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Lugar de acceso y tipo de anticoagulante en pacientes con síndrome coronario agudo en clase Killip avanzada o con parada cardiaca extrahospitalaria

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ABSTRACT

Introduction and objectives: Patients who are vulnerable (VP) to hemodynamic or electrical disorders are often excluded by clinical trials and data on the optimal access-site or antithrombotic treatment are limited. We assessed outcomes of transradial versus transfemoral access and bivalirudin versus unfractionated heparin (UFH) in VP with acute coronary syndrome undergoing invasive management.

Methods: In the MATRIX trial, 8404 patients were randomized to radial or femoral access and 7213 patients to bivalirudin or UFH. Among them, 934 (11.1%) were deemed VP due to advanced Killip class (n = 808), cardiac arrest (n = 168) or both (n = 42). The 30-day co-primary outcomes were major adverse cardiovascular and cerebrovascular events (MACE: death, myocardial infarction, or stroke) and net adverse clinical events (NACE: MACE or major bleeding).

Results: MACE and NACE were similarly reduced with radial compared to femoral in VP and non-VP. Transradial accesss was also associated with consistent relative benefits in all-cause and cardiovascular mortality or Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding with greater absolute benefits in VP. The effects of bivalirudin versus UFH on MACE and NACE were consistent in VP and non-VP. Bivalirudin was associated to lower all-cause and cardiovascular mortality in VP but not in non-VP, with borderline interaction testing. Bivalirudin reduced bleeding in both VP and non-VP with larger absolute benefit in VP.

Conclusions: In acute coronary syndrome patients undergoing invasive management, the effects of randomised treatments were consistent in VP and non-VP, but absolute risk reduction of radial and bivalirudin were greater in VP, with 5 to 10-fold lower number needed to treat for benefits. Trial registry number: NCT01433627.

Keywords: Acute coronary syndrome, radial access, bivalirudin, vulnerable patients, acute heart failure, cardiac arrest.

RESUMEN

Introducción y objetivos: Los pacientes hemodinámica o eléctricamente vulnerables se excluyen a menudo de los ensayos clínicos, por lo que la información sobre el acceso vascular y tratamiento antitrombótico óptimos es limitada. En este trabajo se estudia la evolución de los pacientes vulnerables) con síndrome coronario agudo tratados invasivamente según el acceso fuera radial o femoral y el tratamiento con bivalirudina o con heparina no fraccionada (HNF).

Métodos: El estudio MATRIX aleatorizó a 8.404 pacientes a acceso radial o femoral y a 7.213 pacientes a bivalirudina o a HNF. Un total de 934 (11.1%) pacientes se consideraron vulnerables debido a una clase Killip avanzada (808), parada cardiaca (168) o ambas al tiempo (42). El objetivo primario compuesto a 30 días fueron los eventos cardiovasculares y cerebrovasculares graves (MACE: muerte, infarto de miocardio e ictus) y los eventos clínicos adversos netos (NACE: MACE o hemorragia grave).

Resultados: El acceso radial comparado con el femoral redujo los MACE y NACE de forma similar en pacientes vulnerables y no vulnerables. El acceso radial se asoció con un beneficio relativo consistente en la mortalidad total y cardiovascular, o sangrado BARC 3 o 5, con mayor beneficio absoluto en los pacientes vulnerables. Los efectos de la bivalirudina comparada con la HNF en MACE y NACE fueron consistentes en pacientes vulnerables y no vulnerables. La bivalirudina se asoció a una menor mortalidad cardiovascular y por todas las causas en pacientes vulnerables pero no en los no vulnerables, con test de interacción en el límite. La bivalirudina redujo el

sangrado en ambos grupos de pacientes, con un beneficio absoluto mayor en el caso de los pacientes vulnerables.

Conclusión: En pacientes con síndrome coronario agudo tratados invasivamente, los efectos de los tratamientos aleatorizados fueron consistentes en pacientes vulnerables y no vulnerables, pero la reducción del riesgo absoluto del acceso radial y bivalirudina fue mayor en los vulnerables, con una reducción de 5 a 10 veces en el número necesario que tratar. (Número de registro: NCT01433627)

Palabras clave: Síndrome coronario agudo, acceso radial, bivalirudina, paciente vulnerable, insuficiencia cardiaca aguda, parada cardiaca

ABBREVIATIONS

ACS: acute coronary syndrome

MACE: major adverse cardiovascular events

PCI: percutaneous coronary intervention

TFA: transfemoral access

TRA: transradial access

VP: vulnerable patients

ABBREVIATURAS

SCA: síndrome coronario agudo

MACE: eventos adversos cardiovasculares graves

ICP: intervención coronaria percutánea

ATF: acceso transfemoral

ATR: acceso transradial

PV: paciente vulnerable

INTRODUCTION

Transradial access intervention (TRA) has achieved widespread adoption in percutaneous coronary intervention (PCI) and is recommended by guidelines over transfemoral access (TFA) in acute coronary syndrome (ACS) patients[1,2]. Compared with TFA, TRA has numerous advantages, including lower rates of major bleeding, shorter bed rest time, and earlier hospital discharge, all of which are of particular importance in ACS patients undergoing invasive management. On the other hand, concerns have been raised for the use of TRA in vulnerable patients (VP) such as those with concomitant hemodynamic (advanced Killip class) or electrical (out of hospital cardiac arrest [OHCA] survivors) disorders in whom TFA might still remain preferable to deliver timely treatment. Prior studies, including the pivotal RIVAL trial, have excluded cardiogenic shock patients, and data on OHCA undergoing TRA are limited[3].

Heart failure (HF) is associated with elevated thrombin levels leading to faster formation of compact and resistant fibrin clots. Recent observational data suggest that HF patients undergoing PCI might benefit from a direct, such as bivalirudin, as compared to an indirect, such as unfractionated heparin (UFH), thrombin inhibitor due to lower mortality and bleeding risks[4,5].

