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Radial versus femoral access in patients with acute coronary syndrome undergoing complex PCI

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ABSTRACT (249 words)

Background. The comparative effectiveness of transradial (TRA) compared with transfemoral access (TFA) in acute coronary syndrome (ACS) patients undergoing complex percutaneous coronary intervention (PCI) remains unclear.
Objectives. To investigate the effects of TRA versus TFA for complex PCI.
Methods. Among 8,404 ACS patients in the MATRIX-Access, 5,233 received noncomplex and 1,491 complex PCI (TRA, n=777 and TFA, n=714), defined as three-vessel PCI, ≥3 implanted stents, ≥3 treated lesions, bifurcation stenting, total stent length > 60 mm or chronic total occlusion-PCI. Thirty-day co-primary outcomes were major adverse cardiovascular events (MACE) and the composite of MACE and BARC type 3-5 bleeding (net adverse cardiovascular events, NACE).
Results. 30-day MACE (hazard ratio [HR]: 0.94; 95% confidence interval [CI]: 0.72-1.22) or NACE (0.89; 95% CI: 0.69-1.14) did not differ between groups in the complex PCI group, whereas both primary endpoints were lower (HR 0.84; 95% CI 0.70-1.00, HR 0.83; 95% CI: 0.70-0.98, respectively) with TRA among noncomplex PCI patients, with negative interaction testing. Access-site BARC type 3 or 5 bleeding was lower with TRA, consistently among complex (HR 0.18; 95% CI: 0.05-0.63) and noncomplex (HR 0.41; 95% CI: 0.20-0.85) PCI patients, whereas the former group had a greater absolute risk reduction of 1.7% (number needed to treat: 59) due to their higher absolute risk.
Conclusions. Among ACS patients, PCI complexity does not affect the comparative efficacy and safety of TRA versus TFA. Among complex PCI patients, TRA reduced major access-site bleeding with similar relative but greater absolute risk benefit compared with noncomplex PCI.

Trial Registration: clinicaltrials.gov NCT01433627

KEYWORDS: transradial access; transfemoral access; complex percutaneous coronary intervention; acute coronary syndrome.

CONDENSED ABSTRACT (99 words)
We evaluated the comparative efficacy and safety of transradial (TRA) compared with transfemoral access (TFA) in patients with acute coronary syndrome undergoing complex percutaneous coronary intervention (PCI) in the MATRIX-Access trial. Co-primary outcomes were major adverse cardiovascular events (MACE) and a composite of MACE or BARC type 3-5 bleeding (net adverse cardiovascular events, NACE) at 1 year. The rates of MACE and NACE did not significantly differ with TRA versus TFA in the complex PCI group (n=1,491), whereas TRA was associated with lower rates of both primary endpoints in the noncomplex PCI group (n=5,233), with negative interaction testing.

ABBREVIATIONS AND ACRONYMS

ACS, Acute Coronary Syndrome
MATRIX, Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
MACE, major adverse cardiovascular events
NACE, net adverse clinical events
PCI, Percutaneous Coronary Intervention
STEMI, ST-Elevation Myocardial Infarction
NSTE-ACS, non-ST segment elevation acute coronary syndrome
BARC, Bleeding Academic Research Consortium
GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator
TIMI, Thrombolysis in Myocardial Infarction

INTRODUCTION

The adoption of transradial access (TRA) is recommended as default approach for the invasive management of patients with acute coronary syndrome (ACS) by current American and European guidelines (1,2), given the established benefit in reducing the risk of major bleeding and vascular complications compared with transfemoral access (TFA) (3–5). Furthermore, randomized clinical trials (RCT) have shown, albeit inconsistently, that TRA is associated with lower risk of all-cause mortality and acute kidney injury (AKI) (6,7) among ACS patients undergoing coronary angiography and/or percutaneous coronary intervention (PCI).

Technological advancements, such as sheathless guide catheters or thin-walled introducer sheaths, and increased operator's expertise with TRA have supported its use even in complex interventional procedures, such as PCI for chronic total occlusion (CTO), bifurcations, multivessel disease and calcified lesions. Patients undergoing complex PCI incur higher risks of ischemic and bleeding complications (8–10), owing to more frequent use of large bore catheters and higher prevalence of comorbidities such as peripheral artery disease (PAD) or chronic kidney disease (CKD). Therefore, TRA may be particularly advantageous among patients undergoing complex PCI. However, whether TRA is associated to similar procedural success and comparable clinical outcomes as well as lower major access site bleeding than TFA also for complex PCI remains unclear. Recently, a randomized trial demonstrated the superiority of TRA over TFA in reducing the composite of clinically relevant access-site related bleeding or vascular complications in patients undergoing complex PCI with large-bore guiding catheters (11). The bleeding benefit with TRA was entirely driven my minor bleeding complications. In addition, although not powered for ischemic outcomes, this trial demonstrated a numerical imbalance in MACE events in favor of TFA (12), which may reflect greater challenges in accomplishing a complex PCI through TRA. In addition, this study included only patients who underwent large-bore access site, which may have biased the results in favor of TRA, considering that a large-bore TRA may not always be feasible, requiring either cross-over to TFA or technique adaptations to a 6-french guiding catheter. No large study has so far investigated the effect of TRA on outcomes in ACS patients undergoing complex PCI. We sought therefore to investigate the comparative efficacy and safety of TRA versus TFA in ACS patients undergoing complex PCI from the *Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX* (MATRIX)-Access trial.

METHODS

Study design

This is a post-hoc analysis of the MATRIX trial, a program of 3 independent randomized controlled trials (ClinicalTrials.gov; NCT01433627) in patients with ACS undergoing invasive management (13). The first trial (MATRIX-Access) compared TRA versus TFA in 8,404 ACS patients (4,6), whereas MATRIX-Antithrombin and MATRIX Treatment Duration (6,14) compared bivalirudin versus unfractionated heparin (UFH) and prolonged post-PCI bivalirudin infusion versus short-term bivalirudin administration in patients undergoing PCI. Bivalirudin was given according to the product labeling and UFH was administered at a dose of 70 to 100 U or 50 to 70 U/kg in patients who did not receive or received Glycoprotein IIb/IIIa inhibitors (GPI), respectively.

The study design and main results of the MATRIX-Access trial have been previously published (4,6,13). Briefly, patients with non-ST elevation (NSTE)-ACS were eligible if they had a history consistent with new or worsening cardiac ischemia that occurred while they were at rest or with minimal activity within 7 days before randomization and met at least 2 high-risk criteria among the following: 1) age of 60 years or older, elevation of cardiac biomarkers, or electrocardiographic changes compatible with ischemia; and 2) if they were considered to be candidates for PCI after completion of coronary angiography. Patients with ST-segment elevation myocardial infarction (STEMI) were eligible if they presented within 12 h of the onset of symptoms or between 12 and 24 h after symptom onset if there was evidence of continued ischemia or previous fibrinolytic treatment. The main inclusion and exclusion criteria were previously reported (4,14). Operators' criteria for eligibility were prespecified in the MATRIX trial (13), qualifying operators with high expertise with TRA (≥50% of intervention in ACS with TRA and a number of TRA coronary intervention ≥75 within the previous 12 months). The trial was approved by the institutional review board at each participating site, and all patients gave written informed consent.

Study population

All participants enrolled in the MATRIX-Access trial were considered eligible for this analysis.

Complex PCI was defined as PCI with at least one of the following characteristics: three-vessels PCI, ≥3 implanted stents, ≥3 treated lesions, bifurcation with 2 stents implanted, total stent length > 60 mm or CTO-

PCI. These criteria were previously defined by Giustino et al (8) and are frequently used in clinical studies (9,10,15). Patients undergoing PCI without any of the above-mentioned criteria were classified as noncomplex PCI.

Follow-up and study outcomes

The endpoints of the MATRIX-Access trial have been previously reported (4,6). The two co-primary outcomes were MACE (the composite of all-cause mortality, myocardial infarction [MI], or stroke) and net adverse clinical events (NACE), defined as the composite of MACE or major bleeding not related to coronary artery bypass grafting (Bleeding Academic Research Consortium [BARC] type 3 or 5) at 30-days. Secondary outcomes included the composite of all-cause mortality, MI, stroke, urgent target vessel revascularization (TVR) or definite stent thrombosis, each component of the co-primary outcomes and cardiovascular mortality. Key secondary outcome was BARC type 3 or 5 at 30 days. 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. As secondary endpoints, ischemic and bleeding events were also evaluated at 1 year.
Sensitivity analyses were performed excluding patients with any crossover of the randomized access site or subjects undergoing staged procedures (i.e. only patients who underwent index PCI). An independent clinical events committee, blinded to treatment allocation, adjudicated all adverse events.

