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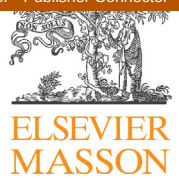

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CLINICAL RESEARCH

Transradial versus transfemoral approach for percutaneous coronary intervention in cardiogenic shock: A radial-first centre experience and meta-analysis of published studies

Abord transradial versus transfémoral pour l'angioplastie coronaire percutanée dans le choc cardiogénique : l'expérience d'un centre radialiste et méta-analyse des études publiées

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KEYWORDS
Cardiogenic shock;
Vascular access;
Transradial access;

Summary
Background. — The transradial approach for percutaneous coronary intervention (PCI) is associated with a better outcome in myocardial infarction (MI), but patients with cardiogenic shock (CS) were excluded from most trials.

Abbreviations: CI, confidence interval; CS, cardiogenic shock; IABP, intra-aortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk; TIMI, thrombolysis in myocardial infarction.

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Death;
Major bleeding

Aims. — To compare outcomes of PCI for MI-related CS via the transradial versus transfemoral approach.
Methods. — A prospective cohort of 101 consecutive patients admitted for PCI for MI-related CS were treated via the transradial ($n=74$) or transfemoral ($n=27$) approach. Cox proportional hazards models adjusted for prespecified variables and a propensity score for approach were used to compare mortality, death/MI/stroke and bleeding between the two groups. A complementary meta-analysis of six studies was also performed.
Results. — Patients in the transradial group were younger ($P=0.039$), more often male ($P=0.002$) and had lower GRACE and CRUSADE scores ($P=0.003$ and 0.001, respectively) and rates of cardiac arrest before PCI ($P=0.009$) and mechanical ventilation ($P=0.006$). Rates of PCI success were similar. At a mean follow-up of 756 days, death occurred in 40 (54.1%) patients in the transradial group versus 22 (81.5%) in the transfemoral group (adjusted hazard ratio [HR]: 0.49, 95% confidence interval [CI] 0.28—0.84; $P=0.012$). The transradial approach was associated with reduced rates of death/MI/stroke (adjusted HR: 0.53, 95%CI: 0.31—0.91; $P=0.02$) and major bleeding (adjusted HR: 0.34, 95%CI: 0.13—0.87; $P=0.02$). The meta-analysis confirmed the benefit of transradial access in terms of mortality (relative risk [RR]: 0.63, 95%CI: 0.58—0.68) and major bleeding (RR: 0.43, 95%CI: 0.32—0.59).
Conclusion. — The transradial approach in the setting of PCI for ischaemic CS is associated with a dramatic reduction in mortality, ischaemic and bleeding events, and should be preferred to the transfemoral approach in radial expert centres.

MOTS CLÉS
Choc cardiogénique ;
Accès vasculaire ;
Voie radiale ;
Décès ;
Saignement majeur

Résumé
Contexte. — L'accès par voie radiale pour l'angioplastie coronaire percutanée est associé à un meilleur pronostic dans le contexte de l'infarctus du myocarde mais les patients en choc cardiogénique ont été exclus de la plupart des études.
But. — Il s'agit d'évaluer le pronostic des patients en choc cardiogénique en post-infarctus du myocarde traités par angioplastie par voie radiale en comparaison à la voie fémorale.
Méthodes. — Une cohorte prospective de 101 patients consécutifs admis pour angioplastie pour un choc cardiogénique lié à un infarctus du myocarde ont été traités par voie radiale ($n=74$) ou fémorale ($n=27$). Un modèle de Cox ajusté sur des variables pré-spécifiées et un score de propension pour la voie d'abord ont été utilisés pour évaluer la mortalité, le critère combiné décès/infarctus/accident vasculaire cérébral et les saignements entre les 2 groupes. Une méta-analyse complémentaire incluant 6 études a également été réalisée.
Résultats. — Dans le groupe radial, les patients étaient plus jeunes ($p=0,03$), plus souvent masculin ($p=0,002$), avaient un score de GRACE et de CRUSADE ($p=0,002$ et 0,001), un taux d'arrêt cardiaque avant angioplastie ($p=0,009$) et de ventilation mécanique ($p=0,006$) plus faible. Le succès des angioplasties était comparable entre les 2 groupes. Sur un suivi moyen de 756 jours, un décès est survenu chez 40 patients (54,1 %) dans le groupe radial contre 22 (81,5 %) dans le groupe fémoral (HR : 0,49 ; IC 95 % : 0,28—0,84 ; $p=0,01$). La voie radiale était associée à une réduction du critère combiné décès/infarctus/accident vasculaire cérébral (HR : 0,53 ; IC 95 % : 0,31—0,91 ; $p=0,02$) et des saignements majeurs (HR : 0,34 ; IC 95 % : 0,13—0,87 ; $p=0,02$). La méta-analyse a confirmé le bénéfice de la voie radiale sur la mortalité (RR : 0,63 ; IC 95 % : 0,58—0,68) et les saignements majeurs (RR : 0,43 ; IC 95 % : 0,32—0,59).
Conclusion. — La voie radiale pour l'angioplastie coronaire dans le cadre du choc cardiogénique d'origine ischémique est associée à une réduction majeure de la mortalité, des événements ischémiques et hémorragiques et doit être préférée à l'approche fémorale dans les centres radialistes experts.

Background

Cardiogenic shock (CS), with a reported incidence of 4—7%, is the leading cause of death in patients with acute myocardial infarction (MI) [1,2]. The randomized SHOCK trial showed that a strategy of early revascularization, with surgery or percutaneous coronary intervention (PCI), was associated with higher survival rates [3] than a strategy of

initial medical stabilization. The rate of PCI in CS patients has increased markedly since the publication of these results [1].

The advantage of the transradial approach for PCI over transfemoral access in the setting of ST-segment elevation myocardial infarction has been reported by different trials [4—6]. In a recent meta-analysis [7], transradial PCI was associated with a decreased risk of mortality and major bleeding compared with transfemoral PCI. Recent European Society of Cardiology guidelines for the management of patients with ST-elevation MI state that radial access for PCI should be preferred if performed by an experienced radial operator [8], and a recent expert consensus paper suggested the use of transradial procedures if the radial artery is palpable in patients with CS [9]. However, most studies excluded patients with CS, and the use of transradial PCI in CS has been scarcely assessed.

