the future of surgical aortic valve replacement

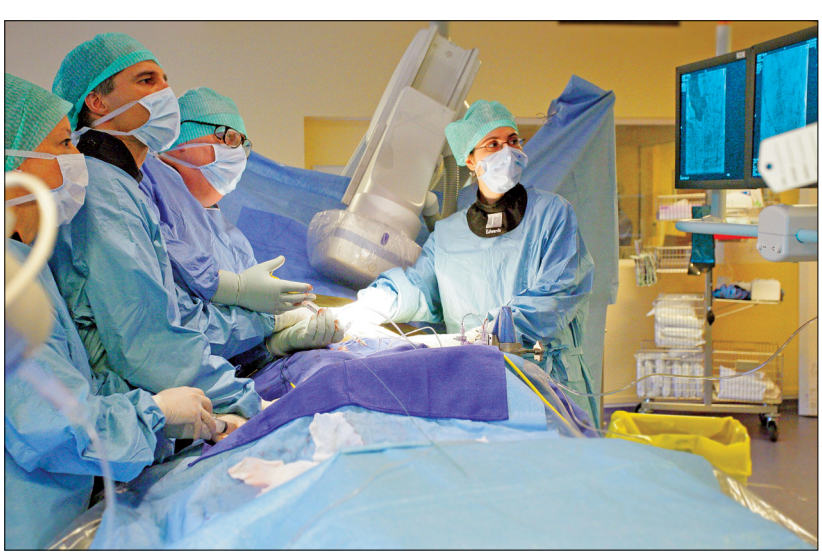
Published **Online**
March 15, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60568-2

See **Articles** pages 2477 and 2485

Aortic stenosis is the most common valve disease, the occurrence of which increases with age.[1] Incidence of aortic stenosis is expected to rise because of population ageing. For decades, surgical aortic valve replacement (SAVR) was the gold standard of care for individuals with symptomatic severe aortic stenosis—in properly selected patients, substantially improving symptoms and life expectancy.[1] Although physicians have learned how to care for critically ill old patients and enable many to survive major surgical procedures, operating on patients at very high risk is often not suitable. Technical limitations—eg, porcelain aorta, chest wall deformity, and chest irradiation—further limit the ability to operate on certain patients with aortic stenosis.

In *The Lancet*, Samir Kapadia and colleagues[2] present the 5-year results of the PARTNER 1 randomised trial in patients with aortic stenosis who were unsuitable for surgery, which compared transcatheter aortic valve replacement (TAVR) with standard treatment. 358 patients were enrolled, and TAVR provided a survival benefit of almost 22% (all-cause mortality 71·8% with TAVR *vs* 93·6% with standard treatment; HR 0·50, 95% CI 0·39–0·65) and a 28% lower cardiovascular mortality (57·5% *vs* 85·9%). Only six patients in the standard treatment group were alive at 5 years, of whom five had had aortic valve replacement leaving only one patient alive at 5 years without. Even more important for elderly patients (mean age was 83 years) is quality of life, and 86% of the 49 survivors who received TAVR in PARTNER 1 had New York Heart Association (NYHA) functional class 1 or 2. A benefit of this size is remarkable for inoperable old patients treated with a first generation medical device.

However, a concern is that 48% of the patients undergoing TAVR were readmitted to hospital in Kapadia and colleagues' study,[2] and the idea of competing risk in



Chassenet/Science Photo Library

Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial

*Marco Valgimigli, Andrea Gagnor, Paolo Calabró, Enrico Frigoli, Sergio Leonardi, Tiziana Zaro, Paolo Rubartelli, Carlo Briguori, Giuseppe Andò, Alessandra Repetto, Ugo Limbruno, Bernardo Cortese, Paolo Sganzerla, Alessandro Lupi, Mario Galli, Salvatore Colangelo, Salvatore Ierna, Arturo Ausiello, Patrizia Presbitero, Gennaro Sardella, Ferdinando Varbella, Giovanni Esposito, Andrea Santarelli, Simone Tresoldi, Marco Nazzaro, Antonio Zingarelli, Nicoletta de Cesare, Stefano Rigattieri, Paolo Tosi, Cataldo Palmieri, Salvatore Brugaletta, Sunil V Rao, Dik Heg, Martina Rothenbühler, Pascal Vranckx, Peter Jüni, for the MATRIX Investigators**

Summary

Background It is unclear whether radial compared with femoral access improves outcomes in unselected patients with acute coronary syndromes undergoing invasive management.

Methods We did a randomised, multicentre, superiority trial comparing transradial against transfemoral access in patients with acute coronary syndrome with or without ST-segment elevation myocardial infarction who were about to undergo coronary angiography and percutaneous coronary intervention. Patients were randomly allocated (1:1) to radial or femoral access with a web-based system. The randomisation sequence was computer generated, blocked, and stratified by use of ticagrelor or prasugrel, type of acute coronary syndrome (ST-segment elevation myocardial infarction, troponin positive or negative, non-ST-segment elevation acute coronary syndrome), and anticipated use of immediate percutaneous coronary intervention. Outcome assessors were masked to treatment allocation. The 30-day coprimary outcomes were major adverse cardiovascular events, defined as death, myocardial infarction, or stroke, and net adverse clinical events, defined as major adverse cardiovascular events or Bleeding Academic Research Consortium (BARC) major bleeding unrelated to coronary artery bypass graft surgery. The analysis was by intention to treat. The two-sided α was prespecified at 0·025. The trial is registered at ClinicalTrials.gov, number NCT01433627.

Findings We randomly assigned 8404 patients with acute coronary syndrome, with or without ST-segment elevation, to radial (4197) or femoral (4207) access for coronary angiography and percutaneous coronary intervention. 369 (8·8%) patients with radial access had major adverse cardiovascular events, compared with 429 (10·3%) patients with femoral access (rate ratio [RR] 0·85, 95% CI 0·74–0·99; p=0·0307), non-significant at α of 0·025. 410 (9·8%) patients with radial access had net adverse clinical events compared with 486 (11·7%) patients with femoral access (0·83, 95% CI 0·73–0·96; p=0·0092). The difference was driven by BARC major bleeding unrelated to coronary artery bypass graft surgery (1·6% *vs* 2·3%, RR 0·67, 95% CI 0·49–0·92; p=0·013) and all-cause mortality (1·6% *vs* 2·2%, RR 0·72, 95% CI 0·53–0·99; p=0·045).

Interpretation In patients with acute coronary syndrome undergoing invasive management, radial as compared with femoral access reduces net adverse clinical events, through a reduction in major bleeding and all-cause mortality.

Funding The Medicines Company and Terumo.

Lancet 2015; 385: 2465–76

Published Online
March 16, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60292-6

See Comment page 2437

*Listed in the appendix

Thoraxcenter, Erasmus Medical Center, Rotterdam, Netherlands (M Valgimigli MD); **Cardiology Unit, Ospedali Riuniti di Rivoli, ASL Torino 3, Turin, Italy** (A Gagnor MD, E Frigoli MD, F Varbella MD); **Division of Cardiology, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy** (P Calabró MD); **EUSTRATEGY Association, Forlì, Italy** (E Frigoli); **UOC Cardiologia, Dipartimento CardioToracoVascolare, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy** (S Leonardi MD, A Repetto MD); **A.O. Ospedale Civile di Vimercate (MB), Vimercate, Italy** (T Zaro MD); **Department of Cardiology, ASL3 Ospedale Villa Scassi, Genoa, Italy** (P Rubartelli MD); **Clinica Mediterranea, Naples, Italy** (C Briguori MD); **Azienda Ospedaliera Universitaria Policlinico "Gaetano Martino", University of Messina, Messina, Italy** (G Andò MD); **UO Cardiologia, ASL 9 Grosseto, Grosseto, Italy** (U Limbruno MD); **Ospedale Fate bene Fratelli, Milan, Italy** (B Cortese MD); **AO Ospedale Treviglio-Caravaggio, Treviglio BG, Italy** (P Sganzerla MD); **University Hospital "Maggiore della Carità", Novara, Italy** (A Lupi MD); **Ospedaliera Sant'Anna, Como, Italy** (M Galli MD); **San Giovanni Bosco Hospital, Turin, Italy** (S Colangelo MD); **Ospedale Sirai—Carbonia, Carbonia, Italy**

Introduction

Over the past two decades early invasive management and the use of combined antithrombotic therapies have lowered the risk of recurrent myocardial infarction in patients with acute coronary syndromes, but have also been associated with a significant increase in bleeding.[1,2] Bleeding is associated with worse short-term and long-term clinical outcomes, and this relation is thought to be causal.[3,4] Therefore, reducing the frequency of bleeding events while maintaining effectiveness is an important goal in the management of patients with acute coronary syndrome, and has the potential to reduce mortality, morbidity, and costs.[5]

A common site of bleeding in invasively managed patients is at the femoral artery puncture site used for heart catheterisation.[6] Compared with the femoral artery, the radial artery is more superficial and has a smaller calibre. Radial access is therefore technically more demanding, but makes access site haemostasis more predictable.[7] Previous studies have come to differing conclusions about the role of radial access in reducing adverse outcomes in patients with acute coronary syndrome undergoing catheterisation or percutaneous coronary intervention.[8,9] Whether avoiding access site bleeding and vascular complications by the use of routine transradial intervention improves