Statistical analysis

All analyses were performed according to the intention-to-treat principle. Differences across groups were assessed using the student t-test in case of continuous variables and the chi-square or Fisher exact test in case of categorical data. The cumulative incidence of the primary and secondary endpoints was estimated by the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated with Cox proportional-hazards models. The consistency of the treatment effect of TRA versus TFA between the complex and noncomplex PCI subgroups was evaluated with formal interaction testing. We performed stratified logistic regressions by subgroups, including center's annual volume of PCI, center's proportion of radial PCI, clinical presentation, age, gender, access sheath size, body mass index, diabetes mellitus, CKD, PAD, randomization

to bivalirudin or UFH. Continuous relation between procedure duration and MACE was assessed using restricted cubic splines. The analyses were done using Stata release 16.1 (StataCorp LLC, College Station, Texas).

RESULTS

Study population

Among 8,404 patients enrolled in the MATRIX-Access trial, 6,724 patients underwent PCI (**Online Figure 1**). Of those, 1,491 (22.2%) patients underwent complex PCI and 5,233 (77.8%) subjects noncomplex PCI. In the complex PCI group 777 were allocated to TRA and 714 subjects to TFA, whereas in the noncomplex PCI group 2,590 and 2,643 patients were randomized to TRA and TFA, respectively.

Baseline and procedural characteristics

Patients undergoing complex PCI were older and presented more frequently diabetes, previous MI, PAD and NSTE-ACS (**Online Table 1**). Patients who underwent complex PCI had more frequently lesions involving the left coronary system (particularly the left main) and had longer fluoroscopy and procedural times compared with the noncomplex PCI group (**Online Table 2**).

Baseline demographics and clinical presentation according to PCI complexity and randomized access site were well matched (**Table 1**). Patients allocated to TRA experienced crossover more frequently than those randomized to TFA, in either complex (10% vs 3%) or noncomplex PCI groups (5% vs 3%). Sheath size varied largely across the randomized access sites, with a significantly higher use of 6 Fr sheath in the TRA group and 7 Fr sheath in the TFA group. Angiographic and procedural characteristics, stratified by PCI complexity, were otherwise well balanced between groups (**Table 2)**. The prevalence of complex PCI features was also well balanced between the two access sites (**Online Figure 2)**.

Clinical outcomes in patients with complex PCI

Thirty-day and 1-year clinical outcomes in patients undergoing complex PCI are shown in **Figure 1** and **Online Table 3**. Complex PCI was associated with an higher risk of MACE (14.8% vs 9.7%; HR: 1.56; 95% CI: 1.33–1.82; P < 0.001) and NACE (16.4% vs 10.9%; HR 1.54, 95% CI: 1.32 to 1.79; p < 0.001) at 30 days, which was driven by an increased risk of all-cause mortality and MI. The risk of BARC type 3 or 5 bleeding was

numerically increased in the complex PCI group at 30 days (2.8% vs 2.0%; HR: 1.38; 95% CI: 0.96 to 1.97; P= 0.083), whereas complex PCI resulted in a significantly higher risk of access site-related BARC 3 or 5 bleeding (1.2% vs 0.7%; HR: 1.82; 95% CI: 1.03 to 3.22; P= 0.039) at 30 days.

Clinical outcomes according to the randomized access site and PCI complexity

Table 3 and **Online Table 4** summarize the primary and secondary outcomes at 30 days and 1 year according to PCI complexity and randomized access site.

Primary outcomes

There was no evidence of significant interactions for the treatment effects on co-primary outcomes between the complex and noncomplex PCI groups (P_{int} for MACE=0.473, P_{int} for NACE=0.666). Among patients who underwent complex PCI, 30-day MACE occurred in 112 (14.4%) patients assigned to TRA and 109 (15.3%) patients assigned to TFA (hazard ratio [HR]: 0.94; 95% confidence interval [CI]: 0.72 to 1.22; P=0.643), and NACE occurred in 121 (15.6%) patients assigned to TRA and 124 (17.4%) patients assigned to TFA (HR: 0.89; 95% CI: 0.69 to 1.14; P=0.349) (**Table 3, CENTRAL ILLUSTRATION**). In the noncomplex PCI group, 30-day MACE occurred in 229 (8.8%) assigned to TRA and 278 (10.5%) assigned to TFA (HR: 0.84; 95% CI: 0.70 to 1.00; P=0.046) and NACE occurred in 257 (9.9%) assigned to TRA and 314 (11.9%) assigned to TFA (HR: 0.83; 95% CI: 0.70 to 0.98; P=0.028) (**Table 3**). These results remained entirely consistent when outcomes at 1 year were analyzed (**Figure 2, Online Table 4)**.
Sensitivity analyses of the two coprimary outcomes excluding patients with crossover to a non-randomized access (**Online Table 5**) or subjects undergoing staged procedures (**Online Table 6**) were consistent with the main analyses.

Secondary outcomes

There was no statistically significant heterogeneity of treatment effect on all-cause and cardiovascular mortality at 30 days according to PCI complexity (P_{int}= 0.096 and 0.135 respectively, **Table 3, CENTRAL ILLUSTRATION**). Yet, TRA was associated with fewer all-cause and cardiovascular death rates compared with TFA in patients with noncomplex (HR: 0.61; 95% CI: 0.39 to 0.96; P= 0.033; HR: 0.62; 95% CI: 0.39

to 0.99; P=0.046; respectively), but not in those with complex PCI (HR: 1.13; 95% CI: 0.64 to 1.98; P=0.675; HR: 1.10; 95% CI: 0.61 to 2.00; P= 0.747; respectively).

MI and definite stent thrombosis did not differ between groups within the complex (HR: 0.95; 95% CI: 0.71 to 1.28; P=0.737, and HR:1.22; 95% CI: 0.42 to 3.53; P=0.708, respectively) and noncomplex PCI strata (HR: 0.88; 95% CI: 0.73 to 1.07; P=0.194, and HR: 1.07; 95% CI: 0.59 to 1.94; P=0.830, respectively), with negative interaction testing (P_{int} =0.671 and 0.824 respectively, **Table 3)**.

There was no statistically significant heterogeneity of treatment effect on stroke according to PCI complexity at 30 days. The treatment effect on stroke was directionally opposite at 1 year (P_{int} = 0.029), with TRA being associated with a lower risk of stroke compared with TFA in patients undergoing complex PCI (HR: 0.11; 95% CI: 0.01 to 0.92; P=0.041) and a similar risk in subjects who underwent noncomplex PCI (HR: 1.33; 95% CI: 0.65 to 2.74; P=0.437).

There was no evidence of interaction for the treatment effects on BARC, TIMI or GUSTO bleeding across PCI complexity strata (**Table 3).** Compared with TFA, TRA was associated with significantly lower rates of BARC type 3 or 5 bleeding in patients undergoing complex PCI (HR: 0.42; 95% CI: 0.22 to 0.81; P=0.010) and numerically lower rates among noncomplex PCI patients (HR: 0.72; 95% CI: 0.49 to 1.06; P=0.097). Of note, TRA resulted in lower rates of BARC type 2, 3 or 5 bleeding in both groups (HR: 0.64; 95% CI: 0.44 to 0.92; P=0.015 for the complex PCI group; HR: 0.60; 95% CI: 0.48 to 0.76; P<0.001 for the noncomplex PCI group).

Access-site BARC type 3 or 5 bleeding was lower with TRA, consistently among complex (HR 0.18; 95% CI: 0.05 to 0.63; P=0.007) and noncomplex (HR 0.41; 95% CI: 0.20 to 0.85; P= 0.016) PCI patients, whereas the former group had a greater absolute risk reduction of 1.7% (number needed to treat: 59) due to their higher absolute risk.

Subgroup analysis and spline functions

The effects of TRA versus TFA for the co-primary outcomes of MACE (**Figure 3**) or NACE (**Figure 4**) in the complex PCI and noncomplex PCI groups were largely consistent across pre-specified subgroups, with no significant interaction. **Figure 5** and **Online Figure 3** show the stratified analysis of all-cause mortality and BARC type 3 or 5 bleeding, which were consistent with the main analysis. Access sheath size was the only

subgroup variable demonstrating a significant interaction with the randomized access site (P_{int} =0.046) for all-cause mortality in patients undergoing complex PCI, suggesting higher mortality rates with TRA than TFA with 6-french but not with > 6-french sheath sizes. Conversely, we found positive tests for trend across tertiles of the centres percentage of radial PCI and randomized antithrombotic therapy for all-cause mortality ($P_{int} \leq$ 0.041) in the noncomplex PCI group, with a more pronounced benefit of TRA in centres that did 80% or more radial PCI or in patients allocated to UFH.