The aim of our study was to compare outcomes — major adverse cardiac events and bleeding complications — in a cohort of consecutive patients with ischaemic CS treated with transradial versus transfemoral PCI in a radial-first centre. We also performed a meta-analysis of the current and similar published studies evaluating the outcome of PCI in CS based on vascular access site.

Methods

Patient selection

Between April 2004 and December 2011, 6245 patients were referred to our hospital for PCI for MI. Radial access was the default approach for performing PCI in our centre during the whole period in all settings. PCI was performed by experienced interventional cardiologists for both transradial (>200 radial PCIs/year/operator) and transfemoral access. Among all the patients, 408 (6.5%) were diagnosed with CS before angiography. The criteria for CS were systolic blood pressure <90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure >90 mmHg and end-organ hypoperfusion (cool extremities or urine output <30 mL/hour with a heart rate >60 beats per minute) [3]. Only patients with CS of ischaemic origin occurring before angiography with an indication for PCI were included. We excluded patients with CS of other aetiologies and those who could have undergone angiography through one of the approaches only (extracorporeal membrane oxygenation before PCI, patients with bilateral mammary artery or radial coronary bypass grafts, severe peripheral artery disease or radial arteriovenous fistula). Both vascular access and intra-aortic balloon pump (IABP) use were at the discretion of the operators. Patients' initial clinical characteristics, including GRACE and CRUSADE scores [10,11], pharmacological treatment, IABP status, details of the procedure, and clinical evolution during the course of the patients' hospital stay and after discharge, were collected.

Procedure

The use of antiplatelet agents, anticoagulants and glycoprotein IIb/IIIa inhibitors was at the treating physician's discretion, consistent with current guidelines. All PCI procedures were retrospectively reviewed by two independent interventional cardiologists, to collect supplementary procedural characteristics. Successful PCI was defined as a residual diameter stenosis of <30% and a thrombolysis in myocardial infarction (TIMI) 3 flow in the culprit vessel after the procedure. After the procedure, femoral access closure was managed by manual compression ($n = 9$; 33.3%), vascular closure device ($n = 6$; 22.2%) or replacement by IABP ($n = 12$; 44.4%). In the case of a radial approach, haemostasis was achieved with a compressive device (TR Band; Terumo, Tokyo, Japan).

Outcomes

The primary endpoint of the study was the occurrence of death. Secondary major endpoints were the occurrence of the composite of death, stroke or new MI, major bleeding and net clinical benefit. Cardiac death was defined as any death due to a cardiac cause. Deaths from unknown cause were considered as cardiac. New MI was defined as new ischaemic symptoms lasting >20 minutes and new or recurrent ST-segment elevation or depression >1 mV in at least two contiguous leads, associated with a new >20% increase in cardiac biomarkers levels, not attributable to the evolution of the index MI.

Minor and major bleedings were defined according to the TIMI definition [12]. Bleeding was further categorized as access site related or non-access site related. Follow-up data (rehospitalization for heart failure, blood transfusions and new revascularization) were collected. New revascularization was defined as any revascularization procedure performed because of angiographic stenosis or thrombosis associated with clinical and/or objective evidence of myocardial ischaemia. Net clinical benefit was defined by the composite of death, stroke, MI or major bleeding.

The patients, their families or their general practitioner and/or cardiologist were contacted in December 2012 to assess clinical follow-up after discharge in-hospital survivors.

Meta-analysis

We conducted a systematic literature review by formal searches of the MEDLINE electronic database covering the period from January 2000 to June 2014. Relevant studies were identified using a combination of medical subject headings, including the following terms: 'cardiogenic shock', 'myocardial infarction', 'PCI', 'vascular access', 'transradial access' and 'radial approach'. References from reviews and selected articles were also reviewed for potential relevant citations. Studies were selected by two independent reviewers (V.R. and A.L.). We restricted our analysis to studies that met all of the following inclusion criteria: outcome comparison of transradial and transfemoral access for PCI in CS patients; and available data on mortality. Exclusion criteria were ongoing studies and irretrievable data. The endpoints were all-cause death, major bleeding and transfusion.

Statistical analysis

Groups were defined by transradial or transfemoral approach. Continuous variables are expressed as mean

values ± standard deviations and were compared using Student's test. Categorical variables are expressed as numbers of patients and percentages and were compared using the χ^2 test. The Kaplan-Meier estimator and log-rank test were used to compare survival between the two groups. A Cox proportional hazards model adjusted for prespecified variables (age, sex, previous peripheral vascular disease, GRACE score, CRUSADE score [for bleeding only] and need for IABP) was used for the primary analysis to assess mortality, combined endpoints of death/stroke/recurrent MI, bleeding and net clinical benefit, in the two groups. A complementary analysis was performed using a Cox proportional hazards model adjusted for the prespecified variables as well as deciles of the propensity score for choosing radial access. The propensity score was calculated using a logistic regression model that included the following prespecified variables: age, sex, diabetes mellitus, cigarette smoker, weight, history of peripheral vascular disease, vitamin K antagonist treatment and systolic blood pressure.

The results of the meta-analysis are presented as relative risks with 95% confidence intervals (CIs). Outcomes from individual studies were combined using the Mantel-Haenszel fixed-effect (primary analysis) and random-effect (sensitivity analysis) models. The fixed-effect model's relative risks are reported in the text. All tests were two-tailed and a *P*-value of <0.05 was considered statistically significant.

R software, version 3.0.0 (2013-04-03) for MacOS (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis and meta-analysis.