(S Ierna MD); **Casa di Cura Villa Verde, Taranto, Italy** (A Ausiello MD); **IRCCS Humanitas, Rozzano, Italy** (P Presbitero MD); **Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy** (Prof G Sardella MD); **Division of Cardiology—Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy** (G Esposito MD); **Cardiovascular Department, Infermi Hospital, Rimini, Italy** (A Santarelli MD); **A.O. Ospedale di Desio (MB), Desio, Italy** (S Tresoldi MD); **San Camillo-Forlanini, Rome, Italy** (M Nazzaro MD); **IRCCS AOU San Martino, Genoa, Italy** (A Zingarelli MD); **Policlinico San Marco, Zingonia, Italy** (N de Cesare MD); **Interventional Cardiology Sandro Pertini Hospital, Rome, Italy** (S Rigattieri MD); **Mater Salutis Hospital-Legnago, Verona, Italy** (P Tosi MD); **Ospedale Pasquinucci, Massa, Italy** (C Palmieri MD); **Hospital Clinic, University of Barcelona, Thorax Institute, Department of Cardiology, Barcelona, Spain** (S Brugaletta MD); **Duke Clinical Research Institute, Durham, NC, USA** (S V Rao MD); **Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium** (P Vranckx MD); **and Clinical Trials Unit** (D Heg PhD, M Rothenbühler MSc, Prof P Jüni MD), **Institute of Primary Health Care** (Prof P Jüni), **and Institute of Social and Preventive Medicine** (D Heg), **University of Bern, Bern, Switzerland**

Correspondence to:
Dr Marco Valgimigli, Thoraxcenter, Ba 587, Erasmus MC, Rotterdam, Netherlands
m.valgimigli@erasmusmc.nl

See Online for appendix

outcomes in largely unselected patients with acute coronary syndrome undergoing invasive management remains unclear.[8]

Therefore, we did a large, multicentre, randomised trial in patients with acute coronary syndrome who were about to undergo coronary angiography and possible percutaneous coronary intervention, if indicated, to assess whether radial access is superior to femoral access.

Methods

Study design and participants

Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX Access) was a randomised multicentre superiority trial comparing transradial against transfemoral access in patients with acute coronary syndrome with or without ST-segment elevation myocardial infarction who were about to undergo coronary angiography and percutaneous coronary intervention, if indicated.[10,11] This trial is part of the MATRIX programme (registered at ClinicalTrials.gov, number NCT01433627), and was done in all patients with an acute coronary syndrome consenting to participate in the programme. The programme was done in 78 centres in Italy, the Netherlands, Spain, and Sweden. Results of subsequent, nested trials will be reported separately.

Patients were eligible if they had an acute coronary syndrome with or without ST-segment elevation myocardial infarction, were about to undergo an invasive approach, and the interventional cardiologist was willing to proceed with either radial or femoral access and had expertise for both, including at least 75 coronary interventions performed, and at least 50% of interventions in acute coronary syndrome via the radial route during the previous year (appendix). Patients presenting with non-ST-segment elevation acute coronary syndrome were eligible if they had a history consistent with new or worsening ischaemia, occurring at rest or with minimal activity within 7 days before randomisation, and fulfilled at least two high-risk criteria (detailed in the appendix). Patients with ST-segment elevation myocardial infarction were eligible if they presented within 12 h of the onset of symptoms or between 12 and 24 h after onset if there was evidence of continuing ischaemia or previous

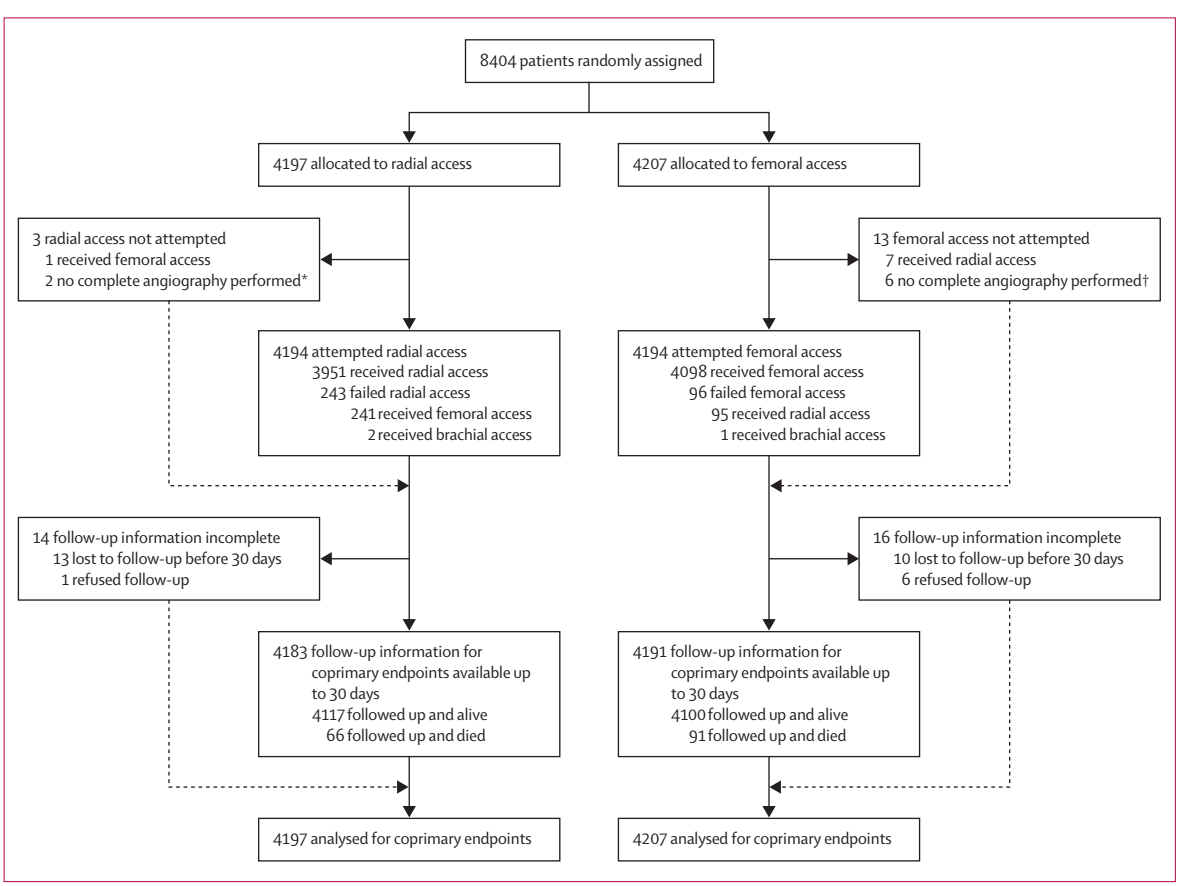


Figure 1: **Trial profile**
*Technical failure of the x-ray system (one patient); angiography aborted due to cerebrovascular event (one patient). †Refused angiography (five patients); angiography aborted due to a cerebrovascular event (one patient).

fibrinolytic treatment, and if they had ST-segment elevation of at least 1 mm in two or more contiguous leads, new left bundle-branch block, or true posterior myocardial infarction. Patients with cardiogenic shock, severe peripheral vascular disease, or previous coronary artery bypass graft surgery were deemed eligible. The principal exclusion criteria were use of low-molecular-weight heparin in the previous 6 h, glycoprotein IIb/IIIa inhibitors in the previous 3 days, or any percutaneous coronary intervention done in the previous 30 days (appendix). The trial was approved by the institutional review board at each participating centre, and all patients gave written informed consent to participate.

Randomisation and masking

Before start of angiography, patients were centrally allocated (1:1) to radial or femoral access for diagnostic angiography and percutaneous coronary intervention, if indicated, using a web-based system to ensure adequate concealment of allocation. The randomisation sequence was computer generated, blocked and stratified by intended new or ongoing use of ticagrelor or prasugrel, type of acute coronary syndrome (ST-segment elevation myocardial infarction, troponin positive or negative, non-ST-segment elevation acute coronary syndrome), and anticipated use of immediate percutaneous coronary intervention. Outcome assessors were masked to the allocated stent, whereas patients and treating physicians were not. Information on the patency of the ulno-palmar arches, according to the modified Allen's and Barbeau's tests, was collected after randomisation.[10,12]