Spline functions of 30-day and 1-year MACE in patients undergoing complex and noncomplex PCI according to procedural duration are displayed in **Online Figure 4**.

Clinical outcomes according to type and numbers of complex criteria fulfilled

The effect of TRA versus TFA for MACE, NACE and all-cause mortality (**Online Figure 5 and 6**) was consistent across the components of the complex PCI definition; results were also stratified according to progressive number of complex PCI criteria fulfilled.

DISCUSSION

The relationship between complex PCI, ischemic and bleeding outcomes is multifactorial in etiology, relying on patient's comorbidities, the extent of coronary artery disease, completeness of revascularization and optimal antithrombotic strategies (16,17). Beyond these contributing factors, access site selection remains key in mitigating the occurrence of bleeding events and adequately supporting revascularization (12). To the best of our knowledge, this is the largest study investigating TRA versus TFA in ACS patients undergoing complex PCI. The main findings of the current analysis can be summarized as follows:

1. The complexity of PCI did not affect the comparative efficacy and safety of TRA versus TFA, which is supported by negative positive interaction testing for the co-primary or major secondary endpoints.
2. While NACE and MACE and mortality were lower with TRA among noncomplex PCI patients, these endpoints no longer differed between groups in patients who had undergone complex PCI, with rates of events still favoring TRA for both co-primary endpoints at 30 days, but disfavoring TRA for MACE at 1 year and mortality at both 30 days and 1 year, with borderline interaction testing across complexity strata for all-cause death at 30 days (P_{int}=0.096).

3. Complex PCI patients experienced a greater than 80% risk reduction with TRA for access-site related BARC 3 or 5 events, with an absolute risk difference of 1.7%, corresponding to a number needed to treat for benefit (NNTB) of 59. Among noncomplex PCI patients, TRA was still associated with a significant almost 60% risk reduction for access-site related BARC 3 or 5 bleeding with an absolute risk difference of 0.5% between the two access groups, corresponding to a NNTB of 200.

Several studies have recently focused on patients undergoing complex interventions. However, the vast majority of these studies has mainly investigated on the optimal revascularization and/or antithrombotic strategies (8,9,18,19), with significant heterogeneity in the definition of complex PCI. A small number of studies analyzed the role of access site selection, in the context of patients with chronic coronary syndrome (CCS) undergoing PCI of CTO, heavily calcified lesions, left main or complex bifurcations (11). Conversely, this is the first study on complex PCI reporting the use of TRA versus TFA in patients with ACS, who typically exhibit higher risk of ischemic events especially following complex procedures.

The COLOR (*Complex Large-Bore Radial PCI*) trial (11) investigated the value of TRA versus TFA in 388 patients undergoing complex PCI with large-bore guiding catheters (≥7 Fr). The primary endpoint (a composite of BARC type 2, 3 or 5 bleeding or vascular complications requiring intervention) occurred in 19.1% in the TFA versus 3.6% in the TRA group (P <0.001), entirely driven by a reduction in BARC 2 bleeding and fewer vascular complications requiring intervention. Our present analysis extends previous observations by showing that TRA mitigates not only minor but also major BARC bleeding compared with TFA among complex PCI patients, in whom the absolute bleeding risk is higher and leads to greater absolute benefit of TRA compared with TFA. A recent meta-analysis of observational studies investigating the use of TRA versus TFA in CTO-PCI also found that TRA was associated with fewer access-site complications and major bleeding with similar procedural success compared with TFA (20).

An unexpected finding from the COLOR trial was a borderline higher MACE rates at 30 days with TRA compared with TFA. The results of our study are reassuring as do not show an increased MACE rate among complex PCI patients who underwent TRA compared with TFA. Additional evidence supporting similar effectiveness between TFA and TRA with respect to MACE among complex PCI patients comes from the lack of relationship between the duration of the procedure (as a proxy of procedural complexity) and

outcomes in the two study groups. Finally, when each of the PCI complexity components where separately appraised, we did not see heterogeneity with respect to the treatment effects between TRA and TFA.

The benefit in terms of MACE and mortality which were observed in the entire study cohort were no longer evident among complex PCI patients. These observations may simply reflect the lack of power to detect treatment effects in the complex PCI patient subset. This interpretation is supported by the negative interaction testing between TRA and TFA across PCI complexity strata. Moreover, the rates of MI or stroke were not higher with TRA compared with TFA in complex PCI patients. The only component of the co-primary endpoints which numerically favored TFA among complex PCI patients was 30-day or 1-year mortality, which reached a borderline interaction testing at 30 days.

It is intriguing that the numerical excess of mortality for TRA among complex PCI patients apparently accrued entirely from patients who were intervened upon with 6-french guiding catheters, in whom there was a numerical excess of fatal events with TRA compared with TFA (HR:1.52; 95% CI: 0.92 to 2.45) whereas no fatal event occurred among patients who received > 6-french access sheath size, with positive interaction testing. This observation should be interpreted with great caution, taking into account that it originates from subgroup analyses of a secondary endpoint and few patients used greater than 6-french access sheath size, especially in the TRA group. Yet, it is interesting that TRA was associated to 3-fold less frequent use of large-bore access site compared with TFA among complex PCI patients.

A significant interaction effect between randomized access site compared with qualifying complexity of PCI on stroke was found at 1 year, but not at 30 days. Given the low number of events, in absence of any plausible biological explanation, it might represent a spurious finding.

Finally, in both patients undergoing complex and noncomplex PCI, we found the greatest reduction of events in centres with the greatest proportion of radial procedures, albeit the test for trends across strata was negative in both subsets, when separately appraised. The existence of a gradient of mortality benefit with TRA according to the operator's expertise in patients undergoing PCI is in line with the RIVAL (3) and the main results of the MATRIX-Access (4) trial.

Study limitations

Some limitations of this study should be considered. Although the present analysis is the largest evaluating patients undergoing complex PCI through TRA or TFA, the MATRIX-Access was not powered to explore differences in outcomes across subgroups. In addition, randomization was not stratified by PCI complexity and stratification of the population in complex and noncomplex PCI groups led to subgroups which are unevenly distributed. Third, these results are not generalizable to all patients undergoing complex PCI, due to the high operator's expertise in the MATRIX trial and the complex PCI definition used for this analysis.

CONCLUSIONS

PCI complexity did not affect the comparative efficacy and safety of TRA versus TFA in ACS patients, based on consistently negative interaction testing across complex or noncomplex PCI strata for both co-primary endpoints of NACE and MACE and other explored secondary endpoints. The benefits of TRA in terms of reduced access site bleeding were entirely preserved among complex PCI patients who derived similar relative but greater absolute bleeding risk reduction with TRA than TFA compared with noncomplex PCI patients.

CLINICAL PERSPECTIVES

Competency in Patient Care and Procedural Skills: The complexity of PCI did not affect the comparative efficacy and safety of TRA versus TFA. Among ACS patients undergoing complex PCI, TRA was associated with comparable rate of major adverse cardiovascular events and net adverse clinical events and resulted in lower major access-site related bleeding with greater absolute bleeding risk reduction compared with noncomplex PCI patients.

Translational Outlook: Prospective and adequately powered studies are needed to definitively investigate the treatment effects of TRA versus TFA in patients with ACS undergoing complex PCI and clarify the role of operators' radial expertise on the comparative effectiveness of these two access sites.

REFERENCES

1. Neumann F-J., Sousa-Uva M., Ahlsson A., et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40(2):87–165. Doi: 10.1093/eurheartj/ehy394.

2. Mason PJ, Shah B, Tamis-Holland JE, et al. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. Circ Cardiovasc Interv 2018;11(9):e000035. Doi: 10.1161/HCV.0000000000000035.

3. 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(9775):1409–20. Doi: 10.1016/S0140-6736(11)60404-2.

4. Valgimigli M., Gagnor A., Calabró P., et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet 2015;385(9986):2465–76. Doi: 10.1016/S0140-6736(15)60292-6.

5. 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(24):2481–9. Doi: https://doi.org/10.1016/j.jacc.2012.06.017.