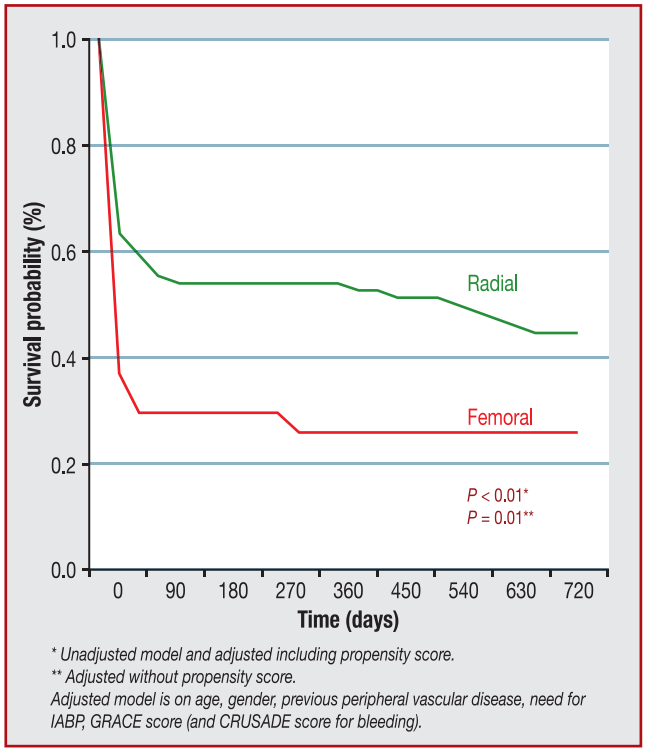

Figure 1. Kaplan-Meier survival curves for radial versus femoral groups ($P < 0.01$), with adjustment for age, sex, previous peripheral vascular disease, need for IABP, GRACE score (and CRUSADE score for bleeding).

Results

A total of 101 consecutive patients were included, of whom 74 (73.3%) were treated by the transradial approach and 27 (26.7%) by the transfemoral approach. Patients' clinical characteristics and treatments are detailed in Table 1. Patients aged >75 years accounted for 41.6% ($n = 42$) of the cohort, with a similar distribution between groups.

Procedure

Angiographic findings and PCI procedures are summarized in Table 2, showing similar rates of procedural success (overall PCI success rate of 70.3%). Final TIMI 3 flow was observed in 81 patients (80.2%) and did not differ between groups (62 patients in the transradial group versus 19 patients in the transfemoral group; $P = 0.13$). There were no crossovers between the groups.

Outcomes

During the 2.1 ± 2.6 years of follow-up, 62 patients (61.4%) died (Fig. 1). Outcomes are detailed in Table 3.

In the transradial group, IABP-related complications were one femoral artery dissection, one acute lower limb ischaemia and two local venous thromboses. In the transfemoral group, IABP-related complications were one artery dissection, one intestinal ischaemia, one minor bleeding, one local venous thrombosis and one documented device infection.

All unadjusted and adjusted Cox proportional hazards models demonstrated that the transradial approach compared with the transfemoral approach was associated with an improved outcome for all endpoints, independent of covariables. All results are detailed in Table 4.

Meta-analysis

Six studies, including ours, were included in the meta-analysis (Fig. 2) [13—17]. Mortality data were collected at 30 days for all studies except one [17], where only in-hospital mortality was reported. Major bleeding and transfusion data were collected during hospital stay, except in one study [15] where major bleeding (but not transfusion) was reported at 30 days. Major bleeding complications were defined according to the TIMI haemorrhage classification [13] or study-specific criteria [14—17]. Patients' major characteristics and endpoint results are detailed for each study in Table 5.

The meta-analysis confirmed that transradial access was associated with lower rates of mortality (relative risk [RR]: 0.63, 95%CI: 0.58—0.68; Fig. 3A), major bleeding (RR: 0.43, 95%CI: 0.32—0.59; Fig. 3B) and transfusion (RR: 0.49, 95%CI: 0.35—0.67; Fig. 3C), without heterogeneity among studies except for transfusion rates.

Discussion

Our study showed that the transradial approach for PCI in patients with acute MI complicated by CS could be used successfully in >70% of the cases in a 'radial-first approach'

Table 1 Patients' characteristics at admission.

	All ($n=101$)	Radial ($n=74$)	Femoral ($n=27$)	P
Baseline patient characteristics				
Age (years)	68.0 ± 13.0	67.0 ± 13.6	73.0 ± 10.3	0.039
Men	69 (68.3)	57 (77.0)	12 (44.4)	0.002
Risk factors				
Systemic hypertension	55 (54.5)	39 (52.7)	16 (59.3)	0.56
Diabetes mellitus	29 (28.7)	18 (24.3)	11 (40.7)	0.11
Hyperlipidaemia	42 (41.6)	31 (41.9)	11 (40.7)	0.92
Current cigarette smoker	28 (27.7)	23 (31.1)	5 (18.5)	0.21
Family history of premature coronary disease	12 (11.9)	10 (13.5)	2 (7.4)	0.40
Body mass index (kg/m^2)	26.9 ± 4.9	27.3 ± 5.1	25.9 ± 4.1	0.21
History				
Myocardial infarction	14 (13.9)	9 (12.2)	5 (18.5)	0.41
Coronary artery bypass	2 (2.0)	2 (2.7)	0 (0)	0.39
PCI	10 (9.9)	7 (9.5)	3 (11.1)	0.81
Peripheral vascular disease	9 (8.9)	6 (8.1)	3 (11.1)	0.64
Vitamin K antagonist treatment	7 (6.9)	5 (6.8)	2 (7.4)	0.91
Presenting characteristics				
Creatinine clearance rate (mL/min)	55.8 ± 27.0	58.4 ± 25.5	48.6 ± 29.9	0.11
Clearance <30 mL/min	14 (13.9)	5 (6.8)	9 (33.3)	0.001
Systolic blood pressure (mmHg)	77.4 ± 14.2	78.6 ± 13.0	73.9 ± 16.7	0.14
Diastolic blood pressure (mmHg)	49.3 ± 12.6	50.6 ± 12.2	45.5 ± 13.1	0.07
Heart rate (beats per minute)	80.6 ± 31.8	77.5 ± 31.6	89 ± 31.2	0.11
Cardiac arrest before PCI	26 (25.7)	14 (18.9)	12 (44.4)	0.009
Shock at admission	55 (54.5)	40 (54.1)	15 (55.6)	0.89
Time between shock and PCI (hours)	3.8 ± 10.6	4.1 ± 11.9	3.1 ± 5.5	0.67
Mechanical ventilation	56 (55.4)	35 (47.3)	21 (77.8)	0.006
LVEF at presentation (%)	36.9 ± 13.3	37.3 ± 14.3	35.9 ± 10.3	0.64
GRACE score	250.8 ± 34.1	244.7 ± 31.3	267.4 ± 36.5	0.003
CRUSADE score	5.1 ± 12.2	48.7 ± 11.3	57.4 ± 12.5	0.001
ST-segment elevation	91 (90.1)	67 (90.5)	24 (88.9)	0.81
Treatment				
Aspirin	101 (100)	74 (100)	27 (100)	—
Clopidogrel	99 (98.0)	72 (97.3)	27 (100)	0.39
Prasugrel	2 (2.0)	2 (2.7)	0 (0)	0.39
Unfractionated heparin	87 (86.1)	63 (85.1)	24 (88.9)	0.63
Enoxaparin	4 (4.0)	4 (5.4)	0 (0)	0.22
Fondaparinux	7 (6.9)	5 (6.8)	2 (7.4)	0.91
Bivalirudin	1 (1.0)	1 (1.4)	0 (0)	0.54
Glycoprotein IIb/IIIa inhibitor	35 (34.7)	28 (37.8)	7 (25.9)	0.27
Prehospital fibrinolysis[a]	39 (42.9)	31 (46.3)	8 (33.3)	0.26
IABP	71 (70.3)	51 (68.9)	20 (74.1)	0.62
Before PCI	30 (29.7)	25 (33.8)	5 (18.6)	0.07
Duration (days)	3.5 ± 1.9	3.44 ± 1.9	3.8 ± 2.1	0.82
Inotropic drugs	94 (93.1)	68 (91.9)	26 (96.3)	0.44