	Radial access (n=4197)	Femoral access (n=4207)
Age (years)	65·6 (11·8)	65·9 (11·8)
≥75 years	1068 (25·4%)	1102 (26·2%)
Men	3126 (74·5%)	3046 (72·4%)
Weight (kg)	77·4 (14·3)	77·0 (13·6)
BMI (kg/m²)	27·1 (4·2)	27·1 (4·2)
≥25 kg/m²	2797 (66·6%)	2816 (66·9%)
Diabetes	951 (22·7%)	932 (22·2%)
Insulin-dependent	204 (4·9%)	250 (5·9%)
Non-insulin-dependent	747 (17·8%)	682 (16·2%)
Smoker	2268 (54·0%)	2269 (53·9%)
Current	1459 (34·8%)	1428 (33·9%)
Previous	809 (19·3%)	841 (20·0%)
Hypercholesterolaemia	1799 (42·9%)	1892 (45·0%)
Hypertension	2625 (62·5%)	2686 (63·8%)
Family history of coronary artery disease	1146 (27·3%)	1147 (27·3%)
Previous myocardial infarction	585 (13·9%)	617 (14·7%)
Previous PCI	610 (14·5%)	585 (13·9%)
Radial access only	119 (2·8%)	84 (2·0%)
Femoral access only	276 (6·6%)	286 (6·8%)
Radial and femoral access	36 (0·9%)	35 (0·8%)
Access site unknown	179 (4·3%)	180 (4·3%)
Previous coronary artery bypass graft	111 (2·6%)	146 (3·5%)
Previous TIA or stroke	195 (4·6%)	230 (5·5%)
Peripheral vascular disease	341 (8·1%)	372 (8·8%)
Chronic obstructive pulmonary disease	250 (6·0%)	283 (6·7%)
Pulmonary hypertension	8 (0·2%)	7 (0·2%)
Renal failure	46 (1·1%)	59 (1·4%)
Dialysis	4 (0·1%)	4 (0·1%)
Clinical presentation		
Cardiac arrest	84 (2·0%)	82 (1·9%)
Killip class		
I	3796 (90·4%)	3800 (90·3%)
II	268 (6·4%)	301 (7·2%)
III	88 (2·1%)	79 (1·9%)
IV	45 (1·1%)	27 (0·6%)
STEMI	2001 (47·7%)	2009 (47·8%)
(Continued from previous column)		
NSTE-ACS	2196 (52·3%)	2198 (52·2%)
NSTE-ACS, troponin negative	243 (5·8%)	269 (6·4%)
NSTE-ACS, troponin positive	1953 (46·5%)	1929 (45·9%)
NSTE-ACS with ST-segment deviation	1015 (24·2%)	987 (23·5%)
NSTE-ACS with T-wave inversion	657 (15·7%)	676 (16·1%)
Systolic blood pressure (mm Hg)	138·5 (25·5)	138·8 (25·7)
Heart rate (beats per min)	76·3 (16·6)	76·0 (16·8)
Left ventricular ejection fraction (%)	51·3 (9·6)	50·8 (9·8)
Estimated glomerular filtration rate (mL/min)	83·9 (25·5)	83·1 (25·5)
Medications given before the catheterisation laboratory		
Aspirin	3953 (94·2%)	3952 (93·9%)
Clopidogrel	2014 (48·0%)	1996 (47·4%)
Prasugrel	484 (11·5%)	468 (11·1%)
Ticagrelor	977 (23·3%)	1026 (24·4%)
Enoxaparin	684 (16·3%)	738 (17·5%)
Fondaparinux	428 (10·2%)	467 (11·1%)
Angiotensin-converting enzyme inhibitor	1245 (29·7%)	1297 (30·8%)
Angiotensin II receptor antagonist	437 (10·4%)	458 (10·9%)
Statin	1809 (43·1%)	1858 (44·2%)
β blocker	1692 (40·3%)	1769 (42·0%)
Warfarin	72 (1·7%)	64 (1·5%)
Proton pump inhibitor	2153 (51·3%)	2190 (52·1%)
Unfractionated heparin	1239 (29·5%)	1236 (29·4%)
Bivalirudin	4 (0·1%)	2 (0·0%)
Glycoprotein IIb/IIIa inhibitor	8 (0·2%)	7 (0·2%)

(Table 1 continues in next column)

Data are n (%) or mean (SD). NSTE-ACS=non-ST-segment elevation acute coronary syndrome. STEMI=ST-segment elevation myocardial infarction. TIA=transient ischaemic attack.

***Table 1*: Baseline characteristics of the intention-to-treat population according to access site**

	Radial access (n=4197)	Femoral access (n=4207)	p value
Coronary angiography			
Attempted coronary angiography	4197 (100%)	4207 (100%)	
Coronary angiography not completed	2 (0·0%)	6 (0·1%)	0·29
Patient refusal	0 (0·0%)	5 (0·1%)	0·062
Technical issue	1 (0·0%)	0 (0·0%)	0·50
Non-fatal cardiovascular accident	1 (0·0%)	1 (0·0%)	1·00
Coronary angiography completed	4195 (100·0%)	4201 (99·9%)	0·29
No PCI attempted after coronary angiography	826 (19·7%)	843 (20·0%)	0·68
CABG	155 (3·7%)	155 (3·7%)	0·98
Patient with significant lesion and medical treatment	490 (11·7%)	499 (11·9%)	0·79
Patient without significant lesion	181 (4·3%)	189 (4·5%)	0·69
PCI attempted	3369 (80·3%)	3358 (79·8%)	0·60
Patient died during PCI	1 (0·0%)	1 (0·0%)	1·00
PCI completed	3368 (80·2%)	3357 (79·8%)	0·60
Medications in the catheterisation laboratory			
Clopidogrel	270 (6·4%)	254 (6·0%)	0·45
Prasugrel	336 (8·0%)	290 (6·9%)	0·0521
Ticagrelor	382 (9·1%)	397 (9·4%)	0·60
Glycoprotein IIb/IIIa inhibitor	574 (13·7%)	520 (12·4%)	0·07
Unfractionated heparin	2094 (49·9%)	1916 (45·5%)	0·0001
Bivalirudin	1683 (40·1%)	1712 (40·7%)	0·58
Intra-aortic balloon pump	79 (1·9%)	95 (2·3%)	0·23
PCIs			
Number of PCIs completed	3368	3357	
TIMI 3 flow post-procedure in all treated lesions	3195 (94·9%)	3195 (95·2%)	0·56
Coronary stenosis after PCI <30% in all treated lesions	3221 (95·6%)	3201 (95·4%)	0·58
Procedural success in all treated lesions	3122 (92·7%)	3115 (92·8%)	0·88
Partial procedural success*	61 (1·8%)	66 (2·0%)	0·64
Procedural failure	185 (5·5%)	176 (5·2%)	0·65
Treated vessel(s)			
Left main coronary artery	154 (4·6%)	119 (3·5%)	0·0328
Left anterior descending artery	1694 (50·3%)	1653 (49·2%)	0·39
Left circumflex artery	906 (26·9%)	922 (27·5%)	0·60
Right coronary artery	1120 (33·3%)	1130 (33·7%)	0·72
Bypass graft	20 (0·6%)	37 (1·1%)	0·0230
≥2 vessels treated	463 (13·7%)	460 (13·7%)	0·96
Lesions treated per patient	1·0 (1·0–1·0)	1·0 (1·0–1·0)	0·75
1	2642 (78·4%)	2657 (79·1%)	
2	594 (17·6%)	577 (17·2%)	
≥3	132 (3·9%)	123 (3·7%)	
≥1 complex lesion	1780 (52·9%)	1720 (51·2%)	0·19
Number of stents per patient	1·0 (1·0–2·0)	1·0 (1·0–2·0)	0·19†
Overall stent length per patient (mm)	31·8 (19·2)	31·4 (19·4)	0·42
Thromboaspiration	964 (28·6%)	1004 (29·9%)	0·25
Lesions‡			
Number of lesions with PCI	4258	4201	
Lesions stented	3881 (91·1%)	3797 (90·4%)	0·22
≥1 drug-eluting stent	2822 (66·3%)	2800 (66·7%)	0·81
≥1 bare-metal stent	1059 (24·9%)	997 (23·7%)	0·30

(Table 2 continues on next page)

Procedures

Access site management during and after the diagnostic or therapeutic procedure was at the discretion of the treating physician, and closure devices were allowed as per local practice. The use of anticoagulants outside the protocol of the MATRIX programme was not allowed. Bivalirudin administration was consistent with the approved product labelling, whereas unfractionated heparin was dosed at 70–100 units per kg in patients not receiving glycoprotein IIb/IIIa inhibitors and at 50–70 units per kg in patients receiving glycoprotein IIb/IIIa inhibitors. Use of all other antithrombotic medications, including oral antiplatelet agents and non-antithrombotic medications, such as β blockers, angiotensin-converting enzyme inhibitors, and other antihypertensive agents, were allowed as per guidelines.[1,2] Staged procedures were allowed, with no restriction with respect to timing, during which the protocol mandated that the access site remained as originally allocated. Clinical follow-up was done at 30 days, with an extended follow-up at 1 year.

Outcomes

Two coprimary 30-day composite outcomes were prespecified: major adverse cardiovascular events, defined as the composite of all-cause mortality, myocardial infarction, or stroke; and net adverse clinical events, defined as the composite of major bleeding not related to coronary artery bypass graft surgery (Bleeding Academic Research Consortium [BARC] type 3 or 5) or major adverse cardiovascular events.[10] Secondary outcomes included each component of the composite outcomes, cardiovascular mortality, and stent thrombosis. Bleeding was also assessed and adjudicated on the basis of the Thrombolysis In Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) scales. Stent thrombosis was defined as the definite or probable occurrence of a stent-related thrombotic event according to the Academic Research Consortium classification.[13] All outcomes were prespecified.[10] An independent clinical events committee masked to treatment allocation adjudicated all suspected outcome events by reviewing relevant medical records after site monitoring by Trial Form Support (Lund, Sweden) in Italy and the Netherlands, FLS-Research Support (Barcelona, Spain) in Spain, and Gothia Forum (Västra Götaland, Sweden) in Sweden. Procedural success in a treated lesion was defined as reaching a post-procedure TIMI 3 flow and less than 30% coronary stenosis.