We sought to investigate the comparative safety and effectiveness of TRA versus TFA and bivalirudin versus UFH in VP with ACS undergoing invasive management.

METHODS

Study design and patients

Design and primary findings of the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) trial have been previously reported[6-8]. Briefly, MATRIX was a program (clinicaltrials.gov; NCT01433627) of 3 independent

randomized controlled trials in an all-comers population with ACS. The first trial, MATRIX-Access-Site, compared TRA with TFA in 8404 ACS patients. The second trial, MATRIX-Antithrombin (n=7213), was a randomized comparison of two antithrombotic strategies: bivalirudin with use of glycoprotein IIb/IIIa inhibitors (GPI) restricted to angiographic complications (no-reflow or giant thrombus) compared with UFH with use of GPI left to the investigator's discretion. The third trial, MATRIX-Treatment-Duration, was a randomized comparison within patients assigned to bivalirudin, comparing prolonged (after PCI) with short-term (during PCI only) bivalirudin administration. VPs were those presenting with acute HF (Killip class II to IV)[9-11] or OHCA at the time of randomization. The trial was approved by the institutional review board at each participating centre, and all patients gave written informed consent.

Study protocol and randomization

Patients were randomized to receive treatments in a 1:1 ratio, with a random block size stratified by type of ACS, intended or ongoing use of P2Y12 inhibitor (clopidogrel versus ticagrelor or prasugrel), and study site. All interventions were administered in an open-label fashion. Access site management during and after the diagnostic or therapeutic procedure was left to the discretion of the treating physician, and closure devices were allowed as per local practice. Bivalirudin was given according to the product labeling, with a bolus of 0.75 mg/kg, followed immediately by an infusion of 1.75 mg/kg/h until completion of the PCI. In those assigned to bivalirudin prolongation, the choice between two regimens (full dose for up to 4 hours or reduced dose of 0.25 mg/kg/h for at least 6 hours) was made at the discretion of the treating physicians. UFH was administered at a dose of 70 to 100 units or 50 to 70 units/kg in patients not receiving or receiving GPI, respectively. Subsequent UFH dose adjustment on the basis of the

activated clotting time was left to the discretion of the treating physicians. A GPI could be administered before PCI in all patients in the UFH group on the basis of the treating physician's judgment, but the drug was to be administered in the bivalirudin group only in patients who had periprocedural ischemic complications after PCI. The use of other medications was allowed according to professional guidelines.

Follow-up and study outcomes

Clinical follow-up was performed at 30 days. The 2 co-primary 30-day composite outcomes of the MATRIX-Access and Antithrombin trials were major adverse cardiovascular events (MACE), defined as the composite of all-cause mortality, MI, or stroke; and net adverse clinical events (NACE), defined as the composite of MACE or non- coronary artery bypass grafting (CABG)-related major bleeding (Bleeding Academic Research Consortium [BARC] type 3 or 5). The primary outcome for MATRIX-Treatment-Duration was a composite of urgent target-vessel revascularization (TVR), definite stent thrombosis (ST), or NACE. Secondary outcomes included each component of the composite outcomes, cardiovascular mortality, and ST (defined as the definite or probable occurrence of a stent-related thrombotic event according to the Academic Research Consortium classification). Bleeding was also assessed and adjudicated on the basis of the TIMI and GUSTO scales. All outcomes were pre-specified. An independent clinical events committee blinded to treatment allocation adjudicated all suspected events.

Statistical analysis

The MATRIX-Access and Antithrombin trials were designed as superiority studies on two co-primary outcomes at 30 days expecting a rate reduction of 30%, corresponding to a rate ratio of 0.70. All analyses were performed per intention-to-treat principle, including all patients in the analysis based on the allocated treatment. Events up to 30 days post-randomization were considered. We analysed primary and secondary outcomes separately for VP and non-VP patients as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding two-sided p values. We did not perform any adjustments for multiple comparisons but set the alpha error at 2.5% to correct for the two co-primary outcomes. We analysed secondary outcomes with a two-sided α set at 5% to allow conventional interpretation of results. Survival curves were constructed using Kaplan–Meier estimates. Absolute risk differences and number needed to treat/harm (NNT/NNH) were also calculated. We performed secondary analyses in the VP group to separately assess clinical outcomes in HF and OHCA subgroups. We also performed stratified analyses according to pre-specified subgroups (centre's annual volume of PCI, centre's proportion of radial PCI, age, gender, type of ACS, body mass index, intended start or continuation of prasugrel or ticagrelor, diabetes, estimated glomerular filtration rate, history of peripheral vascular disease, previous heparin, and randomization to access site/antithrombin type) and estimated possible effect modifications using interaction terms or tests for trend across ordered groups separately for the VP and non-VP study populations. We also performed sensitivity analyses by using Cox regression analysis (unadjusted and adjusted) for co-primary endpoints and all-cause death and competing risk analysis (for death) for individual components of co-primary endpoints (MI, stroke and BARC 3 or 5). All analyses were performed using the statistical package Stata 15.1 and R 3.4.4.

RESULTS

The MATRIX-Access trial enrolled 8404 patients with ACS from 78 centers in Italy, the Netherlands, Spain, and Sweden between October 2011 and November 2014. Among them, 934 (11.1%) were deemed VP —due to advanced Killip class in 808 patients (Killip class II = 569, III = 167, IV = 72) and/or OHCA in 168 with a total of 42 patients (Killip class II = 23, III = 6, IV = 13) exhibiting both conditions—, of whom 462 (5.5%) were allocated to radial and 472 (5.6%) to femoral access. Among the 7213 patients enrolled in the MATRIX-Antithrombin, 819 (11.4%) fulfilled VP criteria —due to advanced Killip class in 698 patients and/or OHCA in 163 with a total of 42 patients exhibiting both conditions—, of whom 397 (5.5%) were allocated to bivalirudin and 422 (5.9%) to UFH.