Data are expressed as mean ± standard deviation or number (%). IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.
[a] In patients with ST-segment elevation.

centre with no crossover to femoral access. This approach appeared to be safer, with a three-fold lower incidence of bleeding complications compared with the transfemoral approach, and was associated with a higher survival rate and a reduction in major adverse cardiac events. The meta-analysis (including our data) confirmed the dramatic reduction in mortality and major bleeding rates associated with the transradial approach.

The SHOCK trial demonstrated that early revascularization in patients with acute MI complicated by CS reduced mortality in patients aged <75 years [3]. As a consequence, rates of PCI in CS patients have dramatically increased in

Table 2 Angiographic data.

	All ($n=101$)	Radial ($n=74$)	Femoral ($n=27$)	P
Angiography				
Right radial approach	98 (97)	72 (97.3)	26 (96.3)	0.79
MVD	78 (77.2)	58 (78.4)	20 (74.1)	0.41
LM stenosis >50%	21 (20.8)	16 (21.6)	5 (18.5)	0.73
Culprit coronary artery				
LAD	48 (47.5)	33 (44.6)	15 (55.6)	0.33
LCx	8 (7.9)	6 (8.1)	2 (7.4)	0.91
RCA	31 (30.7)	24 (32.4)	7 (25.9)	0.53
LM	13 (12.9)	10 (13.5)	3 (11.1)	0.75
Saphenous graft	1 (1.0)	1 (1.4)	0 (0)	0.54
Approach				
≤6 French	98 (97.0)	74 (100)	24 (88.9)	0.004
Number of diagnostic catheters	1.0 ± 0.8	1.1 ± 0.9	0.7 ± 0.7	0.38
PCI				
Number of PCI catheters	1.6 ± 0.8	1.5 ± 0.7	1.7 ± 0.8	0.16
Thrombectomy	12 (11.9)	11 (14.9)	1 (3.7)	0.13
Bare-metal stent	79 (78.2)	54 (73.0)	25 (92.6)	0.034
Number of stents	1.7 ± 0.8	1.6 ± 0.8	2.0 ± 0.9	0.21
Number of revascularized vessels	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	0.79
Complete revascularization	67 (66.3)	51 (68.9)	16 (59.3)	0.36
Procedure success	71 (70.3)	54 (73.0)	17 (63.0)	0.33
Procedure time (minutes)[a]	72.2 ± 40.3	72.6 ± 38.8	71.0 ± 45.8	0.87
Fluoroscopy time (minutes)[b]	14.9 ± 9.8	15.6 ± 9.8	12.7 ± 9.8	0.24
Contrast media volume (mL)[c]	221.6 ± 102.8	231.4 ± 108.8	192.9 ± 78.0	0.15
Complications				
No-reflow	13 (12.9)	11 (14.9)	2 (7.4)	0.32
Coronary dissection	2 (2.0)	2 (2.7)	0 (0)	0.39
Side-branch occlusion	3 (3.0)	1 (1.4)	2 (7.4)	0.11
Distal embolization	6 (5.9)	4 (5.4)	2 (7.4)	0.71

Data are expressed as number (%) or mean ± standard deviation. ACE: angiotensin-converting enzyme; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LM: left main; MVD: multivessel disease; PCI: percutaneous coronary intervention; RCA: right coronary artery.

[a] Data available for 90 patients.

[b] Data available for 85 patients.