6. Valgimigli M., Frigoli E., Leonardi S., et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392(10150):835–48. Doi: 10.1016/S0140-6736(18)31714-8.

7. Andò G., Cortese B., Russo F., et al. Acute Kidney Injury After Radial or Femoral Access for Invasive Acute Coronary Syndrome Management: AKI-MATRIX. J Am Coll Cardiol 2017;69(21):2592–603. Doi: https://doi.org/10.1016/j.jacc.2017.02.070.

8. Giustino G., Chieffo A., Palmerini T., et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol 2016;68(17):1851–64. Doi:

https://doi.org/10.1016/j.jacc.2016.07.760.

9. Serruys PW., Takahashi K., Chichareon P., et al. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. Eur Heart J 2019;40(31):2595–604. Doi: 10.1093/eurheartj/ehz453.

10. Dangas G, Baber U, Sharma S, et al. Ticagrelor With or Without Aspirin After Complex PCI. J Am Coll Cardiol 2020;75(19):2414–24. Doi: 10.1016/j.jacc.2020.03.011.

11. Meijers TA, Aminian A, van Wely M, et al. Randomized Comparison Between Radial and Femoral Large-Bore Access for Complex Percutaneous Coronary Intervention. JACC Cardiovasc Interv 2021;14(12):1293–303. Doi: 10.1016/j.jcin.2021.03.041.

12. Valgimigli M., Landi A. Large-Bore Radial Access for Complex PCI. JACC Cardiovasc Interv 2021;14(12):1304–7. Doi: 10.1016/j.jcin.2021.04.013.

13. Valgimigli M. Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program. Am Heart J 2014;168(6):838-845.e6. Doi: https://doi.org/10.1016/j.ahj.2014.08.013.

14. Valgimigli M., Frigoli E., Leonardi S., et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med 2015;373(11):997–1009. Doi: 10.1056/NEJMoa1507854.

15. Costa F, Van Klaveren D, Feres F, et al. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. J Am Coll Cardiol 2019;73(7):741–54. Doi: 10.1016/j.jacc.2018.11.048.

16. Coughlan JJ., Aytekin A., Ndrepepa G., et al. Twelve-month clinical outcomes in patients with acute coronary syndrome undergoing complex percutaneous coronary intervention: insights from the ISAR-REACT 5 trial. Eur Hear Journal Acute Cardiovasc Care 2021. Doi: 10.1093/ehjacc/zuab077.

17. Valgimigli M., Landi A. Ischemic and bleeding risk in patients with acute coronary syndrome undergoing complex percutaneous coronary intervention: is it time to REACT? Eur Hear J Acute

Cardiovasc Care 2021;in press.

18. Chieffo A., Burzotta F., Pappalardo F., et al. Clinical expert consensus document on the use of percutaneous left ventricular assist support devices during complex high-risk indicated PCI: Italian Society of Interventional Cardiology Working Group Endorsed by Spanish and Portuguese Interventional Card. Int J Cardiol 2019;293:84–90. Doi: https://doi.org/10.1016/j.ijcard.2019.05.065.

19. Burzotta F., Russo G., Ribichini F., et al. Long-Term Outcomes of Extent of Revascularization in Complex High Risk and Indicated Patients Undergoing Impella-Protected Percutaneous Coronary Intervention: Report from the Roma-Verona Registry. J Interv Cardiol 2019;2019:5243913. Doi: 10.1155/2019/5243913.

20. Megaly M., Karatasakis A., Abraham B., et al. Radial Versus Femoral Access in Chronic Total Occlusion Percutaneous Coronary Intervention. Circ Cardiovasc Interv 2019;12(6):e007778. Doi: 10.1161/CIRCINTERVENTIONS.118.007778.

FIGURE LEGENDS

Figure 1. Clinical outcomes in patients undergoing complex (blue bars) versus noncomplex (green bars) PCI at 30 days and 1 year. Light and dark colors represent event rates at 30 days and 1 year, respectively. *Abbreviations: PCI= percutaneous coronary intervention; MACE= major adverse cardiovascular events; NACE= net adverse clinical events; CV= cardiovascular; MI= myocardial infarction; TVR= target vessel revascularization; ST= stent thrombosis; BARC= Bleeding Academic Research Consortium.*

Figure 2. Kaplan-Meier estimates and HRs for MACE (A) and NACE (B) at 12 months comparing radial versus femoral access in patients undergoing complex and noncomplex PCI. HR= hazard ratio; CI= confidence interval; PCI= percutaneous coronary intervention; other abbreviations as in Figure 1.

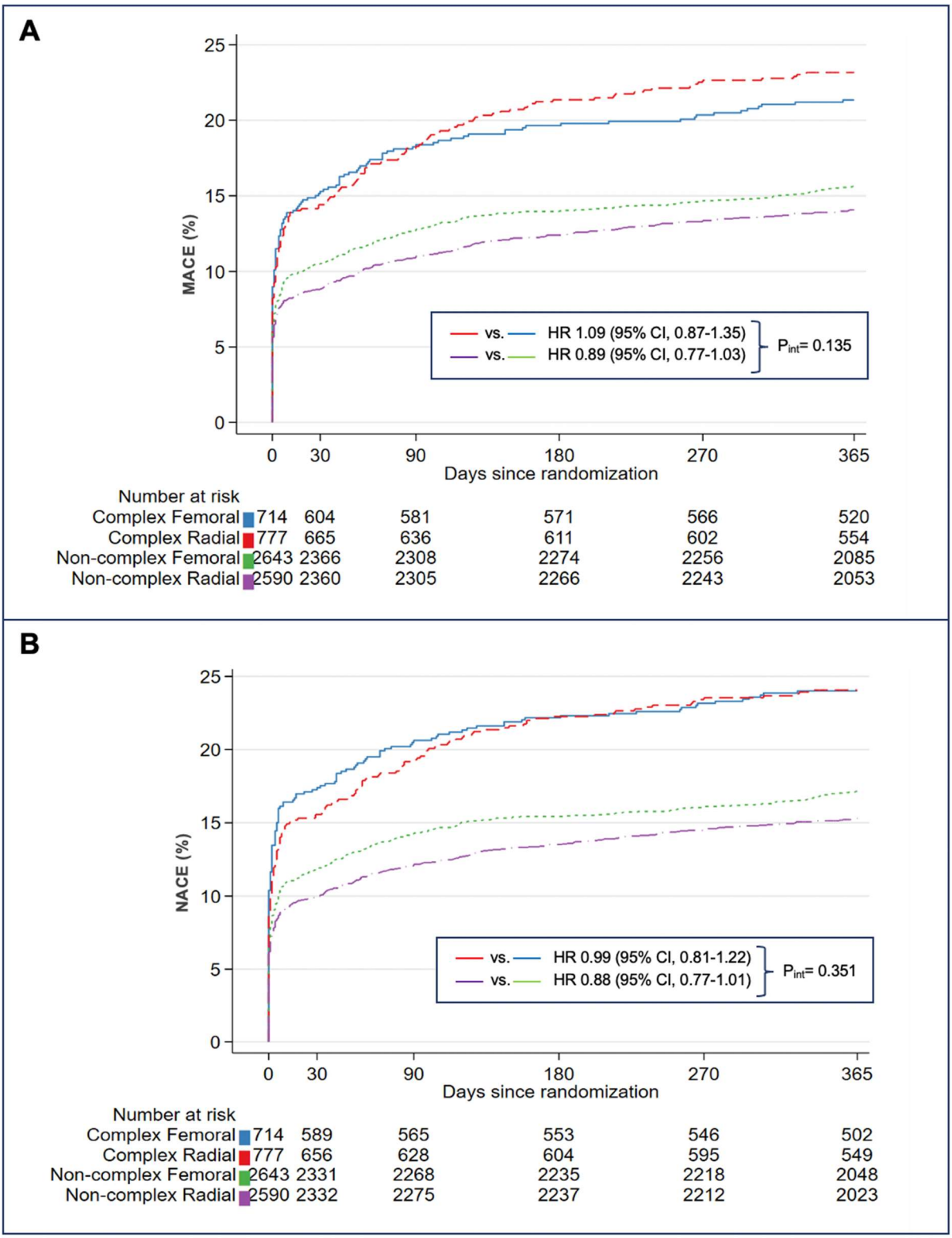


Figure 3. Sub-groups analysis for major adverse cardiovascular events (MACE) in patients undergoing complex and noncomplex PCI. *PCI=percutaneous coronary intervention. ACS=acute coronary syndrome. STEMI=ST-segment elevation myocardial infarction. NSTE-ACS=non-ST-segment elevation acute coronary syndrome; BMI= body mass index; CKD= chronic kidney disease; UFH= unfractionated heparin; CI= confidence interval.* *p values are for trend across ordered groups.