Baseline and procedural characteristics were largely imbalanced between VP and non-VP (Tables 1-2), while VP and non-VP subgroups allocated to radial versus femoral access or bivalirudin versus UFH were generally well matched across demographics, medical history, clinical presentation, and procedural characteristics (tables 1-4 of the supplementary data).

Clinical outcomes according to VP and randomized treatments

Rates of MACE and NACE were higher in VP compared with non-VP, as were nearly all secondary outcomes (table 5 of the supplementary data).

No significant interaction was noted between access site and VP criteria with respect to 30-day MACE and NACE co-primary endpoints (interaction *P* = .77 and 0.89, respectively; figure 1, table 3, figure 1 of the supplementary data, and table 6 of the supplementary data). MACE and NACE were similarly reduced with radial as compared to femoral in VP (MACE: 14.9% vs 16.5%; RR,

0.89; 95%CI, 0.64-1.25; *P* = .51; NACE: 15.8% vs 18.9%; RR, 0.82; 95%CI, 0.59-1.13; *P* = .22) or in non-VP (MACE: 8.1% vs 9.5%; RR, 0.85; 95%CI: 0.72-0.99; *P* = .039; NACE: 9.0% vs 10.7%; RR, 0.84; 95%CI: 0.72-0.97; *P* = .022) patients (figure 1, table 3, and table 6 of the supplementary data). TRA provided consistent relative benefits over TFA in terms of individual endpoints (Supplementary figure 2 of the supplementary data, table 3, and table 6 of the supplementary data), including all-cause mortality (interaction *P* = .55), cardiovascular mortality (interaction p=0.46) and BARC 3 or 5 bleeding (interaction *P* = .30). Absolute benefits in favor of TRA over TFA were at least four-fold greater in VP as compared to non-VP (absolute risk difference of -1.7%, -1.5% and -2.7% in VP and -0.4%, -0.4% and -0.6% in non-VP for all-cause mortality, cardiovascular mortality and BARC 3 or 5 bleeding respectively; as shown on table 3, and on table 6 of the supplementary data).

There was also no interaction between allocation to antithrombin treatment and VP criteria for MACE or NACE (interaction *P* = .43 and.17, respectively; see figure 2 and table 3, and figure 3 of the supplementary data and table 7 of the supplementary data). Bivalirudin was associated with a nominally significant reduction of all-cause and cardiovascular mortality as compared with UFH in VP (all-cause mortality: RR, 0.51; 95%CI, 0.31-0.84; *P* = .007; cardiovascular mortality: RR, 0.50; 95%CI, 0.30-0.83; *P* = .006; with risk differences of -5.3% for both), but not in non-VP (all-cause mortality: RR, 0.99; 95%CI, 0.62-1.58; *P* = .97; cardiovascular mortality: RR, 0.99; 95%CI: 0.60-1.65; *P* = .97; with risk differences of 0% for both; see table 3, and table 7 of the supplementary data). However, interaction testing for both endpoints did not reach statistical significance (interaction *P* = .056 and .060 respectively, figure 4 of the supplementary data). Bivalirudin reduced BARC 3 or 5 bleeding rates in both VP (RR, 0.30; 95%CI, 0.13-0.66; *P* = .0015) and non-VP (RR 0.65; 95%CI, 0.45-0.95; *P* = .023) groups as compared with UFH (interaction *P* = .073), with

somewhat greater absolute benefit in the former (absolute risk difference -4.4%) as compared to the latter group (absolute risk difference -0.8%; table 3, table 7 of the supplementary data).

Additional analyses

Overall findings were largely consistent when the VP group was stratified according to the presence, absence or severity of advanced Killip class or OHCA at presentation as well as according to pre-specified subgroups (data not shown) or alternative statistical methods were applied (table 8 of the supplementary data).

DISCUSSION

MATRIX is the largest and most contemporary randomized trial comparing TRA versus TFA and the only study nesting the access site comparison with a random selection of antithrombin types, including bivalirudin or UFH (± GPI) in ACS patients undergoing invasive management. In this study, 11.1% of patients presented with hemodynamic (advanced Killip class) or electrical instability (OHCA survivors) and were deemed VP according to the post-hoc analysis.

Our main findings can be summarized as follows:

VP (9.6% with acute HF and 2.0% with OHCA, with 0.5% exhibiting both conditions) presented more frequently with cardiovascular risk factors, fulfilled more frequently procedural complexity criteria and experienced a higher risk of adverse clinical outcomes compared with non-VP.

Radial access was associated with a consistent relative risk reduction of composite primary as well as key secondary endpoints, including mortality and severe bleeding events, in VP and non-

VP groups compared with TFA. However, since event rate was much higher in VP, those experienced larger absolute risk reduction by TFA as compared to non-VP group.

The comparative safety and effectiveness of bivalirudin versus UFH were consistent between VP and non-VP, with greater absolute bivalirudin-related benefits in the former as compared to the latter group.

Access site selection in patients with hemodynamic or electrical vulnerability

Patients with ACS presenting with hemodynamic or electrical vulnerability are frequent in daily practice and suffer from a higher risk of morbidity and mortality. ESC guidelines underline that high-risk ACS patients with acute HF, cardiogenic shock or OHCA are those who benefit the most from expediting all steps of the care pathway[1,2]. Yet, there is no specific recommendation concerning the preferable access site or antithrombotic treatment combination for angiography and/or PCI, if clinically indicated. This reflects the paucity of randomized data on this high-risk ACS patient population undergoing invasive management.