[c] Data available for 79 patients.

the last 20 years [1]. In parallel, the radial approach has been used increasingly for PCI. The benefits of transradial access for PCI compared with transfemoral access in the setting of ST-elevation MI have been reported in different trials [4–6]. However, most of these trials excluded patients with CS. So far, studies focusing on transradial access for PCI in CS patients are scarce [13–17]. Reported rates of radial approach in such studies range from 26–70% of all procedures. In our study, the rate of PCI via radial access was higher (73.3%) than most studies; this finding may reflect the high expertise in radial use in our centre, where the radial approach started more than 5 years before the current data collection period. Mamas et al. [16] recently reported data on the nationwide practice of PCI in the UK, showing highly variable rates of radial approach use between centres, with an overall rate of use of only 26%. The feasibility of PCI by radial access is clearly lower than the 90% recently described in a 'real-life' population of uncomplicated ST-elevation MI [18]. Indeed, CS is a strong independent predictor of transradial approach PCI failure [19]. Nevertheless, the rate of radial access in our study remained high, considering the critical basal status of our population, underlined by the high proportion of patients requiring inotropic drugs – nearly six-fold higher than the rate reported by Mamas et al. [16]. This is probably a consequence of their definition of CS, with a blood pressure threshold <100 mmHg rather than the <90 mmHg usually used in other studies. Our procedural success rate of 70.3% is broadly similar to previous series in CS [13,14,16], with the exception of one study that reported an impressive success rate of 95.3% [15].

The clinical benefit of transradial access in terms of bleeding and mortality is the most important finding of our study. The benefits of transradial compared with transfemoral access for PCI in the setting of ST-elevation MI have been reported by different trials [4–6]. A meta-analysis of recent trials showed that, compared with femoral access, radial access was associated with a nearly two-fold reduction in the odds of death and a 1.5-fold reduction in the odds

Table 3 Clinical outcomes.

	All ($n=101$)	Radial ($n=74$)	Femoral ($n=27$)	P
In-hospital outcome				
Death	47 (46.5)	28 (37.8)	19 (70.4)	0.0037
PCI vascular site complication	4 (4.0)	0 (0)	4 (14.8)	0.0007
IABP vascular site complication	9 (8.9)	4 (5.4)	5 (18.5)	0.041
Transfusion	30 (29.7)	20 (27.0)	10 (37.0)	0.33
Bleeding				
Any	18 (17.8)	10 (13.5)	8 (29.6)	0.06
Major	5 (5.0)	1 (1.4)	4 (14.8)	0.006
Maximum Hb loss (g/dL)	0.73 ± 1.8	0.5 ± 1.6	1.4 ± 2.2	0.021
Outcome at follow-up				
Follow-up time (days)	756.9 ± 961.5	864.5 ± 979.0	462.0 ± 860.9	0.06
Death	62 (61.4)	40 (54.1)	22 (81.5)	0.012
Cardiac death	51 (50.5)	35 (47.3)	16 (59.3)	0.29
Recurrent myocardial infarction	4 (4.0)	3 (4.1)	1 (3.7)	0.94
Any new revascularization	10 (9.9)	9 (12.2)	1 (3.7)	0.21
Stroke	1 (1.0)	0 (0)	1 (3.7)	0.10
Rehospitalization for HF	8 (7.9)	7 (9.5)	1 (3.7)	0.34
Composite endpoints				
Death and new MI	64 (63.4)	42 (56.8)	22 (81.5)	0.022
Death, stroke or new MI	64 (63.4)	42 (56.8)	22 (81.5)	0.022
Bleeding				
Any	21 (20.8)	12 (16.2)	9 (33.3)	0.06
Major	5 (5.0)	1 (1.4)	4 (14.8)	0.006

Data are expressed as number (%) or mean ± standard deviation. Hb: haemoglobin; HF: heart failure; IABP: intra-aortic balloon pump; MI: myocardial infarction; PCI: percutaneous coronary intervention.

of major adverse cardiac events in ST-elevation MI patients undergoing primary PCI [7]. However, patients with CS were excluded from most of these trials, except RIFLE-STEACS, where an IABP was used in 8% of the patients [6]. Nevertheless, the details of such a subgroup are not reported. Herein we reported our radial experience in CS, showing a substantial reduction in mortality, major adverse cardiac events and bleeding associated with radial access. The mortality reduction in similar studies was variable but consistent between the three largest studies [13,16,17]. Nevertheless, the results of these studies may be tempered, as patients with transfemoral access were more critically ill, as outlined by higher rates of mechanical ventilation before PCI and diabetes [13,16,17], more frequent use of inotrope or IABP support and renal insufficiency [16,17] and lower systolic and diastolic pressures [17] compared with the transradial group. Concordantly in our study, the transradial approach was associated with lower predictors of poor outcome, as attested by lower GRACE and CRUSADE scores [10,11,20]. Nevertheless, the persistence of a similar superiority of the transradial approach after adjustment for co-variables, including risk scores and the propensity score, highlights the probable independence of such a relationship. The similar magnitude of mortality reduction in the current study and prior studies also tends to underscore the robustness of the findings.

Table 4 Cox proportional hazard models.

	Unadjusted		Adjusted[a]		PS-adjusted[b]	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
All-cause death	0.46 (0.27–0.77)	<0.01	0.49 (0.28–0.84)	0.01	0.37 (0.18–0.75)	<0.01
Death, stroke or new infarction	0.49 (0.29–0.83)	<0.01	0.53 (0.31–0.91)	0.02	0.37 (0.18–0.75)	<0.01
Bleeding	0.30 (0.12–0.71)	<0.01	0.34 (0.13–0.87)	0.02	0.33 (0.12–0.94)	0.04
Net clinical benefit	0.43 (0.26–0.70)	<0.001	0.52 (0.30–0.89)	0.02	0.39 (0.20–0.78)	<0.01

CI: confidence interval; HR: hazard ratio.
[a] Adjusted for age, sex, previous peripheral vascular disease, need for intra-aortic balloon pump and GRACE score (and CRUSADE score for bleeding).
[b] Further adjusted for propensity score.

Table 5 Patients' characteristics and endpoints from studies included in the meta-analysis.