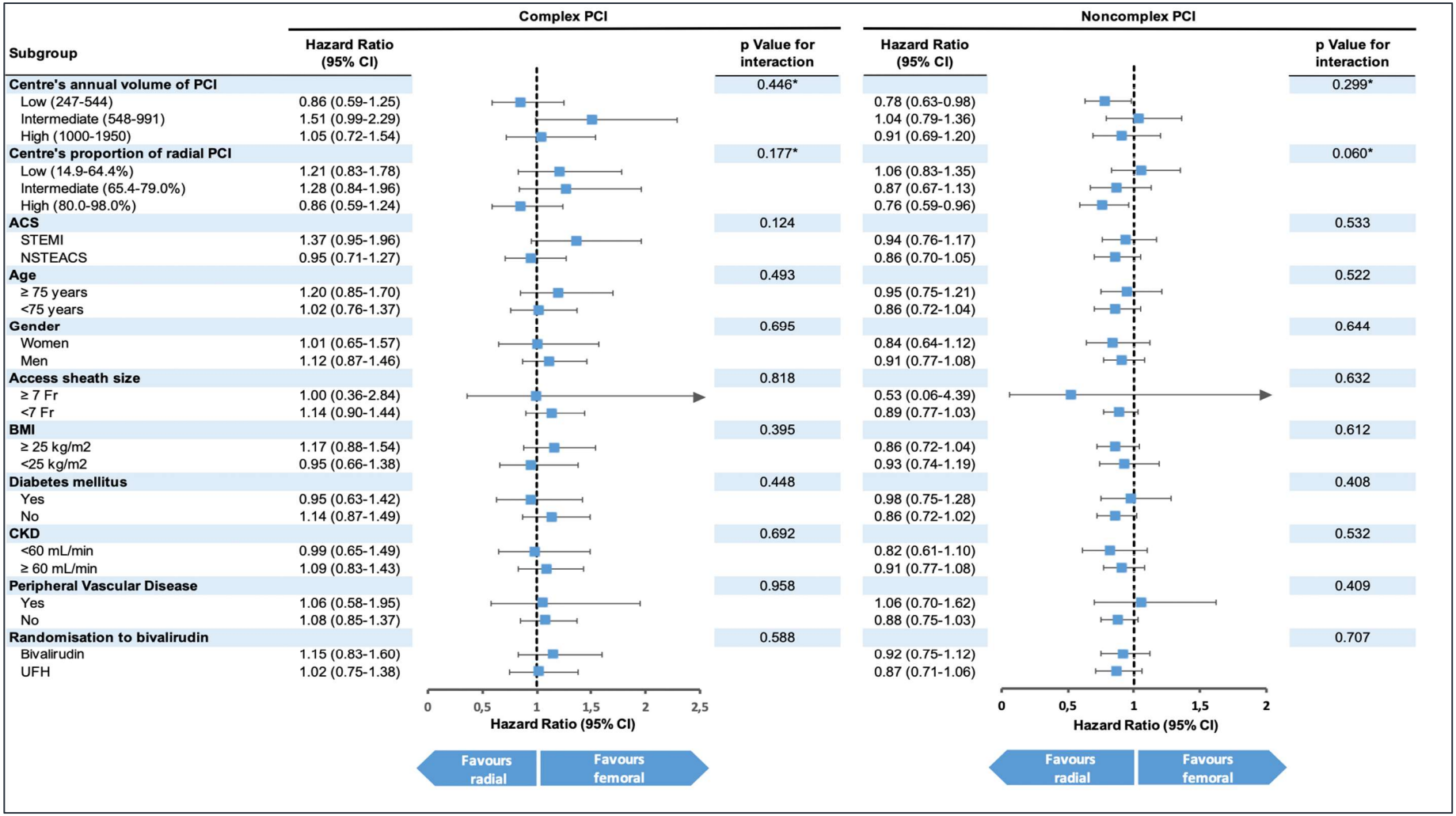


Figure 4. Sub-groups analysis for net adverse clinical events (NACE) in patients undergoing complex and noncomplex PCI. *Abbreviations as in figure 3.* *p values are for trend across ordered groups.