TRA is recommended over TFA in ACS patients across the board in the ESC but no in the ACC/AHA guidelines. In vulnerable patients with hemodynamic or electrical instability, TFA is more frequently undertaken, as low systolic and mean arterial pressure hampers radial artery accessibility, coronary intervention is typically more complex and the need for concomitant hemodynamic support devices more frequent. Advanced Killip class has been repeatedly identified among the main causes of radial failure[12-14]. However, over the last years, experience and emerging techniques have facilitated the use of TRA. A large analysis of the NCDR CathPCI Registry on 692 433 STEMI patients undergoing primary PCI explored the temporal trends of TRA,

which increased from 2% in 2009 to 23% in 2015, with significant geographic variation[15]. Age, sex, cardiogenic shock, cardiac arrest, operators entering practice before 2012, and non-academically affiliated institutions were all associated with lower rates of TRA[15]. Among the 7,231 patients with advanced Killip class in the British Cardiovascular Intervention Society database, TFA was used in 5354 and TRA in 1877 patients. TRA was independently associated with lower 30-day mortality, in-hospital MACE and major bleeding[16]. In the present study, we observed that TRA remained associated with consistent benefits in VP as compared to non-VP, with a treatment effect on absolute basis being larger in the former as compared to the latter group. A reasonable interpretation of our findings is that use of TRA does not seem to be associated to specific penalties in VP, who suffer from greater absolute risks and derive a higher absolute risk reduction from this intervention. Our observation, therefore, supports the use of TRA as default access in all ACS patients undergoing invasive management. At subgroup analysis, the effect of TRA versus TFA remained consistent throughout all pre-specified covariates with the notable exception for centre proportion of radial PCI. Both VP and non-VP groups allocated to TRA in centres with the highest proportion of radial PCI experienced a clinically meaningful reduction of MACE or NACE endpoints as compared to TFA. On the other hand, in centres with a low or average proportion of radial PCI, TRA was apparently associated with somewhat smaller benefits in non-VP or even a slightly increased risk, especially for MACE, in VP. The current findings should be interpreted by taking into account that operators enrolling in MATRIX had to be adequately trained to both TRA and TFA. This observation carries important clinical implications[17], reinforcing the notion that especially for VP undergoing invasive management, TRA should be the default access site only if performed by routine radial operators. Conversely, less expert centres/operators might further expand their training by selecting TRA in less vulnerable patients.

Antithrombin type in patients with hemodynamic or electrical vulnerability

Data comparing bivalirudin to UFH in ACS patients presenting with HF and/or OHCA are limited[18]. Some evidence suggests that chronic HF, independent of atherosclerosis and ACS, is associated with elevated thrombin levels and faster formation of compact, resistant fibrin clots, thus bivalirudin might be even more beneficial in these patients[4,5]. In the EUROMAX, there was no significant interaction for the primary endpoint across patients with Killip class I vs II-IV, but this latter group was small (77 and 69 in the bivalirudin and heparin, respectively)[19]. In the HEAT-PPCI, the primary endpoint was consistent across stratification according to left ventricular function impairment (defined by left ventricle ejection fraction < 55%)[20]. Pinto et al. reported an analysis of the Premier Hospital Database comparing the use of bivalirudin and heparin in more than 116 000 congestive HF patients undergoing PCI. In-hospital mortality, which was the primary outcome of the study, was lower for bivalirudin monotherapy (2.3%) as compared to heparin monotherapy (4.8%)[5]. In a matched propensity-score analysis, a mortality benefit remained associated with the use of bivalirudin compared to heparin. Bivalirudin therapy was also associated with lower bleeding or transfusion rates, as well as shorter hospitalizations[5].

In the MATRIX trial, bivalirudin failed to significantly reduce the composite co-primary endpoints compared with UFH, but was associated with lower rates of major bleeding and all-cause mortality, irrespective of GPI use in the comparator arm[7,21]. In the current analysis, we observed that VP showed greater absolute benefits from bivalirudin as compared to UFH with respect to both co-primary endpoints, likely reflecting the higher event rates observed in these patients. The trends in favour of bivalirudin in VP at interaction testing for all-cause, cardiovascular fatalities or major bleeding might suggest that a direct as compared to an indirect thrombin inhibitor might be particularly beneficial in this selected population. The significant reduction of

mortality and cardiovascular mortality, despite a trend towards higher MI, with bivalirudin observed in VP, might be probably attributed to the greater benefit that these patients had in terms of major bleeding, and partially to the trend in lower stroke rates compared with Non-VP group. However, our analyses remain inconclusive and at best hypothesis generating. Subgroup analyses showed that prior administration of UFH but not ticagrelor or prasugrel might further optimize the MACE or NACE endpoints as compared to UFH in VP, which is at variance with the corresponding observation in the non-VP group. The notion that the uptake of even newer P2Y12 oral inhibitors is particularly delayed in VP[22] may provide a possible mechanistic explanation for our current findings, which altogether reinforce the message that parenteral strategies (i.e., cangrelor or short glycoprotein IIb/IIIa inhibitors infusion or prolonged bivalirudin at full PCI dose)[22-24] more than oral antiplatelet agents might be prioritized in VP.

Limitations

This is a post-hoc analysis of the MATRIX trial, which was not powered to investigate the effects of the experimental treatment strategies in the VP subgroup. Our results should be interpreted in the context of uncontrolled Type I and Type II errors and regarded as hypothesis-generating. We did not adjust for multiple comparisons, increasing the risk of type I error. The MATRIX study did not exclude patients based on advanced Killip class or OHCA at presentation. Yet, it remains unknown if and how much this high-risk patient category was consecutively included in the study. The requirement of written informed consent before patient participation obviously skewed inclusion towards conscious and collaborative patients only, to whom our results should apply. Yet, the proportion of VP (11.1%) compares favourably to many other previous ACS studies, which almost completely excluded them from inclusion.

Our definition of VP was not pre-specified and encompasses a heterogeneous patient population and only few patients with overt cardiogenic shock (Killip class IV) were included at the time of PCI.

CONCLUSIONS

In patients with ACS undergoing invasive management, the effects of radial versus femoral and bivalirudin versus unfractionated heparin were consistent in patients with or without hemodynamic and/or electrical vulnerability. Absolute event rates were greater in VP, and both TRA and bivalirudin were associated with greater absolute risk reduction for both ischemic and bleeding endpoints in this patient subset as compared to TFA or UFH, respectively.