	Rodriguez ($n=122$)	Bernat ($n=197$)	Fujii ($n=81$)	Mamas ($n=7231$)	Iga ($n=85$)	Roule ($n=101$)
Radial approach	80 (65.6)	108 (55.0)	38 (46.9)	1877 (26.0)	60 (70.6)	74 (73.3)
Age (years)	66.0 ± 12.0	66.0 ± 12.0	71.9 ± 11.0	67.2 ± 0.3	68.8 ± 11.4	68.0 ± 13.0
Men	102 (83.6)	140 (77.0)	61 (75.3)	5055 (70.1)	68 (80.0)	69 (68.3)
Risk factors						
Systemic hypertension	70 (57.4)	99 (50.3)	71 (87.6)	3149 (43.5)	48 (56.5)	55 (54.5)
Diabetes mellitus	53 (43.4)	37 (18.8)	45 (55.6)	1338 (18.5)	30 (35.3)	29 (28.7)
Hyperlipidaemia	67 (55.0)	82 (42.0)	44 (54.3)	3060 (42.3)	39 (45.9)	42 (41.6)
Active cigarette smoker	40 (32.8)	80 (41.0)	47 (58.0)	1754 (24.3)	45 (52.9)	28 (27.7)
Family history of coronary disease	–	–	9 (11.1)	–	16 (18.8)	12 (11.9)
Body mass index (kg/m^2)	27.4 ± 5.0	26.0 ± 4.0	23.4 ± 3.8	–	23.6 ± 3.8	26.9 ± 4.9
History						
Myocardial infarction	41 (33.6)	31 (16.0)	11 (13.6)	1506 (20.8)	8 (9.4)	14 (13.9)
Coronary bypass	5 (4.1)	2 (1.0)	1 (1.2)	331 (4.6)	1 (1.2)	2 (2.0)
PCI	10 (8.2)	19 (9.8)	7 (8.6)	865 (12.0)	8 (9.4)	10 (9.9)
Peripheral vascular disease	41 (33.6)	–	–	–	0 (0)	9 (8.9)
ST-segment elevation	89 (72.9)	197 (100)	81 (100)	5493 (76.0)	78 (91.8)	91 (90.1)
Time between shock and PCI (minutes)	227 (106–435)	231 (151–389)	115.2 ± 45.1	–	102.9 ± 38.7	228.0 ± 636.0
Biology at presentation						
Creatinine clearance rate (mL/min)	61 ± 32.0	72 ± 35.0	51.2 ± 17.8	–	–	55.8 ± 27.0
Hb (g/dL)	–	13.8 ± 2.0	13.0 ± 3.4	–	–	12.8 ± 2.2
Systolic blood pressure (mmHg)	76.0 ± 17.0	–	77.6 ± 39.6	–	46.8 ± 44.3	77.4 ± 14.2
Diastolic blood pressure (mmHg)	46.0 ± 14.0	–	31.9 ± 32.1	–	–	49.3 ± 12.6
Heart rate (beats per minute)	87.0 ± 30.0	–	75.9 ± 29.8	–	54.5 ± 41.4	80.6 ± 31.8
Cardiac arrest before PCI	–	–	38 (46.9)	–	26 (30.6)	26 (25.7)
Mechanical ventilation	61 (50.0)	131 (66.5)	–	1954 (27.0)	–	56 (55.4)
LVEF at presentation (%)	33.0 ± 15.0	–	–	–	42.8 ± 15.5	36.9 ± 13.3

Table 5 (*Continued*)

	Rodriguez ($n=122$)	Bernat ($n=197$)	Fujii ($n=81$)	Mamas ($n=7231$)	Iga ($n=85$)	Roule ($n=101$)
Aspirin	109 (89.3)	—	—	—	—	101 (100)
Clopidogrel	84 (68.8)	—	—	—	—	99 (98.0)
Heparin	46 (37.7)	—	—	—	—	97 (90.1)
Glycoprotein IIb/IIIa inhibitors	60 (49.2)	80 (41.0)	—	3954 (54.7)	—	35 (34.7)
IABP	52 (42.6)	88 (45.0)	54 (66.7)	2446 (33.8)	76 (89.4)	71 (70.3)
Inotropic drugs	88 (72.1)	—	—	1153 (15.9)	—	94 (93.1)
Procedure success	92 (75.4)	—	78 (96.3)	—	81 (95.3)	71 (70.3)
Final TIMI 3 grade	—	134 (68.0)	66 (81.5)	—	—	81 (80.2)
Procedure time (minutes)	—	47 (35—66)	125.1 ± 46.4	—	—	72.2 ± 40.3
Fluoroscopy time (minutes)	15.8 ± 11.6	10 (6—17)	—	—	30.8 ± 18.3	14.9 ± 9.8
Dose surface product (cGy.cm^2)	2842.5 ± 5101.5	—	—	—	1225.0 ± 886.0	4723.2 ± 3303.6
Contrast media volume (mL)	244.0 ± 129.0	170 (130—200)	237.1 ± 102.1	—	184.1 ± 66.5	221.6 ± 102.8
Endpoints						
Death	53 (43.4)	91 (46.2)	22 (27.2)	2296 (31.8)	26 (30.6)	47 (46.5)
Major bleeding	15 (12.3)	36 (18.3)	1 (1.2)	192 (3.0)	11 (12.9)	5 (5.0)
Transfusion	24 (19.7)	41 (20.8)	4 (4.9)	127 (1.8)	—	30 (29.7)

Data are expressed as number (%), mean ± standard deviation or median (interquartile range). Hb: haemoglobin; LEVF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction.