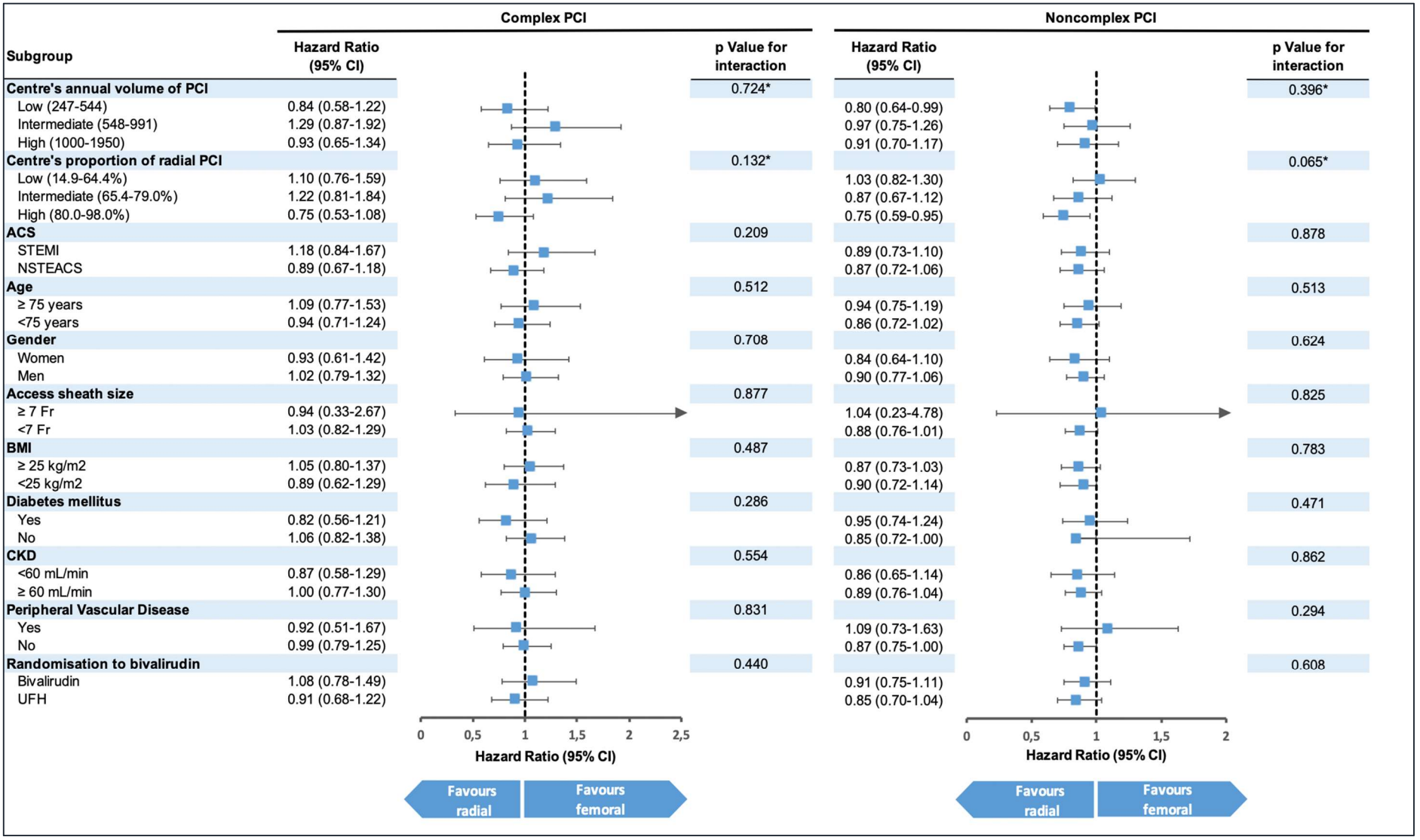
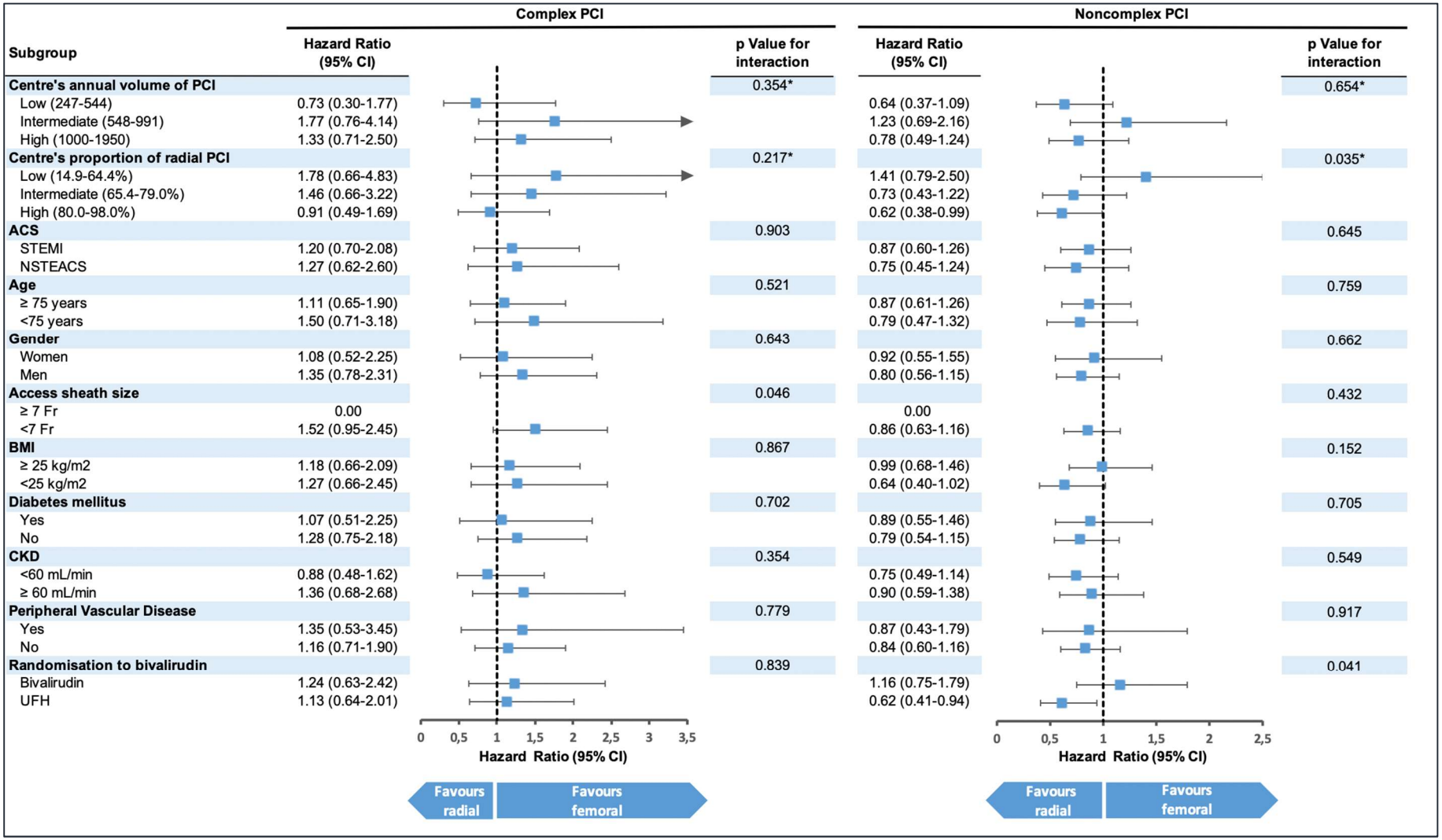
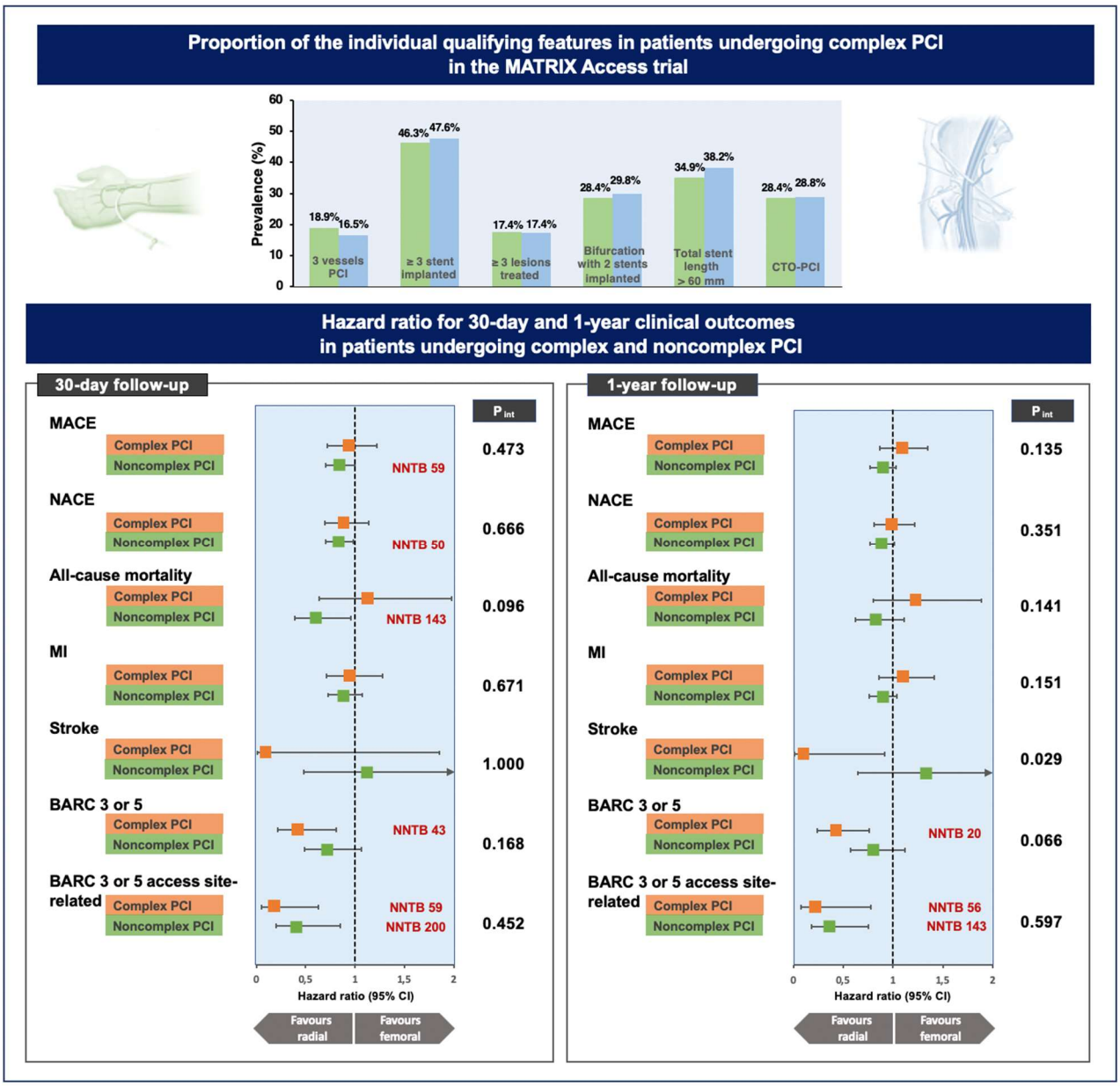


Figure 5. Sub-groups analysis for all-cause mortality in patients undergoing complex and noncomplex PCI. *Abbreviations as in figure 3.* *p values are for trend across ordered groups.