WHAT IS KNOWN ABOUT THIS TOPIC?

- TRA has various advantages compared with TFA and is currently the recommended approach in ACS patients undergoing PCI.
- Concerns have been raised particularly among patients with hemodynamic (i.e. advanced Killip class) or electrical (OHCA survivors) vulnerability (HVP) in whom TFA may constitute a more reliable and quicker access to achieve a diagnosis and deliver timely treatment.
- In these patients the optimal antithrombotic therapy is also uncertain.

WHAT DOES THIS STUDY ADD?

- In this large and contemporary randomized clinical trial, vulnerable patients (VP: 9.6% with acute HF and 2.0% with OHCA, with 0.5% exhibiting both conditions) presented more frequently with cardiovascular risk factors, fulfilled more frequently procedural complexity criteria and experienced a higher risk of adverse clinical outcomes compared with non-VP.
- Radial access was associated with a consistent relative risk reduction of composite primary as well as key secondary endpoints, including mortality and severe bleeding events, in VP and non-VP groups compared with TFA. However, since event rate was much higher in VP, those experienced larger absolute risk reduction by TFA.
- The comparative safety and effectiveness of bivalirudin versus UFH were consistent between VP and non-VP, with greater absolute bivalirudin-related benefits in the former as compared to the latter group.

CONFLICT OF INTEREST

M. Sunnåker is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. The conflicts of interest of CTU Bern can be found on the University website. P. Vranckx reports consulting fees from AstraZeneca and the Medicines Company during the study; speaking or consulting fees from Bayer, Health Care, Terumo and Daiichi-Sankyo outside the submitted work. S. Leonardi reports consulting fees from AstraZeneca, Chiesi and the Medicines Company during the study and outside the submitted work. S. Windecker reports research contracts to the institution from Abbott, Amgen, Boston Scientific, Biotronik, Medtronic, Edwards Lifesciences, St Jude and Terumo. M. Valgimigli reports grants from The Medicines Company, grants from Terumo, during the conduct of the study; grants and personal fees from AstraZeneca, personal fees and nonfinancial support from The Medicines Company, personal fees from Terumo, St Jude Vascular, Alvimedica, Abbott Vascular, and Correvio, outside the submitted work.

Other authors have nothing to disclose.

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FIGURE LEGEND

Figure 1. Main outcomes of radial versus femoral access in VP and non-VP

Radial and femoral access were compared on the basis of hemodynamic/electric vulnerability, with rare ratios and 95% confidence intervals (CI), for the co-primary endpoints and their components (death, myocardial infarction, stroke, BARC 3 or 5). BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; VP, vulnerable patients.

Figure 2. Main outcomes of bivalirudin versus UFH in VP and non-VP

Bivalirudin and UFH were compared on the basis of hemodynamic/electric vulnerability, with rare ratios and 95% confidence intervals (CIs), for the co-primary endpoints and their components (death, myocardial infarction, stroke, BARC 3 or 5). BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; UFH, unfractionated heparin; VP, vulnerable patients.

Table 1. Baseline characteristics in patients with or without hemodynamic or electrical vulnerability

	VP (HF and/or OHCA)	HF (KC > 1)	OHCA	Non-VP	*P* *
Number of patients	934	808	168	7470	
Age (years)	69.5 (11.6)	70.4 (11.2)	64.0 (11.9)	65.3 (11.8)	< .0001
≥75 years	367 (39.3)	340 (42.1)	36 (21.4)	1815 (24.3)	< .0001
Men	637 (68.2)	546 (67.6)	125 (74.4)	5535 (74.1)	.0001
BMI (kg/m²)	27.1 (4.6)	27.2 (4.6)	26.9 (4.5)	27.1 (4.1)	.5861
Diabetes mellitus	300 (32.1)	281 (34.8)	28 (16.7)	1603 (21.5)	< .0001
Insulin-dependent	94 (10.1)	88 (10.9)	9 (5.4)	372 (5.0)	< .0001
Current Smoker	290 (31.0)	239 (29.6)	69 (41.1)	2597 (34.8)	.0241
Hypercholesterolemia	390 (41.8)	340 (42.1)	69 (41.1)	3301 (44.2)	.1576
Hypertension	650 (69.6)	587 (72.6)	83 (49.4)	4661 (62.4)	< .0001
Previous myocardial infarction	190 (20.3)	177 (21.9)	22 (13.1)	1013 (13.6)	< .0001
Previous PCI	166 (17.8)	154 (19.1)	22 (13.1)	1029 (13.8)	.0010
Previous CABG	44 (4.7)	41 (5.1)	3 (1.8)	213 (2.9)	.0019
Previous TIA or stroke	67 (7.2)	62 (7.7)	9 (5.4)	358 (4.8)	.0017
Peripheral vascular disease	134 (14.3)	125 (15.5)	16 (9.5)	579 (7.8)	< .0001

Renal failure	41 (4.4)	40 (5.0)	2 (1.2)	64 (0.9)	< .0001
Dialysis	2 (0.2)	2 (0.2)	0 (0.0)	6 (0.1)	.2206
ST-segment elevation myocardial infarction	517 (55.4)	418 (51.7)	139 (82.7)	3493 (46.8)	< .0001
NSTE-ACS	417 (44.6)	390 (48.3)	29 (17.3)	3977 (53.2)	< .0001
NSTE-ACS, troponin positive	384 (41.1)	360 (44.6)	26 (15.5)	3502 (46.9)	.0009
Left ventricular ejection fraction (%)	44.4 (11.4)	43.8 (11.7)	45.9 (10.1)	51.9 (9.1)	< .0001
Systolic arterial pressure	131.5 (30.6)	131.8 (31.3)	123.6 (28.1)	139.6 (24.7)	< .0001
Heart rate	82.2 (21.0)	83.3 (21.2)	77.4 (21.3)	75.4 (15.9)	< .0001
eGFR	74.3 (27.1)	73.1 (±27.2)	78.9 (25.4)	84.9 (25.0)	< .0001
eGFR<60 ml/min	305 (33.0)	280 (35.1)	41 (24.6)	1110 (15.0)	< .0001

Data are expressed as no. (%) or mean (±) standard deviation. BMI,body mass index; CABG,coronary artery bypass graft; eGFR,estimated glomerular filtration rate; HF,heart failure; NSTE-ACS,non-ST-segment elevation acute coronary syndrome; OHCA,out of hospital cardiac arrest; PCI,percutaneous coronary intervention; TIA,transient ischemic attach; VP,hemodynamic/electrical vulnerable patients; KC,Killip class.