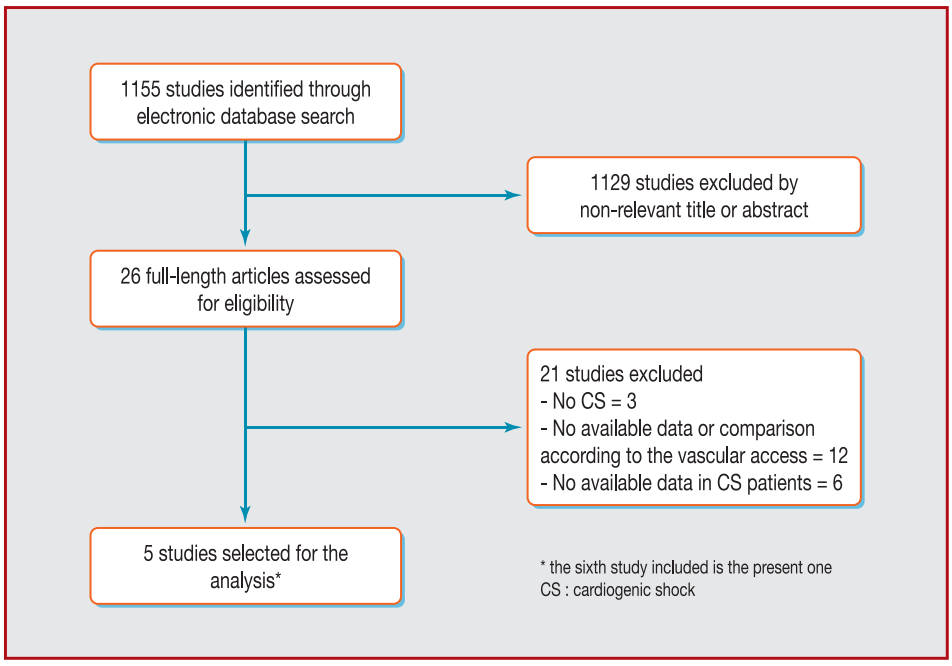

Figure 2. Flow diagram of the study selection.

The proportion of patients with ST-elevation MI and non-ST-elevation MI differed between studies and may explain some differences. Indeed, the benefit of radial access on mortality was not observed in patients with non-ST-segment elevation acute coronary syndrome in the RIVAL trial [5]. However, our meta-analysis confirmed the overall reduction of mortality in CS with radial access. Moreover, the benefits of transradial access in our cohort persisted despite high rates of IABP use (70.3%), as previously described in the RADIAL PUMP UP registry [21]. In the setting of CS of ischaemic origin, the prognosis is not related to the presence of ST-segment elevation, but to revascularization success, the extent of haemodynamic compromise and possibly periprocedural complications, such as bleeding.

Extensive data have shown that bleeding and transfusion in ACS are associated with a high risk of mortality [22,23]. Patients with an acute coronary syndrome complicated by CS are at higher risk of major bleeding compared with those without CS [2], and CS itself is an independent risk factor for bleeding [22]. ST-elevation MI patients represent the majority of patients with CS in published studies [1,2], as well as in our study (90%). Such patients are treated with potent combinations of antiplatelet and antithrombotic regimens, including fibrinolytic therapy. Hence the association between bleeding and mortality in this population is a plausible explanation for the benefit of radial access in terms of the primary endpoint and mortality rates in patients with ST-elevation MI, but not in those with non-ST-elevation MI, in the RIVAL trial [5]. The rate of major bleeding in our cohort was similar to those in previous studies in general acute coronary syndrome populations [23], but lower than those reported in patients with CS [13,15,17], despite an important use of prehospital fibrinolysis, similar demographic characteristics and overall mortality rate. This may be explained by the 70% radial access rate and the use of smaller diameter sheaths (5F and 6F) in our centre. Two other studies reported a lower rate of major bleeding [14,16]. However, under-reporting of bleeding complications is a common bias: outcome data were not available for 10% of the cohort in one study [16], and no precise definition of bleeding was provided in another study [14]. Rates of major bleeding in general and access site bleeding were both lower in the transradial group in our study. Major bleeding at the vascular site represents nearly 30% of the major bleeding in ACSs [22,24], but this rate reaches nearly 50% in patients with ST-elevation MI [25]. By reducing vascular access site complication, the transradial approach has been reported to reduce transfusion rates by 50% and to be associated with a significant reduction in 30-day and 1-year mortality [26]. One major advantage of the primary transradial approach in a critically ill population, particularly the elderly (>40% of our patients), is that these patients are at highest risk of complications related to the transfemoral approach [27]; this may also be an explanation for our results.

The majority of bleedings are, however, non-access site complications [22,24]. As the vascular access in our study was not randomized, we could not exclude selection bias. Such a bias was minimized in our study, as the model adjusted for the propensity score still confirmed the dramatic reduction in bleedings with radial access, with a similar HR. A recent meta-analysis showed that in the setting of primary PCI for ST-elevation MI, the risk of major bleeding was halved with the radial approach [7]. When considering studies in CS patients, the reduction in major bleeding remained variable, highlighting the issue of bleeding definitions. However, our meta-analysis also showed a two-fold decrease in both major bleeding and transfusion with the transradial approach, without significant heterogeneity among studies.

Despite overwhelming results in favour of the radial approach, this access site is considered challenging by some