Statistical analysis

The trial was powered for superiority on the two coprimary composite outcomes at 30 days. For major adverse cardiovascular events, we expected rates of 6·0% in the femoral group and 4·2% in the radial

group, corresponding to a rate ratio (RR) of 0·70. For net adverse clinical events, we expected rates of 9·0% in the femoral group and 6·3% in the radial group, again corresponding to an RR of 0·70. A total of 4100 patients per group would provide greater than 90% power for these differences to be detected for the first coprimary outcome and greater than 99% power for the second coprimary outcome, with a two-sided α set at 2·5%. The final sample size was driven by the power analysis for the nested MATRIX anti-thrombin trial,[10] taking into account the fact that patients with non-ST-segment elevation acute coronary syndrome were eligible only if proceeding to percutaneous coronary intervention. No interim analysis was prespecified or done. We analysed secondary outcomes with a two-sided α set at 5% to allow conventional interpretation of results.

We did all analyses according to the intention-to-treat principle, including all patients in the analysis according to the allocated access. We analysed primary and secondary outcomes as time-to-first-event using the Mantel–Cox method, accompanied by log-rank tests to calculate corresponding two-sided p values. Survival curves were constructed using Kaplan-Meier estimates. We stratified analyses according to prespecified subgroups including age, sex, BMI, presenting syndrome, type of $P2Y_{12}$ inhibitor, overall or transradial percutaneous coronary intervention volume by centre, renal function, diabetes, and peripheral vascular disease, and with χ^2 tests for interaction or tests for trend across ordered groups.

We did a post-hoc nested case-control study to examine factors associated with deaths not directly attributed to a bleeding event. Cases were defined as all patients who died up to 30 days after randomisation from a cause other than bleeding (ie, we excluded BARC type 5 bleedings). Ten control patients per case were randomly selected from the overall cohort of randomised patients to construct a matched case-control set for each case. To qualify as control, the patient had to be alive until the time the case patient had died. We fitted conditional logistic regression models to obtain odds ratios (ORs) and 95% CIs for the association of characteristics of patients at baseline and BARC type 2 or 3 actionable bleedings with deaths from causes other than bleeding. We did crude univariable analyses for all variables. The final multivariable model was based on all variables associated with the case-control status, with automated hierarchical backward selection of variables. p was 0·10 for initial inclusion and retention of variables in the model. All analyses were done in Stata Release 13.

Role of the funding source

The programme was designed by the principal investigator (MV), sponsored by the Gruppo Italiano Studi Emodinamica (GISE), a non-profit organisation,

	Radial access (n=4197)	Femoral access (n=4207)	p value
(Continued from previous page)			
Lesions not stented	377 (8·9%)	404 (9·6%)	0·22
TIMI flow before PCI			
0 or 1	1628 (38·2%)	1623 (38·6%)	0·93
2	533 (12·5%)	532 (12·7%)	0·78
3	2097 (49·2%)	2046 (48·7%)	0·98
TIMI flow after PCI			
0 or 1	76 (1·8%)	71 (1·7%)	0·76
2	107 (2·5%)	102 (2·4%)	0·80
3	4075 (95·7%)	4028 (95·9%)	0·64
Coronary stenosis after PCI <30%	4097 (96·2%)	4036 (96·1%)	0·66
Procedural success	3989 (93·7%)	3944 (93·9%)	0·77
Number of lesions stented	3881	3797	
Total stent length per lesion (mm)	25·9 (14·4)	25·9 (14·1)	0·81
Average stent diameter per lesion (mm)	3·1 (0·5)	3·0 (0·5)	0·29
≥1 direct stenting	864 (22·3%)	840 (22·1%)	0·87
Post-stenting dilatation	1726 (44·5%)	1717 (45·2%)	0·57

Data are n (%), mean (SD), or median (IQR). PCI=percutaneous coronary intervention. TIMI=Thrombolysis in Myocardial Infarction. *TIMI 3 flow and coronary stenosis less than 30% in at least one lesion. †p value for count from Poisson regression. ‡p values from mixed models accounting for lesions nested within patients.

Table 2: **Procedural characteristics in patients undergoing attempted coronary angiography**

	Radial access (n=4197)	Femoral access (n=4207)	Rate ratio (95% CI)	p value
Adjudicated events				
Coprimary composite of all-cause mortality, myocardial infarction, or stroke	369 (8·8%)	429 (10·3%)	0·85 (0·74–0·99)	0·0307
Coprimary composite of all-cause mortality, myocardial infarction, stroke, or BARC 3 or 5 bleed	410 (9·8%)	486 (11·7%)	0·83 (0·73–0·96)	0·0092
Composite of all-cause mortality, myocardial infarction, stroke, urgent TVR, definite stent thrombosis, or BARC 3 or 5 bleed	419 (10·0%)	491 (11·8%)	0·84 (0·74–0·97)	0·0142
All-cause mortality	66 (1·6%)	91 (2·2%)	0·72 (0·53–0·99)	0·0450
Cardiovascular	64 (1·5%)	85 (2·1%)	0·75 (0·54–1·04)	0·08
Cardiac	62 (1·5%)	79 (1·9%)	0·78 (0·56–1·09)	0·15
Vascular	2 (0·0%)	6 (0·1%)	0·33 (0·07–1·65)	0·16
Non-cardiovascular	2 (0·0%)	6 (0·2%)	0·33 (0·07–1·65)	0·16
Myocardial infarction	299 (7·2%)	330 (7·9%)	0·90 (0·77–1·06)	0·20
Q-wave	6 (0·1%)	3 (0·1%)	2·00 (0·50–7·99)	0·32
STEMI	37 (0·9%)	30 (0·7%)	1·23 (0·76–2·00)	0·39
NSTEMI	197 (4·7%)	238 (5·7%)	0·82 (0·68–1·00)	0·0450
Unclassified*	65 (1·6%)	63 (1·5%)	1·03 (0·73–1·46)	0·86
Stroke	16 (0·4%)	16 (0·4%)	1·00 (0·50–2·00)	1·00
Ischaemic	12 (0·3%)	11 (0·3%)	1·09 (0·48–2·47)	0·84
Haemorrhagic	3 (0·1%)	5 (0·1%)	0·60 (0·14–2·51)	0·48
Uncertain origin†	1 (0·0%)	0 (0·0%)	3·01 (0·12–73·87)	0·50
Transient ischaemic attack	5 (0·1%)	13 (0·3%)	0·38 (0·14–1·08)	0·0588
Urgent target vessel revascularisation	49 (1·2%)	40 (1·0%)	1·23 (0·81–1·86)	0·34

(Table 3 continues on next page)

	Radial access (n=4197)	Femoral access (n=4207)	Rate ratio (95% CI)	p value
(Continued from previous page)				
Stent thrombosis				
Definite	30 (0·7%)	27 (0·6%)	1·11 (0·66–1·87)	0·69
Acute	21 (0·5%)	12 (0·3%)	1·75 (0·86–3·57)	0·12
Subacute	10 (0·2%)	15 (0·4%)	0·66 (0·30–1·48)	0·31
Definite or probable	42 (1·0%)	38 (0·9%)	1·10 (0·71–1·71)	0·66
Acute	24 (0·6%)	14 (0·3%)	1·72 (0·89–3·32)	0·11
Subacute	20 (0·5%)	24 (0·6%)	0·83 (0·46–1·50)	0·54
Bleeding	350 (8·4%)	606 (14·6%)	0·55 (0·48–0·63)	<0·0001
BARC classification				
Type 1	168 (4·0%)	306 (7·4%)	0·54 (0·44–0·65)	<0·0001
Type 2	127 (3·1%)	215 (5·2%)	0·58 (0·47–0·73)	<0·0001
Type 3	54 (1·3%)	84 (2·1%)	0·64 (0·45–0·90)	0·0098
Type 3a	29 (0·7%)	44 (1·1%)	0·66 (0·41–1·05)	0·08
Type 3b	23 (0·6%)	37 (0·9%)	0·62 (0·37–1·04)	0·07
Type 3c	2 (0·0%)	4 (0·1%)	0·50 (0·09–2·72)	0·41
Type 4	6 (0·1%)	6 (0·1%)	1·00 (0·32–3·10)	1·00
Type 5	10 (0·2%)	11 (0·3%)	0·91 (0·39–2·14)	0·82
Type 5a	6 (0·1%)	9 (0·2%)	0·67 (0·24–1·87)	0·44
Type 5b	4 (0·1%)	2 (0·0%)	2·00 (0·37–10·92)	0·41
Type 3 or 5	64 (1·6%)	95 (2·3%)	0·67 (0·49–0·92)	0·0128
Related to access site	16 (0·4%)	43 (1·1%)	0·37 (0·21–0·66)	0·0004
Not related to access site	48 (1·2%)	52 (1·3%)	0·92 (0·62–1·36)	0·68
Type 2, 3, or 5	189 (4·6%)	307 (7·4%)	0·60 (0·50–0·73)	<0·0001
Related to access site	69 (1·7%)	197 (4·8%)	0·34 (0·26–0·45)	<0·0001
Not related to access site	121 (2·9%)	115 (2·8%)	1·05 (0·81–1·36)	0·70
TIMI classification				
Major bleeding	26 (0·6%)	37 (0·9%)	0·70 (0·42–1·16)	0·16
Minor bleeding	24 (0·6%)	32 (0·8%)	0·75 (0·44–1·27)	0·28
Major or minor bleeding	50 (1·2%)	69 (1·7%)	0·72 (0·50–1·04)	0·08
GUSTO classification				
Severe bleeding	23 (0·6%)	27 (0·6%)	0·85 (0·49–1·48)	0·57
Moderate bleeding	23 (0·6%)	32 (0·8%)	0·72 (0·42–1·22)	0·22
Mild bleeding	306 (7·4%)	549 (13·3%)	0·54 (0·47–0·62)	<0·0001
Moderate or severe bleeding	46 (1·1%)	59 (1·4%)	0·78 (0·53–1·14)	0·20
Non-adjudicated events				
Composite of surgical access site repair or blood products transfusion	41 (1·0%)	73 (1·8%)	0·56 (0·38-0·82)	0·0025
Surgical access site repair	4 (0·1%)‡	15 (0·4%)	0·27 (0·09–0·80)	0·0115
Red blood cell transfusion	40 (1·0%)	64 (1·5%)	0·62 (0·42-0·92)	0·0176