*P value for comparison of VP versus non-VP.

Table 2. Procedural characteristics in patients with or without hemodynamic or electrical vulnerability

	VP (HF and/or OHCA)	HF (KC > 1)	OHCA	Non-VP	*P* *
Number of patients	934	808	168	7470	
Only radial access site	428 (45.8)	369 (45.7)	80 (47.6)	3592 (48.1)	.1921
Only femoral access site	455 (48.7)	391 (48.4)	82 (48.8)	3642 (48.8)	.9817
Both radial and femoral access site	51 (5.5)	48 (5.9)	6 (3.6)	229 (3.1)	.0001
Other access site	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.1)	-
Crossover	51 (5.5)	48 (5.9)	6 (3.6)	232 (3.1)	.0002
Coronary angiography completed	934 (100.0)	808 (100.0)	168 (100.0)	7461 (99.9)	-
Medications in the catheterization laboratory					
Aspirin	52 (5.6)	41 (5.1)	14 (8.3)	429 (5.7)	.8277
Clopidogrel	70 (7.5)	63 (7.8)	8 (4.8)	453 (6.1)	.0880
Prasugrel	59 (6.3)	41 (5.1)	29 (17.3)	567 (7.6)	.1623
Ticagrelor	92 (9.9)	73 (9.0)	24 (14.3)	684 (9.2)	.4901
Unfractionated heparin	439 (47.0)	381 (47.2)	82 (48.8)	3457 (46.3)	.6758
Glycoprotein IIb/IIIa inhibitor (GPI)	150 (16.1)	128 (15.8)	34 (20.2)	945 (12.7)	.0035
Planned GPI	105 (11.2)	88 (10.9)	28 (16.7)	678 (9.1)	.0318
Bailout GPI	45 (4.8)	40 (5.0)	6 (3.6)	267 (3.6)	.0580
Bivalirudin	373 (39.9)	314 (38.9)	75 (44.6)	3054 (40.9)	.5784

Post-PCI Bivalirudin	181 (19.4)	151 (18.7)	40 (23.8)	1544 (20.7)	.3573
Intra-aortic balloon pump	81 (10.9)	77 (12.2)	14 (9.3)	75 (1.3)	< .0001
CABG after coronary angiography	48 (5.1)	47 (5.8)	2 (1.2)	262 (3.5)	.0128
Completed PCI after coronary angiography	741 (79.3)	630 (78.0)	151 (89.9)	5983 (80.1)	.5852
At least one planned staged procedure	168 (18.0)	136 (16.8)	35 (20.8)	1340 (17.9)	.9708
Treated vessel(s)					
Left main coronary artery	84 (11.3)	81 (12.9)	10 (6.6)	185 (3.1)	< .0001
Left anterior descending artery	399 (53.8)	342 (54.3)	77 (51.0)	2915 (48.7)	.0085
Left circumflex artery	201 (27.1)	178 (28.3)	34 (22.5)	1599 (26.7)	.8167
Right coronary artery	217 (29.3)	178 (28.3)	53 (35.1)	1998 (33.4)	.0247
Bypass graft	10 (1.3)	10 (1.6)	0 (0.0)	45 (0.8)	.0886
≥2 vessels treated	153 (20.6)	143 (22.7)	19 (12.6)	733 (12.3)	< .0001
Overall stent length (mm)	34.7 (22.0)	35.3 (22.1)	32.8 (22.2)	31.3 (19.1)	< .0001
Duration of procedure, min	58.3 (28.5)	59.3 (28.9)	56.8 (29.3)	54.2 (28.1)	.0002

Data are expressed as no. (%) or mean ± standard deviation. CABG, coronary artery bypass graft; HF, heart failure; KC, Killip class; OHCA, out of hospital cardiac arrest; PCI, percutaneous coronary intervention; VP, hemodynamic/electrical vulnerable patients.