CENTRAL ILLUSTRATION. Radial versus femoral access in patients undergoing complex or noncomplex percutaneous coronary intervention (PCI). Complex PCI was defined as any of the following: three-vessel PCI, ≥ 3 implanted stents, ≥ 3 treated lesions, bifurcation with 2 stents implanted, total stent length > 60 mm or chronic total occlusion (CTO)-PCI. Abbreviations: *MACE= major adverse cardiovascular events; NACE= net adverse clinical events; MI, myocardial infarction; BARC= Bleeding Academic Research Consortium; CI= confidence interval; NNTB= number needed to treat for benefit.*



TABLES

Table 1. Baseline characteristics in patients undergoing complex and noncomplex PCI randomized to radial versus femoral access. *Abbreviations: BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI= percutaneous coronary intervention; CABG= coronary artery bypass grafting; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; STE-ACS= ST-segment elevation acute coronary syndrome; NSTE-ACS= non-ST elevation acute coronary syndrome; LVEF= left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.*

	Complex PCI (n=1,491)			**Noncomplex PCI (n= 5,233)**		
	Radial Access (n= 777)	**Femoral Access (n=714)**	**P-value**	**Radial Access (n=2,590)**	**Femoral Access (n=2,643)**	**P-value**
Age ≥ 75 years	217 (28%)	200 (28%)	1.000	607 (23%)	645 (24%)	0.418
Male sex	613 (79%)	550 (77%)	0.416	2021 (78%)	1992 (75%)	0.024
BMI, kg/m^2	27.0 ± 4.0	27.1 ± 4.1	0.466	27.2 ± 4.1	27.1 ± 4.1	0.561
Diabetes mellitus	232 (30%)	176 (25%)	0.027	541 (21%)	552 (21%)	1.000
Smoker	434 (56%)	381 (53%)	0.349	1485 (57%)	1523 (58%)	0.845
Hypercholesterolemia	338 (44%)	331 (46%)	0.274	1116 (43%)	1186 (45%)	0.200
Hypertension	500 (64%)	461 (65%)	0.957	1582 (61%)	1647 (62%)	0.363
Family history of CAD	211 (27%)	181 (25%)	0.444	729 (28%)	751 (28%)	0.830
Previous MI	131 (17%)	119 (17%)	0.945	335 (13%)	365 (14%)	0.372
Previous PCI	128 (16%)	108 (15%)	0.479	377 (15%)	364 (14%)	0.428
Previous CABG	38 (5%)	32 (4%)	0.715	53 (2%)	83 (3%)	0.015
Previous CVA	48 (6%)	45 (6%)	1.000	108 (4%)	130 (5%)	0.208
Peripheral Vascular Disease	85 (11%)	65 (9%)	0.263	170 (7%)	209 (8%)	0.062
COPD	43 (6%)	54 (8%)	0.116	136 (5%)	169 (6%)	0.087
Anemia*	187 (24%)	152 (21%)	0.216	458 (18%)	483 (18%)	0.589
Clinical presentation						
STEMI	334 (43%)	306 (43%)	1.000	1506 (58%)	1512 (57%)	0.502
NSTE-ACS	414 (53%)	360 (50%)	0.276	972 (38%)	1012 (38%)	0.588
Cardiac arrest	17 (2%)	12 (2%)	0.575	66 (3%)	56 (2%)	0.315
Killip class III or IV	47 (6%)	28 (4%)	0.075	58 (2%)	50 (2%)	0.383
Systolic arterial pressure, mmHg	137.0 ± 26.7	139.2 ± 27.6	0.115	138.4 ± 25.5	138.8 ± 25.5	0.580
LVEF (<35%)	86/751 (11%)	76/692 (11%)	0.803	190/2503 (8%)	213/2534 (8%)	0.299
eGFR at baseline	83.6 ± 26.1	82.9 ± 24.9	0.571	84.6 ± 25.1	84.2 ± 25.2	0.606
Medications administered before catheterization						
Lytic therapy	13 (2%)	14 (2%)	0.702	72 (3%)	80 (3%)	0.622
Aspirin	737 (95%)	681 (95%)	0.719	2443 (94%)	2498 (95%)	0.810

Clopidogrel	376 (48%)	351 (49%)	0.795	1170 (45%)	1192 (45%)	0.978
Prasugrel	74 (10%)	73 (10%)	0.665	370 (14%)	354 (13%)	0.357
Ticagrelor	203 (26%)	177 (25%)	0.592	603 (23%)	649 (25%)	0.285
Enoxaparin	125 (16%)	148 (21%)	0.023	362 (14%)	404 (15%)	0.184
Fondaparinux	77 (10%)	88 (12%)	0.160	225 (9%)	239 (9%)	0.662
Unfractionated heparin	197 (25%)	182 (25%)	0.953	918 (35%)	908 (34%)	0.417

Values are mean ± SD or n (%). * Hb <12 g/dl for women, <13 g/dl for men.

Table 2. Angiographic and procedural characteristics. *PCI= percutaneous coronary intervention; GPI= glycoprotein IIb/IIIa inhibitors; UFH= unfractionated heparin; TIMI= thrombolysis in myocardial infarction.*

	Complex PCI (n=1,491)			Noncomplex PCI (n= 5,233)		
	Radial Access (n= 777)	Femoral Access (n=714)	P-Value	Radial Access (n=2,590)	Femoral Access (n=2,643)	P-Value
Any crossover during index hospitalization	75 (10%)	19 (3%)	<0.001	131 (5%)	58 (2%)	<0.001
Intra-aortic balloon pump	44 (6%)	46 (6%)	0.587	27 (1%)	40 (2%)	0.141
Sheath size						
5Fr	6 (1%)	5 (1%)	1.000	24 (1%)	24 (1%)	1.000
6Fr	750 (97%)	638 (89%)	<0.001	2553 (99%)	2499 (95%)	<0.001
7Fr	20 (3%)	66 (9%)	<0.001	12 (0%)	106 (4%)	<0.001
8Fr	0 (0%)	5 (1%)	0.025	0 (0%)	14 (1%)	<0.001
Medication used during catheterization						
Aspirin	52 (7%)	65 (9%)	0.101	166 (6%)	182 (7%)	0.506
Clopidogrel	54 (7%)	54 (8%)	0.690	209 (8%)	193 (7%)	0.300
Prasugrel	59 (8%)	49 (7%)	0.618	273 (11%)	235 (9%)	0.045
Ticagrelor	90 (12%)	100 (14%)	0.163	284 (11%)	281(11%)	0.722
Planned GPI	99 (13%)	89 (12%)	0.876	318 (12%)	281 (11%)	0.062
Bailout GPI	45 (6%)	37 (5%)	0.650	108 (4%)	109 (4%)	0.945
UFH	428 (55%)	374 (52%)	0.299	1391 (54%)	1358 (51%)	0.097
UFH total dose, U/kg	80.6 ± 33.1	80.8 ± 32.1	0.937	74.6 ± 29.7	73.9 ± 27.2	0.523
Bivalirudin	379 (49%)	352 (49%)	0.876	1282 (49%)	1314 (50%)	0.890
Prolonged infusion post-PCI	190 (24%)	176 (25%)	0.952	648 (25%)	661 (25%)	1.000
Full bivalirudin regimen post-PCI	68 (9%)	56 (8%)	0.574	239 (9%)	228 (9%)	0.467
Low bivalirudin regimen post-PCI	122 (16%)	120 (17%)	0.574	409 (16%)	433 (16%)	0.573
Full procedural success	701 (90%)	640 (90%)	0.731	2421 (93%)	2476 (94%)	0.778
Treated vessel(s)						
Left main coronary artery	134 (17%)	102 (14%)	0.119	18 (1%)	17 (1%)	0.866
Left anterior descending a.	446 (58%)	414 (58%)	0.875	1239 (48%)	1235(47%)	0.422
Left circumflex artery	285 (37%)	258 (36%)	0.829	619 (24%)	651 (25%)	0.540
Right coronary artery	277 (36%)	271 (38%)	0.389	839 (32%)	852 (32%)	0.906
Bypass graft	10 (1%)	8 (1%)	0.816	10 (0%)	28 (1%)	0.005
Overall stent length, mm	52.8 ± 25.0	54.1 ± 26.4	0.344	25.3 ± 11.0	25.1 ± 10.7	0.534
Fluoroscopy time, min	20.3 ± 12.9	25.0 ±135.1	0.347	13.2 ± 8.9	13.4 ± 48.2	0.852
Duration of procedure, min	67.7 ± 36.5	68.6 ± 35.2	0.641	51.6 ± 24.4	49.9 ± 24.1	0.013
Lesions treated with PCI	n= 1,332	n = 1,234		n = 2,919	n=2,969	
At least one DES	980 (74%)	898 (73%)	0.656	1836 (63%)	1897 (64%)	0.433
At least one BMS	225 (17%)	207 (17%)	0.958	837 (29%)	797 (27%)	0.123
TIMI flow pre-procedure						
0 or 1	452 (34%)	437 (35%)	0.430	1179 (40%)	1188 (40%)	0.770
2	143 (11%)	140 (11%)	0.659	388 (13%)	390 (13%)	0.878

3	735 (55%)	655 (53%)	0.302	1352 (46%)	1391 (47%)	0.695
TIMI flow post-procedure						
0 or 1	36 (3%)	29 (2%)	0.616	41 (1%)	44 (1%)	0.828
2	32 (2%)	28 (2%)	0.896	73 (3%)	73 (2%)	0.933
3	1262 (95%)	1175 (95%)	0.583	2805 (96%)	2852 (96%)	0.947
Coronary stenosis less than 30% per treated lesion	1269 (95%)	1174 (95%)	0.925	2816 (96%)	2863 (96%)	0.944

Values are mean ± SD, or n (%).