Percentages are cumulative incidence estimates. BARC=Bleeding Academic Research Consortium. GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. MI=myocardial infarction. NSTEMI=non-ST-segment elevation myocardial infarction. STEMI=ST-segment elevation myocardial infarction. TIMI=Thrombolysis In Myocardial Infarction. TVR=target vessel revascularisation. *Includes patients with left bundle-branch block and patients with paced rhythm. †Continuity corrected rate ratio (95% CI) with p value from Fisher's test. ‡Occurred in one patient at the radial artery access site due to a large haematoma and in three patients at the femoral access site, which was used for inserting an intra-aortic balloon pump or after failed radial access.

Table 3: **Adjudicated and non-adjudicated clinical outcomes**

and received grant support from The Medicines Company and TERUMO (appendix). Sponsors and companies had no role in study design, data collection, data monitoring, analysis, interpretation, or writing of the report. MV, MR, DH, and PJ had unrestricted access to all the data of the trial. MV and PJ had final responsibility for the decision to submit for publication.

Results

Between Oct 11, 2011, and Nov 7, 2014, 8404 patients were randomly allocated to receive radial (4197 patients) or femoral access (4207 patients). Of these patients, 3951 (94·1%) received radial access and 4098 (97·4%) received femoral access. Access was attempted but failed in 243 (5·8%) radial patients and 96 (2·3%) femoral patients, and access was not attempted in three (0·1%) radial and 13 (0·3%) femoral patients. Complete follow-up to 30 days was available in 4183 radial and 4191 femoral patients (figure 1). Baseline characteristics were similar between groups (table 1). Overall, 4010 (47·7%) patients had an ST-segment elevation myocardial infarction and 4394 (52·3%) patients had non-ST-segment elevation acute coronary syndrome. Clopidogrel was given before angiography in 4010 (47·7%) patients, ticagrelor in 2003 (23·8%) patients, and prasugrel in 952 (11·3%) patients.

Procedural results according to access strategy are presented in table 2. The management strategy after index angiography was similar in both groups, consisting of percutaneous coronary intervention in 6727 (80·1%) patients, coronary artery bypass graft surgery in 310 (3·7%) patients, and medical management in 1359 (16·2%) patients. In the catheterisation laboratory, 2094 (49·9%) patients received unfractionated heparin in the radial group and 1916 (45·5%) patients in the femoral group (p<0·0001), 574 (13·7%) patients received glycoprotein IIb/IIIa inhibitors in the radial group and 520 (12·4%) patients in the femoral group (p=0·07), and 1683 (40·1%) patients were treated with bivalirudin in the radial group and 1712 (40·7%) patients in the femoral group (p=0·58). Among patients with percutaneous coronary intervention, procedural success was achieved in all treated lesions in 3122 (92·7%) radial patients and 3115 (92·8%) femoral patients. Results of staged procedures and medications at discharge are detailed in the appendix.

Clinical outcomes are shown in table 3, figures 2 and 3. The first coprimary outcome of major adverse cardiac events occurred in 369 (8·8%) patients with radial access and 429 (10·3%) patients with femoral access, with a RR of 0·85 (95% CI 0·74–0·99) and a two-sided p of 0·0307, which was formally non-significant at the prespecified α of 0·025. The second coprimary outcome of net adverse clinical events was experienced by 410 (9·8%) patients with radial access and 486 (11·7%) patients with femoral access, with a formally significant RR of 0·83 (95% CI 0·73–0·96; p=0·0092). Radial access was associated with a lower risk of all-cause mortality (table 3, figure 3); rates of cardiac mortality, myocardial infarction, and stroke were not significantly different (table 3, figure 3). The two groups had similar rates of urgent target vessel revascularisation and stent thrombosis. Major BARC 3 or 5 bleeding was significantly reduced in the radial group

(table 3, figure 3), as were minor non-actionable BARC 1 and actionable BARC 2 bleeding. Bleeding events fulfilling the TIMI or GUSTO criteria did not differ significantly between groups, but the estimated relative risk reductions were consistent with what we noted for major BARC 3 or 5 bleeding. Radial access was associated with significantly lower rates of surgical access site repair or transfusion of blood products. No cases of compartment syndrome were reported.

Figure 4 and the appendix show the stratified analyses of the two coprimary outcomes, all-cause mortality, and BARC 3 or 5 bleeding. The effect of radial versus femoral access appeared consistent across major patient subgroups defined by acute coronary syndrome type, age, sex, BMI, intended start or ongoing use of prasugrel or ticagrelor, diabetes, renal function, and history of peripheral vascular disease, and in an analysis stratified according to tertiles of the centres' annual volume of percutaneous coronary intervention. Conversely, we found positive tests for trend across tertiles of the centres' percentage of radial percutaneous coronary intervention for both coprimary outcomes and all-cause mortality (p≤0·0157), with a pronounced benefit of radial access in centres that did 80% or more radial percutaneous coronary interventions (figure 4, appendix). In a post-hoc analysis of the subgroup of 7213 patients who were randomly allocated to bivalirudin or unfractionated heparin, we found no evidence for an interaction between the effect of radial versus femoral access and allocation to bivalirudin or unfractionated heparin for the two coprimary outcomes, all-cause mortality, or BARC 3 or 5 bleeding (p for interaction ≥0·64; data not shown).

Sensitivity analyses of the two coprimary outcomes, all-cause mortality, and BARC 3 or 5 bleeding were all compatible with the main analyses (appendix). Estimated numbers needed to treat were 71 for preventing one major adverse cardiovascular event, 56 for preventing one net adverse clinical event, 136 for preventing one BARC type 3 or 5 bleeding, and 169 for preventing one death, when using radial rather than femoral access (appendix).

In the nested case-control study of the 137 patients who died within 30 days from a cause other than bleeding and 1370 matched control patients, we found BARC 2 or 3 actionable bleeding associated with deaths from causes other than bleeding, with a crude OR of 3·10 (95% CI 1·75–5·50; p<0·0001) and an adjusted OR of 2·35 (95% CI 1·18–4·67; p=0·015; appendix).

Discussion

Among patients with an acute coronary syndrome, with or without ST-segment elevation who underwent invasive management, the use of radial access for coronary angiography followed by percutaneous coronary intervention, if indicated, significantly reduced the rate of net adverse clinical events, defined as the composite of major adverse cardiovascular events or major bleeding, with a number needed to treat of 56. The 15% relative risk