**P* value for comparison of VP versus non-VP.

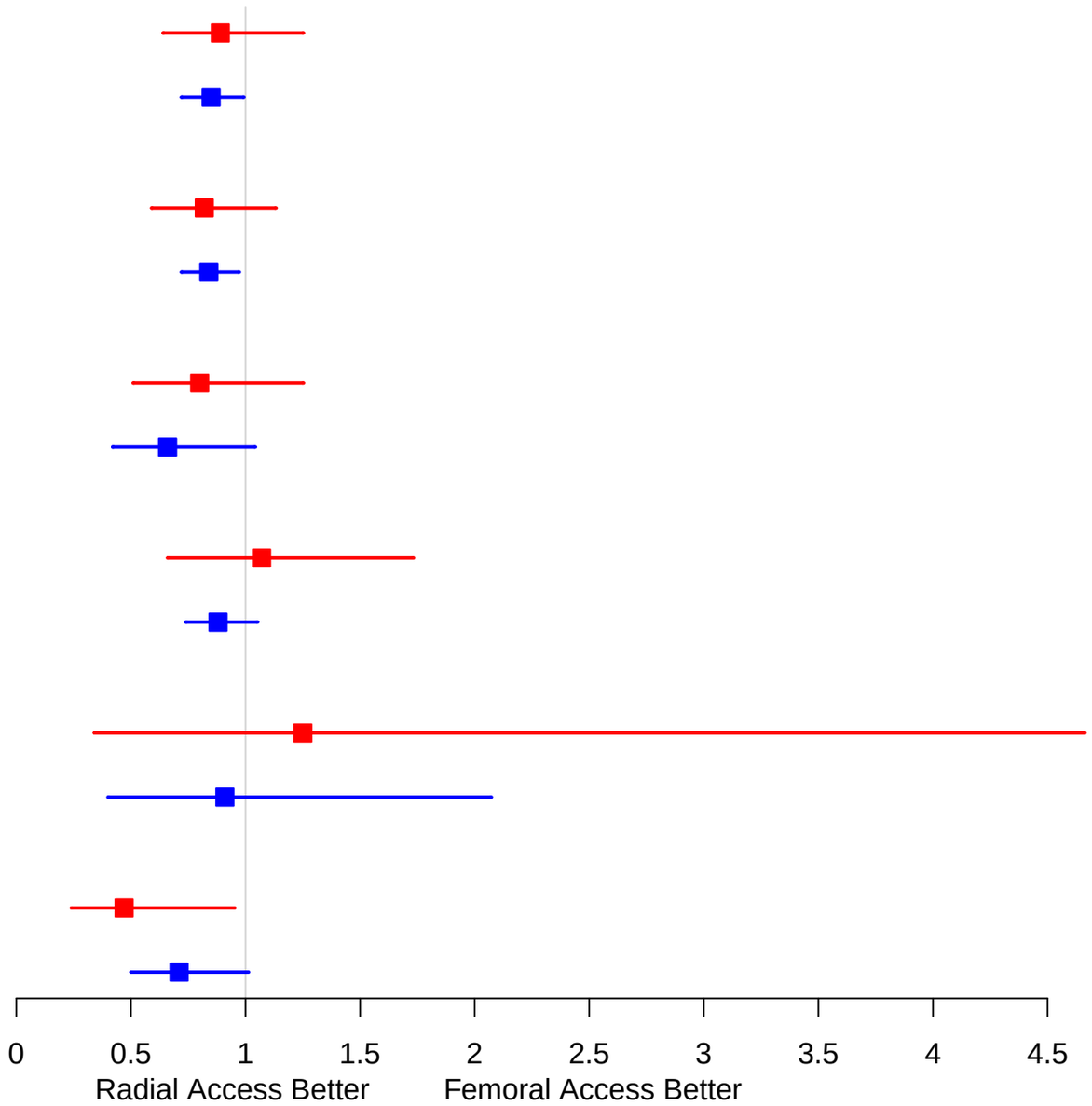
Table 3. Main clinical outcomes at 30 days of TRA vs TFA and bivalirudin vs UFH in patients with or without hemodynamic or electrical vulnerability

	VP						Non-VP						
	Radial access	Femoral access	Risk difference (%)	NNT/NNH	Rate ratio (95%CI)	*P*	Radial access	Femoral access	Risk difference (%)	NNT/NNH	Rate ratio (95% CI)	*P*	*P* for interaction
Number of patients	462	472					3735	3735					
Co-primary composite endpoint of all-cause mortality, MI or stroke	69 (14.9)	78 (16.5)	-1.6 (-6.3 to 3.1)	63	0.89 (0.64-1.25)	0.51	300 (8.1)	351 (9.5)	-1.4 (-2.6 to -0.1)	73	0.85 (0.72-0.99)	.039	.77
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	73 (15.8)	89 (18.9)	-3.1 (-7.9 to 1.8)	33	0.82 (0.59-1.13)	0.22	337 (9.0)	397 (10.7)	-1.6 (-3.0 to -0.3)	62	0.84 (0.72-0.97)	0.022	0.89
Composite of all-cause mortality, MI, stroke, urgent TVR, definite stent thrombosis	74 (16.0)	89 (18.9)	-2.8 (-7.7 to 2.0)	35	0.83 (0.60-1.14)	0.25	345 (9.3)	402 (10.9)	-1.5 (-2.9 to -0.2)	66	0.85 (0.73-0.98)	0.030	0.91
All-cause mortality	35 (7.6)	44 (9.3)	-1.7 (-5.3 to 1.8)	57	0.80 (0.51-1.25)	0.32	31 (0.8)	47 (1.3)	-0.4 (-0.9 to 0.0)	233	0.66 (0.42-1.04)	0.068	0.55
Cardiovascular death	34 (7.4)	42 (8.9)	-1.5 (-5.0 to 2.0)	65	0.81 (0.51-1.28)	0.37	26 (0.7)	41 (1.1)	-0.4 (-0.8 to 0.0)	249	0.63 (0.39-1.03)	0.065	0.46
Myocardial infarction	36 (7.8)	34 (7.2)	0.6 (-2.8 to 4.0)	-170	1.07 (0.66-1.73)	0.78	263 (7.1)	296 (7.9)	-0.9 (-2.1 to 0.3)	113	0.88 (0.74-1.05)	0.15	0.46
Stroke	5 (1.1)	4 (0.9)	0.2 (-1.0 to 1.5)	-426	1.25 (0.34-4.66)	0.74	11 (0.3)	12 (0.3)	-0.0 (-0.3 to 0.2)	3735	0.91 (0.40-2.07)	0.83	0.69
BARC Type 3 or 5	12 (2.7)	25 (5.5)	-2.7 (-5.2 to -0.2)	37	0.47 (0.24-0.95)	0.031	53 (1.4)	74 (2.0)	-0.6 (-1.1 to 0.0)	178	0.71 (0.50-1.01)	0.059	0.30
Composite of surgical access site repair or blood products transfusion	8 (2.0)	18 (4.0)	-2.1 (-4.2 to 0.0)	48	0.44 (0.19-1.01)	0.047	34 (0.9)	55 (1.5)	-0.6 (-1.1 to -0.1)	178	0.62 (0.40-0.94)	0.025	0.48
	Bivalirudin	UFH					Bivalirudin	UFH					
Number of patients	397	422					3213	3181					
Co-primary composite endpoint of all-cause mortality, MI or stroke	61 (15.4)	76 (18.0)	-2.6 (-7.7 to 2.5)	38	0.84 (0.59-1.19)	0.33	313 (9.8)	316 (10.0)	-0.2 (-1.7 to 1.3)	520	0.98 (0.83-1.15)	0.80	0.43
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	63 (15.9)	89 (21.1)	-5.2 (-10.5 to 0.1)	19	0.73 (0.52-1.02)	0.064	345 (10.8)	361 (11.4)	-0.6 (-2.1 to 0.9)	164	0.94 (0.81-1.10)	0.45	0.17