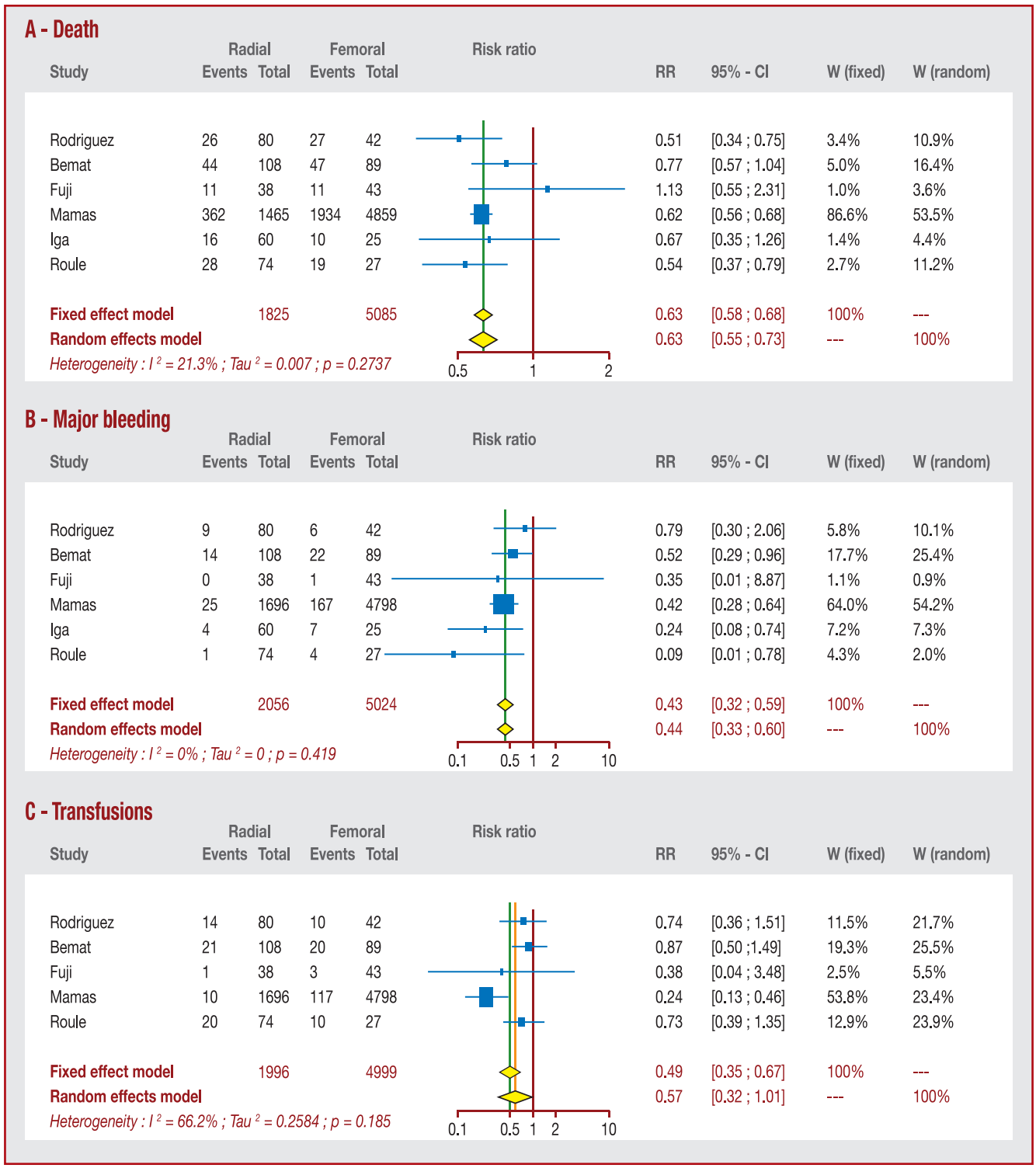

Figure 3. Forest plot of included studies for (A) death, (B) major bleeding and (C) transfusion with radial versus femoral approach. CI: confidence interval; RR: relative risk; W: weight.

operators. The transradial technique requires specific skill sets and follows a significant learning curve. The femoral artery seems to remain the preferred access site in the most serious cases, even in radial-experienced centres. One explanation may be a poor or absent radial pulse resulting from profound haemodynamic compromise. Supporting the latter explanation, Bernat et al. [13] found that an intravenous norepinephrine bolus, by transiently increasing blood pressure, was helpful in obtaining radial access. Haematomas or radial artery spasm or thrombosis, following a prior puncture of the radial artery for arterial blood sampling or invasive blood pressure monitoring, may be other

reasons for the use of femoral artery access. The demographic characteristics of patients with CS — high rates of the elderly and women — may also explain the higher rates of femoral access, because of the anticipation of potential access difficulties in such patients. The less restrictive choice of sheath size (>6F) with femoral access may also explain its preference in this setting. Finally, some operators may prefer the femoral approach to have the possibility of using IABPs or percutaneous ventricular assist devices during or following PCI, using the same access site. However, the pertinence of such a strategy is highly questionable given the high rate of IABP-related complications and the negative results of the IABP-SHOCK II trial [28].

Similar success rates can be achieved with both approaches with appropriate training, as outlined by the similar rates of procedural success and absence of site crossover in our study. Crossover to the contralateral artery is, in general, more frequent with the radial than with the femoral approach [7], but the rates of crossover decrease with operator experience. We did not find differences between the two approaches in terms of contrast volume and procedural or fluoroscopy times. This important finding underlines the fact that, when considered possible by experienced operators, radial access does not delay PCI, even in CS patients. A recent meta-analysis [7] in the setting of primary PCI for ST-elevation MI showed that, compared with the femoral approach, the procedure time with the radial approach was on average only 1.5 minutes longer, suggesting that procedural delay is not a significant concern. The benefits of radial access as well as radiation doses again depend on the experience of the centres. High-volume centres show better results with the radial approach in terms of access site crossover, major vascular complications and clinical outcome [24], and differences in radiation dose between radial and femoral access are present only in lower-volume centres and operators [29].

Considering the results of our study, we suggest that the transradial approach should be the default strategy in patients with CS, when considered feasible and performed by trained operators. In case of radial puncture failure, a contralateral radial artery approach may be preferred to a crossover to the femoral artery approach, again, if it is considered feasible and does not delay the PCI. In our study, we did not use ulnar access. Ipsilateral ulnar access after failure of attempted radial approach is not usually recommended because of the risk of radial artery occlusion and subsequent hand ischaemia in the event of ulnar artery puncture-related complications. Ulnar access may be an initial choice in cases of difficult radial anatomy, such as laterally positioned or deep radial access. Although not used in our study, ultrasound guidance may be helpful in such situations, to improve the success rate and time to access [30]. Based on these considerations we suggest the promotion and generalization of training in radial access, and the concept of radial artery as the first approach in any case.

Study limitations

This was an observational, non-randomized, relatively small-size cohort study, and several known or unknown variables associated with the endpoints may have not been analysed. Nevertheless, we tried to minimize such pitfalls by the use of adjusted models, improving the robustness of our analyses. We should add that all operators were highly skilled in the radial approach, thereby limiting the validity of our results in lower-volume radial centres.

The results of our meta-analysis should be tempered, as it is a pooled analysis of unadjusted outcomes from observational studies. An interaction between access site choice and outcomes remains possible.

Conclusion

The transradial approach for PCI for MI-related CS can be performed in the majority of patients; it is associated with significant reductions in mortality and ischaemic and bleeding events, leading to a dramatic net clinical benefit. The transradial approach may be recommended in such critically ill patients when performed by trained operators in experienced centres.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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