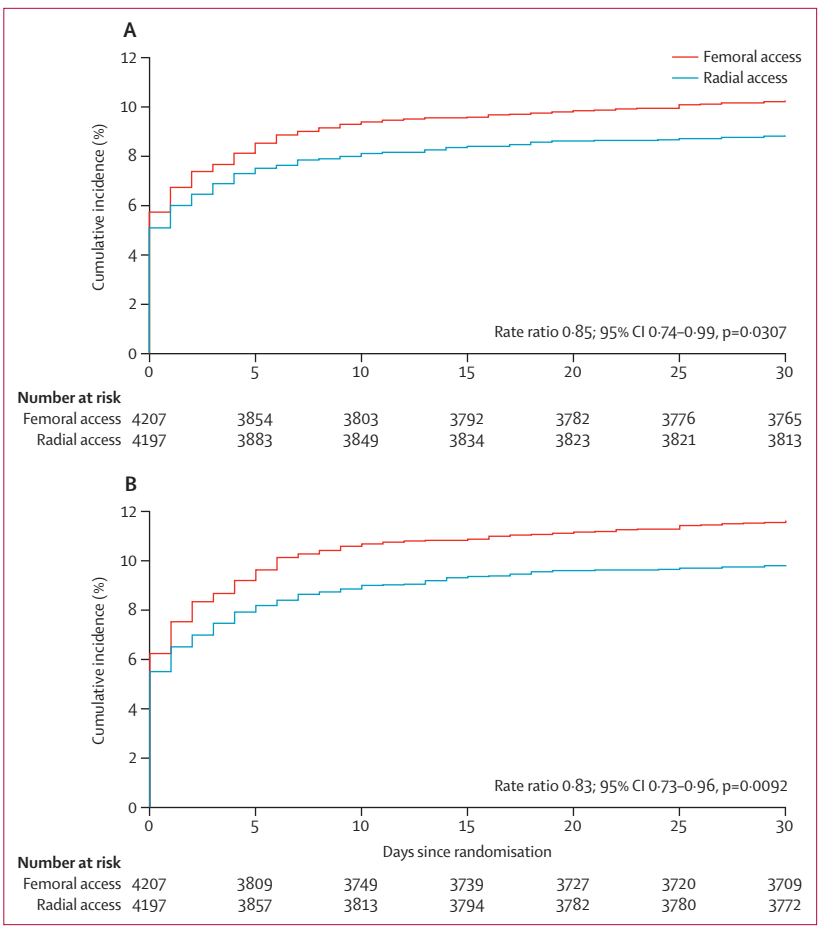
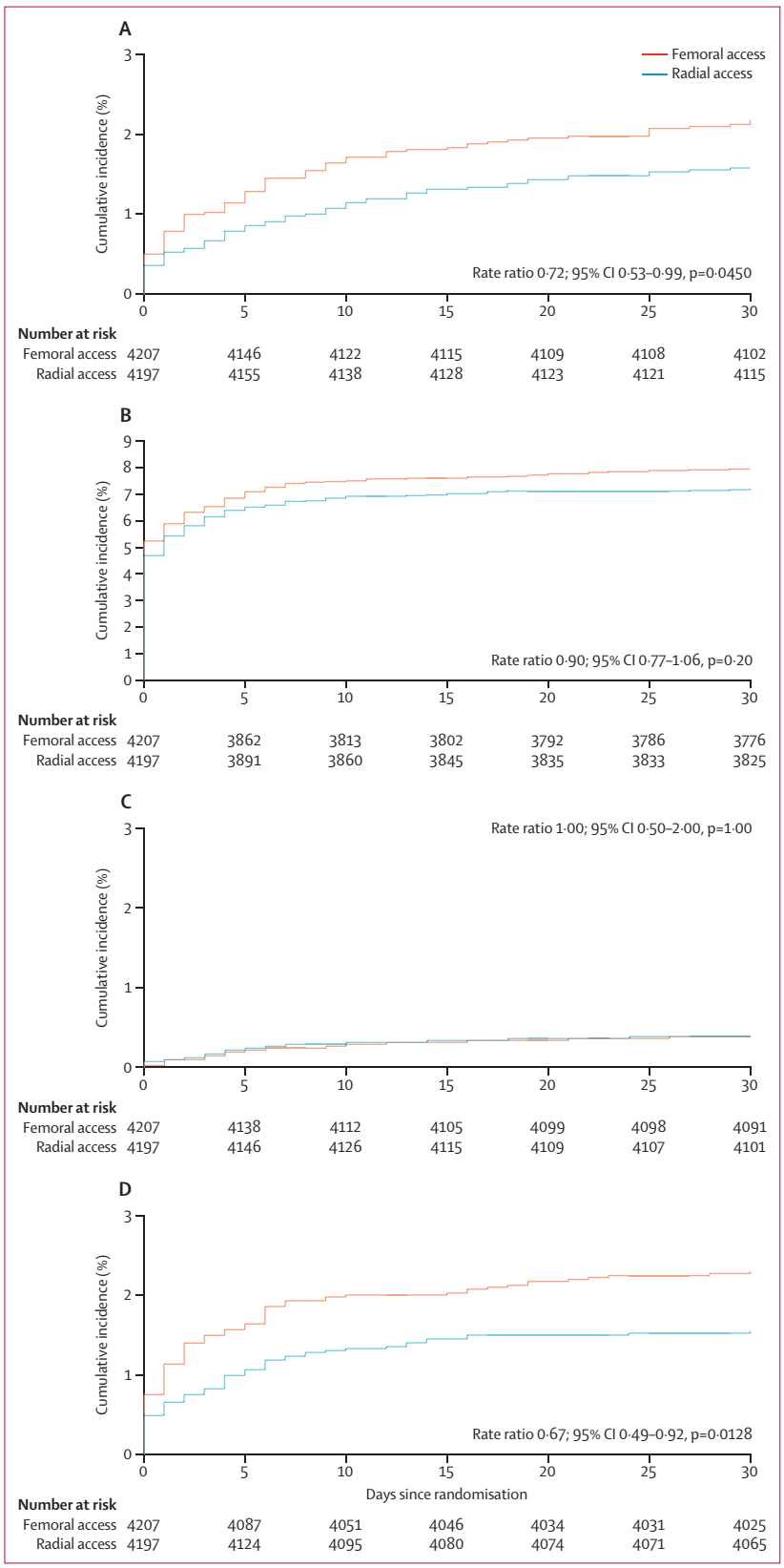


***Figure 2*: Coprimary composite outcomes at 30 days**
(A) All-cause mortality, myocardial infarction, or stroke, and (B) all-cause mortality, myocardial infarction, stroke, or Bleeding Academic Research Consortium 3 or 5 bleeding.

reduction for major adverse cardiovascular events did not meet the prespecified α level of 2·5% (p=0·031). Differences between groups were driven by reductions in BARC major bleeding unrelated to coronary artery bypass graft surgery and all-cause mortality with radial access. No difference was found with respect to rates of myocardial infarction or stroke, which appears reassuring in view of previous concerns that radial compared with femoral access might increase cerebrovascular embolisation.[8,14] In a nested case-control study, we found BARC-actionable bleeding associated with deaths from causes other than bleeding, which suggests that a reduction in all-cause death with radial access could be mediated by a reduction of bleeding events, thus providing a mechanistic explanation for our findings.

In our meta-analysis of trials in patients with acute coronary syndromes (figure 5, panel), updated with all trials that randomly assigned patients to radial or femoral access after the landmark RadIal Vs femorAL access for coronary intervention (RIVAL) study,[8] we found a statistically robust and clinically relevant reduction in all-cause mortality by radial compared with femoral



access, which could not be shown in a previous update done by the RIVAL investigators.[8] Altogether, the results of our trial, in conjunction with the findings of the updated meta-analysis, suggest that radial access should become the default approach in patients with an acute coronary syndrome undergoing invasive management.

The clinical equipoise, or lack thereof, between radial and femoral access sites in patients undergoing coronary angiography or percutaneous coronary intervention, or both, has been debated extensively over recent years. Data from registries,[7,16,17] small-to-medium-sized studies,[18] and meta-analyses[14,19] have suggested that radial access might be associated with improved outcomes when compared with femoral access. As a result, position papers, expert opinion papers, and guidelines from Europe[2,20] or North America[21–23] have endorsed the preferential use of radial over femoral access. However, the unexpected results of the large-scale RIVAL trial tempered enthusiasm towards use of radial access for coronary angiography and intervention, as neither the primary composite outcome of death, myocardial infarction, stroke, or major bleeding unrelated to coronary artery bypass graft surgery, nor the outcomes of major bleeding or all-cause death differed significantly between the two access site groups.[8] Widely overlapping 95% CIs for all outcomes suggest that results from RIVAL[8] and our trial are mutually compatible and that differences are mostly due to random variation. In view of a significant interaction for the primary outcome in the RIVAL trial, with a benefit for radial access in the highest-volume radial centres,[8,15,24] some variation might also be explained by the levels of expertise with radial access. Additional explanations are the larger sample size of our study, combined with a higher rate of primary endpoint events, a higher proportion of patients in whom percutaneous coronary intervention was deemed indicated, and different bleeding definitions.

In the RIVAL trial, operators were allowed to participate if they had done cumulatively 50 or more transradial catheterisations.[25] In our trial, operators qualified on the basis of the number of transradial interventions done previously—not any catheterisation—with a cutoff of 75 or more done in the year before study initiation at each site. This number is in keeping with the minimum annual number of percutaneous coronary intervention procedures recommended in the American College of Cardiology, American Heart Association, and Society of Cardiac Angiography and Intervention guidelines for an interventional cardiologist to enhance patient safety.[26] The proportion of percutaneous coronary interventions undertaken transradially emerged as a potential effect modifier for both coprimary endpoints and overall mortality, but not for major bleeding. This finding suggests that although the bleeding benefit accrues at an

Figure 3: **Components of coprimary composite at 30 days**
(A) All-cause mortality, (B) myocardial infarction, (C) stroke, and (D) Bleeding Academic Research Consortium 3 or 5 bleeding.