Table 3. Adjudicated bleeding and ischemic events at 30 days according to randomized access site and PCI complexity. *PCI= percutaneous coronary intervention; MI= myocardial infarction; BARC= Bleeding Academic Research Consortium; TVR= target vessel revascularization; TIMI= Thrombolysis in Myocardial Infarction; GUSTO= Global Use of Strategies to Open Occluded Arteries; CI= confidence interval.*

	Complex PCI (n=1,491)				**Noncomplex PCI (n= 5,233)**				
	Radial Access (n= 777)	**Femoral Access (n=714)**	**Hazard Ratio (95% CI)**	**P-value**	**Radial Access (n=2,590)**	**Femoral Access (n=2,643)**	**Hazard Ratio (95% CI)**	**P-value**	**P-value for interaction**
Co-primary composite endpoint of all-cause mortality, MI or stroke	112 (14.4%)	109 (15.3%)	0.94 (0.72-1.22)	0.643	229 (8.8%)	278 (10.5%)	0.84 (0.70-1.00)	0.046	0.473
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5 bleeding	121 (15.6%)	124 (17.4%)	0.89 (0.69-1.14)	0.349	257 (9.9%)	314 (11.9%)	0.83 (0.70-0.98)	0.028	0.666
Composite of all-cause mortality, MI, stroke, urgent TVR, definite stent thrombosis	123 (15.8%)	126 (17.7%)	0.89 (0.69-1.14)	0.344	262 (10.1%)	317 (12.0%)	0.84 (0.71-0.99)	0.036	0.712
All-cause mortality	27 (3.5%)	22 (3.1%)	1.13 (0.64-1.98)	0.675	30 (1.2%)	50 (1.9%)	0.61 (0.39-0.96)	0.033	0.096
Cardiovascular death	24 (3.1%)	20 (2.8%)	1.10 (0.61-2.00)	0.747	28 (1.1%)	46 (1.7%)	0.62 (0.39-0.99)	0.046	0.135
MI	88 (11.4%)	85 (12.0%)	0.95 (0.71-1.28)	0.737	194 (7.5%)	224 (8.5%)	0.88 (0.73-1.07)	0.194	0.671
Stroke	0 (0.0%)	4 (0.6%)	0.10 (0.01-1.85)		11 (0.4%)	10 (0.4%)	1.12 (0.48-2.64)	0.796	1.000
Urgent TVR	11 (1.4%)	6 (0.9%)	1.69 (0.62-4.57)	0.302	34 (1.3%)	33 (1.3%)	1.05 (0.65-1.70)	0.840	0.400
Definite stent thrombosis	8 (1.0%)	6 (0.9%)	1.22 (0.42-3.53)	0.708	22 (0.9%)	21 (0.8%)	1.07 (0.59-1.94)	0.830	0.824
Acute definite stent thrombosis	2 (0.3%)	2 (0.3%)	0.92 (0.13-6.53)	0.933	19 (0.7%)	10 (0.4%)	1.94 (0.90-4.17)	0.091	0.488
Subacute definite stent thrombosis	6 (0.8%)	4 (0.6%)	1.38 (0.39-4.88)	0.620	4 (0.2%)	11 (0.4%)	0.37 (0.12-1.16)	0.088	0.131
Definite or probable stent thrombosis	13 (1.7%)	10 (1.4%)	1.19 (0.52-2.72)	0.672	27 (1.0%)	27 (1.0%)	1.02 (0.60-1.74)	0.944	0.751
Acute definite or probable stent thrombosis	3 (0.4%)	3 (0.4%)	0.92 (0.19-4.55)	0.918	21 (0.8%)	10 (0.4%)	2.14 (1.01-4.55)	0.048	0.349

Subacute definite or probable stent thrombosis	10 (1.3%)	7 (1.0%)	1.31 (0.50-3.45)	0.580	8 (0.3%)	17 (0.6%)	0.48 (0.21-1.11)	0.085	0.122
Bleeding									
BARC classification									
Type 1	32 (4.2%)	71 (10.0%)	0.41 (0.27-0.62)	<0.001	114 (4.4%)	202 (7.7%)	0.57 (0.45-0.71)	<0.001	0.168
Type 2	37 (4.8%)	45 (6.3%)	0.75 (0.49-1.16)	0.201	75 (2.9%)	136 (5.2%)	0.56 (0.42-0.74)	<0.001	0.257
Type 3	10 (1.3%)	26 (3.7%)	0.35 (0.17-0.73)	0.005	37 (1.4%)	50 (1.9%)	0.75 (0.49-1.15)	0.189	0.075
Type 3a	2 (0.3%)	11 (1.6%)	0.17 (0.04-0.75)	0.020	25 (1.0%)	30 (1.1%)	0.85 (0.50-1.44)	0.542	0.046
Type 3b	8 (1.0%)	15 (2.1%)	0.49 (0.21-1.15)	0.101	11 (0.4%)	17 (0.6%)	0.66 (0.31-1.41)	0.280	0.609
Type 3c	0 (0.0%)	1 (0.1%)	0.31 (0.01-7.60)	-	1 (0.0%)	3 (0.1%)	0.34 (0.04-3.26)	0.349	-
Type 4	0 (0.0%)	0 (0.0%)	-	-	1 (0.0%)	0 (0.0%)	3.06 (0.12-75.08)	-	-
Type 5	3 (0.4%)	2 (0.3%)	1.38 (0.23-8.24)	0.726	7 (0.3%)	12 (0.5%)	0.59 (0.23-1.51)	0.273	0.413
Type 5a	2 (0.3%)	2 (0.3%)	0.92 (0.13-6.52)	0.932	4 (0.2%)	8 (0.3%)	0.51 (0.15-1.69)	0.270	0.615
Type 5b	1 (0.1%)	0 (0.0%)	2.76 (0.11-67.64)	-	3 (0.1%)	4 (0.2%)	0.76 (0.17-3.41)	0.724	-
Type 3 or 5	13 (1.7%)	28 (4.0%)	0.42 (0.22-0.81)	0.010	44 (1.7%)	62 (2.4%)	0.72 (0.49-1.06)	0.097	0.168
Related to access site	3 (0.4%)	15 (2.1%)	0.18 (0.05-0.63)	0.007	10 (0.4%)	25 (0.9%)	0.41 (0.20-0.85)	0.016	0.277
Type 2, 3 or 5	50 (6.5%)	71 (10.0%)	0.64 (0.44-0.92)	0.015	118 (4.6%)	197 (7.5%)	0.60 (0.48-0.76)	<0.001	0.805
Related to access site	22 (2.8%)	47 (6.6%)	0.43 (0.26-0.71)	0.001	40 (1.5%)	120 (4.6%)	0.34 (0.24-0.48)	<0.001	0.452
TIMI classification									
Major bleeding	4 (0.5%)	9 (1.3%)	0.41 (0.13-1.32)	0.135	14 (0.5%)	18 (0.7%)	0.79 (0.39-1.59)	0.513	0.341
Minor bleeding	3 (0.4%)	8 (1.1%)	0.34 (0.09-1.29)	0.115	20 (0.8%)	25 (1.0%)	0.81 (0.45-1.47)	0.493	0.245
Major or minor bleeding	7 (0.9%)	17 (2.4%)	0.38 (0.16-0.91)	0.029	34 (1.3%)	43 (1.6%)	0.80 (0.51-1.26)	0.343	0.131
GUSTO classification									
Severe bleeding	5 (0.7%)	7 (1.0%)	0.66 (0.21-2.06)	0.470	14 (0.5%)	18 (0.7%)	0.79 (0.39-1.59)	0.512	0.782
Moderate bleeding	3 (0.4%)	10 (1.4%)	0.27 (0.08-1.00)	0.050	14 (0.5%)	20 (0.8%)	0.71 (0.36-1.41)	0.330	0.200
Severe or moderate bleeding	8 (1.0%)	17 (2.4%)	0.43 (0.19-1.00)	0.049	28 (1.1%)	38 (1.4%)	0.75 (0.46-1.22)	0.247	0.261