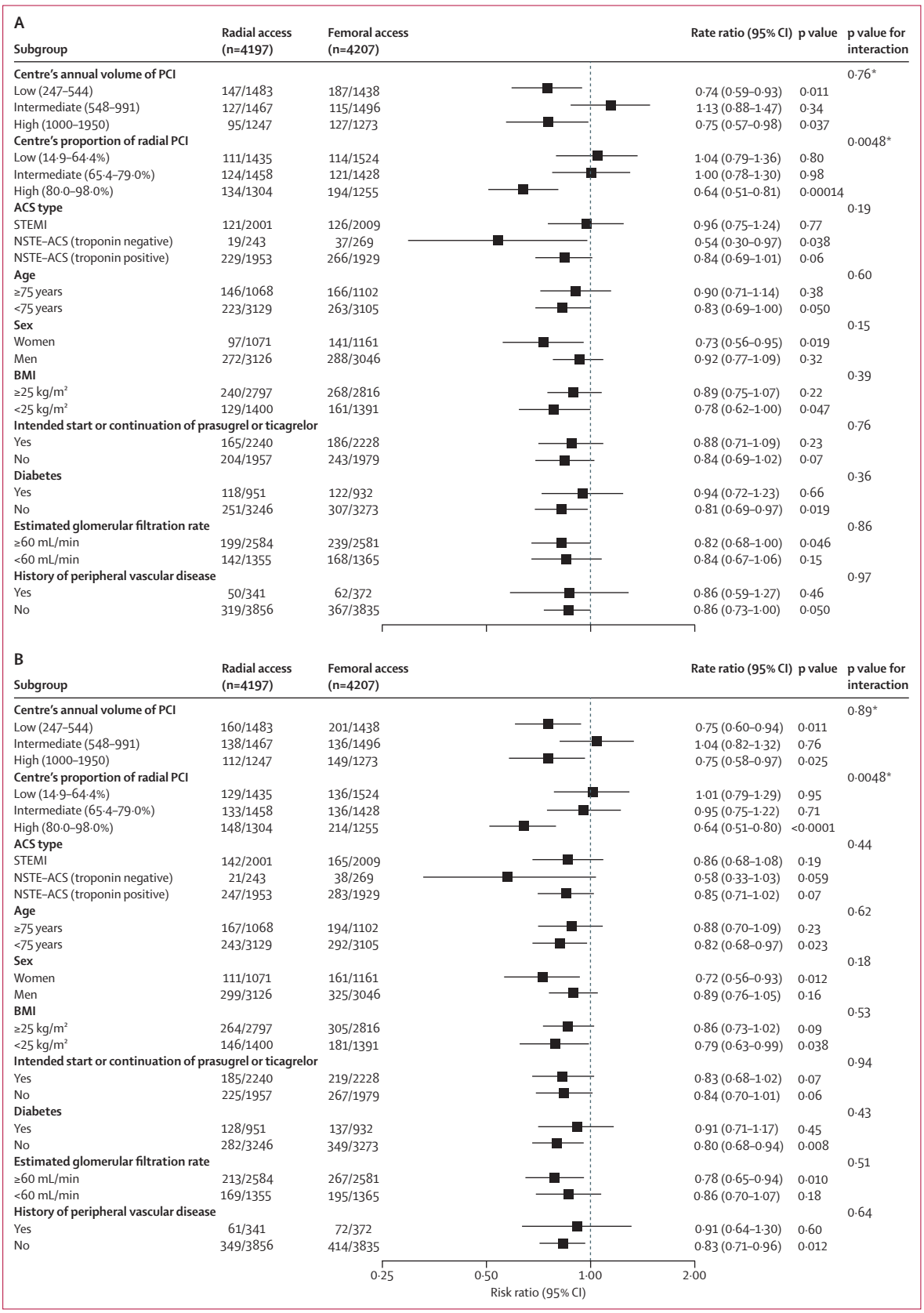


***Figure 4*: Stratified analysis of coprimary outcomes**
(A) All-cause mortality, myocardial infarction, or stroke, and (B) all-cause mortality, myocardial infarction, or stroke, or Bleeding Academic Research Consortium 3 or 5 bleeding. PCI=percutaneous coronary intervention. ACS=acute coronary syndrome. STEMI=ST-segment elevation myocardial infarction. NSTE-ACS=non-ST-segment elevation acute coronary syndrome. *p values are for trend across ordered groups.

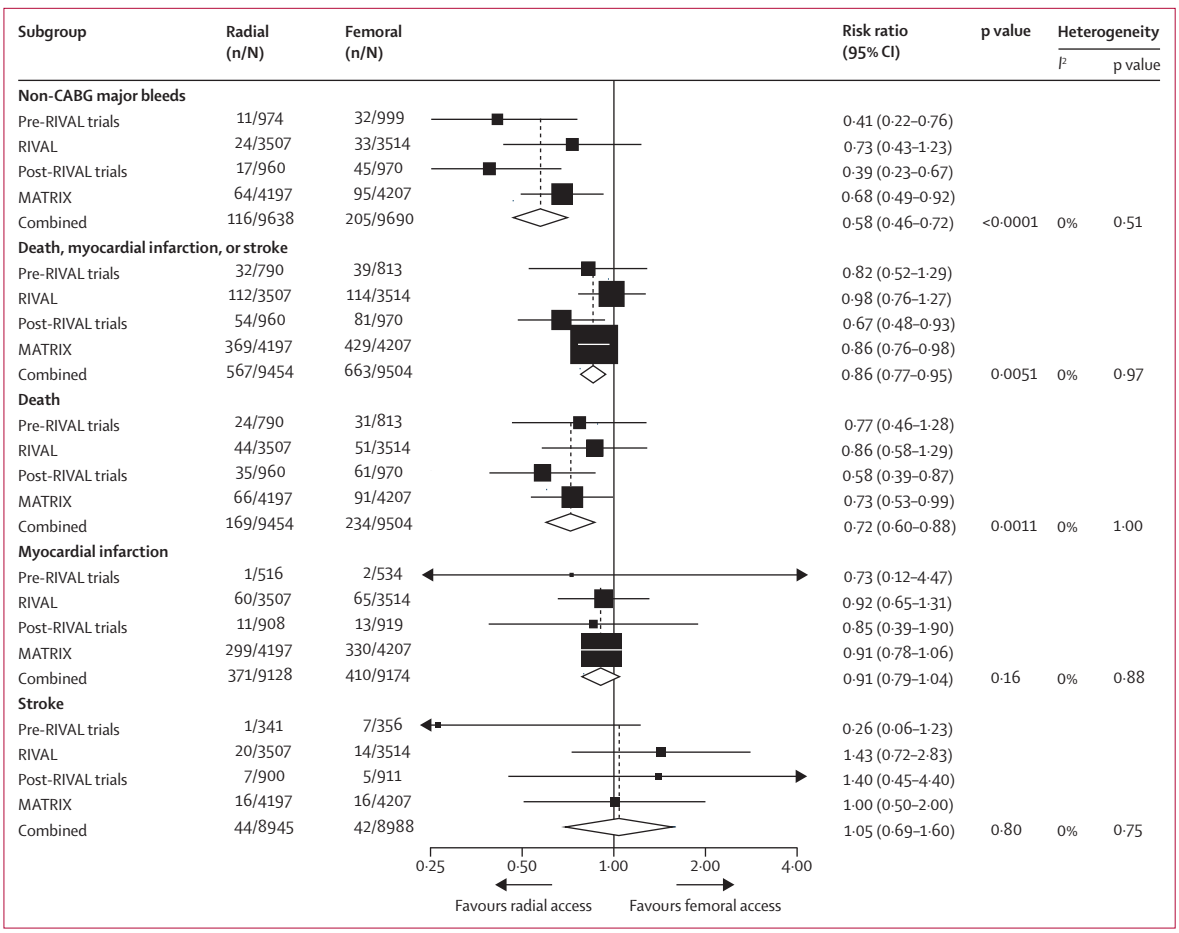


Figure 5: **Forest plot of the updated meta-analyses of trials in patients with acute coronary syndromes**
References for trial studies are listed in the appendix. CABG=coronary artery bypass graft. n/N=events/total number of patients.

Panel: Research in context

Systematic review

We searched PubMed and ISI Web of Science from Jan 1, 2001, to Feb 3, 2015 (see appendix for the search strategy) to update the meta-analyses previously done by the RIVAL trial,[15] and used identical methods for data extraction and identical outcomes, except for restricting the analysis to trials in patients with acute coronary syndrome to ensure comparability with our trial and RIVAL,[15] and omitting transfusion unrelated to coronary artery bypass graft surgery and major vascular access complication, since statistically robust reductions in these outcomes were previously shown.[15] We used the Mantel-Haenszel method to pool risk ratios.

Interpretation

MATRIX Access is the largest randomised trial to compare radial and femoral access. The updated meta-analysis (figure 5) shows that radial access reduces major bleeds, major adverse cardiovascular events, and all-cause mortality, but not myocardial infarction or stroke. The case-control study nested in MATRIX Access suggests that BARC 2 or 3 actionable bleeding is strongly associated with mortality from causes other than bleeding. In conjunction, MATRIX Access and the updated meta-analysis suggest radial access should become the default access for patients with acute coronary syndrome undergoing invasive management.

earlier stage of the learning curve of transradial intervention, superior efficacy compared with femoral access needs substantial expertise that can be met only by high-volume radial operators, which is in keeping with recent observations from registry data.[27]

The Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) study,[9] in which 1001 patients with ST-segment elevation myocardial infarction were randomly assigned to the radial or femoral approach, reported a decrease in the rate of major adverse cardiac events in the radial group, driven by reductions in mortality and bleeding. By contrast, the ST Elevation Myocardial Infarction treated by RADIAL or femoral approach (STEMI-RADIAL) trial[28] showed a significant reduction in bleeding and access site complications with radial access, but no mortality benefit was shown among 707 patients with ST-segment elevation myocardial infarction undergoing primary intervention within 12 h of symptom onset.

Anticoagulation strategies with low use of the direct thrombin inhibitor bivalirudin (<10%) and higher than contemporary use of glycoprotein IIb/IIIa inhibitors

(30–70%) might have favoured the radially treated patients when considering access site bleeding as an outcome, and might have contributed to the mortality difference in the two groups in patients with ST-segment elevation myocardial infarction included in the RIVAL and RIFLE-STEACS studies.[29] Bivalirudin was used during percutaneous coronary intervention in more than 40% of patients in our trial; less than 14% received glycoprotein IIb/IIIa inhibitors at the time of intervention, and more than 50% of the patients were treated with ticagrelor or prasugrel, more closely following contemporary clinical practice.

Before the MATRIX Access trial was done, the number of patients with non-ST-segment elevation acute coronary syndrome included in randomised trials of radial versus femoral access was restricted largely to those recruited in the RIVAL study, which showed similar rates of the primary outcome in the radial (3·8%) and femoral (3·5%) groups, and a trend towards higher mortality risk in those allocated to radial access (1·25% *vs* 1·66%; p=0·082).[8] In multivariable analysis, the interaction between pre-randomisation acute coronary syndrome type and access site allocation on mortality remained highly significant, even after adjustment for operator radial experience and centre radial volume.[15] The results of our trial do not lend support to the previous observation that the benefit of radial access, compared with femoral, in terms of combined outcomes or all-cause mortality might be variable across patients with acute coronary syndrome. All causes of death (ie, cardiac, vascular, and non-cardiovascular) consistently contributed to the lower risk of all-cause mortality in the radial group. The magnitude of such benefit, in the range of six fewer fatal events for every 1000 treated patients, appeared less than previously reported in patients with ST-segment elevation myocardial infarction.[9,15] However, in view of the millions of individuals with acute coronary syndrome undergoing invasive management, including the more than one million undergoing percutaneous coronary intervention annually worldwide, the mortality benefit reported with radial access site could have substantial consequences for public health. This benefit might be especially relevant for countries such as the USA where use of the radial approach is currently uncommon.[30]

Differences did not reach statistical significance for major adverse cardiovascular events as one of the two coprimary outcomes, and one can argue that the results for secondary outcomes, including all-cause mortality, are not definite since their α levels were not adjusted for multiple comparisons. However, our results need to be interpreted in the context of the updated meta-analysis (panel), which suggests highly significant benefits of radial access in acute coronary syndrome patients for major adverse cardiovascular events (p=0·0051) and all-cause mortality (p=0·0011) with no evidence of statistical heterogeneity between trials. The higher than expected event rate in our study can be explained by the inclusion of a high-risk acute coronary syndrome population, including 10% of patients with Killip class greater than 1, 90% of patients with non-ST-segment elevation acute coronary syndrome with raised biomarker concentrations, and 2% with resuscitated cardiac arrest at presentation. It remains unclear how the risk profile of the included patients compares with an all-comer acute coronary syndrome population given the absence of a screening log at recruiting sites in our trial.

In conclusion, our results show that in patients with acute coronary syndrome, with or without ST-segment elevation, undergoing invasive management, the use of radial access compared with femoral access decreases net adverse clinical events.

Contributors

MV was responsible for conception and design and obtained funding for the study. MR, DH, MV, and PJ did the analysis and interpreted it in collaboration with all the remaining authors. MV, AG, PC, EF, SL, TZ, PR, CB, GA, AR, UL, BC, PS, AL, MG, SC, SI, AA, PP, GS, FV, GE, AS, ST, MN, AZ, NdC, SR, PT, CP, SB, SVR, and PV were responsible for the acquisition of data. MV and PJ had full access to the final data, co-wrote the manuscript, had final responsibility for content, and the decision to submit for publication. All authors critically revised the paper for important intellectual content and approved the final version.

Declaration of interests

MV reports grants from The Medicines Company, grants from Terumo, during the study; grants and personal fees from AstraZeneca, personal fees and non-financial support from The Medicines Company, and personal fees from Terumo, St Jude Vascular, Alvimedica, Abbott Vascular, and Correvio, outside the submitted work. UL reports personal fees from The Medicines Company, AstraZeneca, Lilly, Boston Scientific, Biotronik, and Merck, outside the submitted work. BC reports personal fees and non-financial support from Medtronic, The Medicines Company, and Terumo, and personal fees from Abbott and Hexacath, outside the submitted work. SC reports personal fees from Abbott Vascular, outside the submitted work. FV reports personal fees from AstraZeneca, Eli Lilly, Bayer, travel expenses from Biosensors, grants from Medtronic, Kardia SRL, and Boston Scientific, outside the submitted work. SB reports grants from AstraZeneca, outside the submitted work. SVR reports personal fees from Terumo Medical, outside the submitted work. PJ reports funding for research projects to the institution from Abbott Vascular, Biosensors, Medtronic, Johnson & Johnson, Ablynx, Amgen, AstraZeneca, Boehringer Ingelheim, Eisai, Eli Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novartis, Novo Nordisk, Padma, Roche, Schering-Plough, St. Jude Medical, and Swiss Cardio Technologies, outside the submitted work; and is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic, and St. Jude Medical. The remaining authors declare no competing interests.

Acknowledgments

We are grateful for statistical advice from Marcel Zwahlen about the nested case-control study. Editorial support restricted to editing for style was provided by Sophie Rushton-Smith (MedLink Healthcare Communications) and was funded by the GISE.

References

1 Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2012; **126:** 875–910.

2 Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.

3 Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; **358:** 2218–30.

4 Majure DT, Aberegg SK. Fondaparinux versus enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354:** 2829; author reply 30.

5 Chhatriwalla AK, Amin AP, Kennedy KF, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA* 2013; **309:** 1022–29.

6 Vranckx P, Campo G, Anselmi M, et al. Does the site of bleeding matter? A stratified analysis on location of TIMI-graded bleedings and their impact on 12-month outcome in patients with ST-segment elevation myocardial infarction. *EuroIntervention* 2012; **8:** 71–78.

7 Valgimigli M, Saia F, Guastaroba P, et al. 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. *JACC Cardiovasc Interv* 2012; **5:** 23–35.

8 Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 2011; **377:** 1409–20.

9 Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol* 2012; **60:** 2481–89.

10 Valgimigli M, MATRIX Investigators. Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program. *Am Heart J* 2014; **168:** 838–45.

11 Valgimigli M, Calabro P, Cortese B, et al. Scientific foundation and possible implications for practice of the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX (MATRIX) trial. *J Cardiovasc Transl Res* 2014; **7:** 101–11.

12 Valgimigli M, Campo G, Penzo C, et al. Trans-radial coronary catheterization and intervention across the whole spectrum of Allen's test results. *J Am Coll Cardiol* 2014; **63:** 1833–41.

13 Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115:** 2344–51.

14 Agostoni P, Biondi-Zoccai GG, de Benedictis ML, et al. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures; systematic overview and meta-analysis of randomized trials. *J Am Coll Cardiol* 2004; **44:** 349–56.

15 Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol* 2012; **60:** 2490–99.

16 Chase AJ, Fretz EB, Warburton WP, et al. Association of the arterial access site at angioplasty with transfusion and mortality: the M.O.R.T.A.L. study (Mortality benefit Of Reduced Transfusion after percutaneous coronary intervention via the Arm or Leg). *Heart* 2008; **94:** 1019–25.

17 Ratib K, Mamas MA, Anderson SG, et al. Access site practice and procedural outcomes in relation to clinical presentation in 439 947 patients undergoing percutaneous coronary intervention in the United kingdom. *JACC Cardiovasc Interv* 2015; **8:** 20–29.

18 Chodor P, Krupa H, Kurek T, et al. RADIal versus femoral approach for percutaneous coronary interventions in patients with Acute Myocardial Infarction (RADIAMI): a prospective, randomized, single-center clinical trial. *Cardiol J* 2009; **16:** 332–40.

19 Joyal D, Bertrand OF, Rinfret S, Shimony A, Eisenberg MJ. Meta-analysis of ten trials on the effectiveness of the radial versus the femoral approach in primary percutaneous coronary intervention. *Am J Cardiol* 2012; **109:** 813–18.

20 Hamon M, Pristipino C, Di Mario C, et al. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care** and Thrombosis of the European Society of Cardiology. *EuroIntervention* 2013; **8:** 1242–51.

21 Dauerman HL, Rao SV, Resnic FS, Applegate RJ. Bleeding avoidance strategies. Consensus and controversy. *J Am Coll Cardiol* 2011; **58:** 1–10.

22 Caputo RP, Tremmel JA, Rao S, et al. Transradial arterial access for coronary and peripheral procedures: executive summary by the Transradial Committee of the SCAI. *Catheter Cardiovasc Interv* 2011; **78:** 823–39.

23 Eleid MF, Rihal CS, Gulati R, Bell MR. Systematic use of transradial PCI in patients with ST-segment elevation myocardial infarction: a call to "arms". *JACC Cardiovasc Interv* 2013; **6:** 1145–48.

24 Jolly SS, Cairns J, Yusuf S, et al. Procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. *J Am Coll Cardiol* 2014; **63:** 954–63.

25 Ball WT, Sharieff W, Jolly SS, et al. Characterization of operator learning curve for transradial coronary interventions. *Circ Cardiovasc Interv* 2011; **4:** 336–41.

26 King SB, 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol* 2008; **51:** 172–209.

27 Hess CN, Peterson ED, Neely ML, et al. The learning curve for transradial percutaneous coronary intervention among operators in the United States: a study from the National Cardiovascular Data Registry. *Circulation* 2014; **129:** 2277–86.

28 Bernat I, Horak D, Stasek J, et al. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. *J Am Coll Cardiol* 2014; **63:** 964–72.

29 Lee MS, Wolfe M, Stone GW. Transradial versus transfemoral percutaneous coronary intervention in acute coronary syndromes: re-evaluation of the current body of evidence. *JACC Cardiovasc Interv* 2013; **6:** 1149–52.

30 Bradley SM, Rao SV, Curtis JP, et al. Change in hospital-level use of transradial percutaneous coronary intervention and periprocedural outcomes: insights from the national cardiovascular data registry. *Circ Cardiovasc Qual Outcomes* 2014; **7:** 550–59.