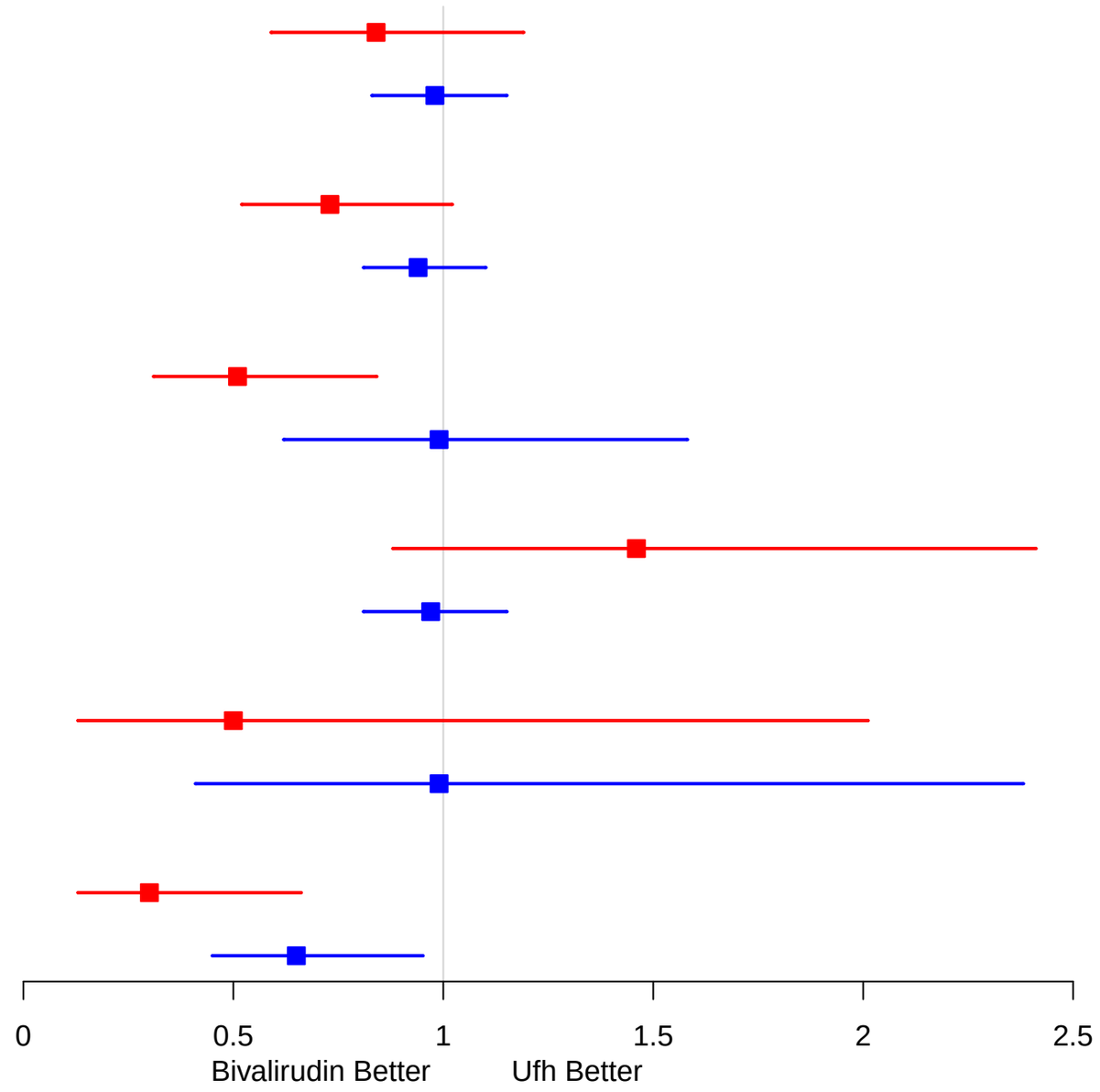
Composite of all-cause mortality, MI, stroke, urgent TVR, definite stent thrombosis	64 (16.1)	89 (21.1)	-5.0 (-10.3 to 0.3)	20	0.74 (0.53-1.04)	0.079	351 (11.0)	367 (11.6)	-0.6 (-2.2 to 0.9)	163	0.94 (0.81-1.10)	0.45	0.20
All-cause mortality	24 (6.0)	48 (11.4)	-5.3 (-9.2 to -1.5)	19	0.51 (0.31-0.84)	0.0070	35 (1.1)	35 (1.1)	-0.0 (-0.5 to 0.5)	9125	0.99 (0.62-1.58)	0.97	0.056
Cardiovascular death	23 (5.8)	47 (11.1)	-5.3 (-9.1 to -1.6)	19	0.50 (0.30-0.83)	0.0063	30 (0.9)	30 (1.0)	-0.0 (-0.5 to 0.5)	10 646	0.99 (0.60-1.65)	0.97	0.060
Myocardial infarction	39 (10.0)	28 (6.9)	3.2 (-0.6 to 7.0)	-31	1.46 (0.88-2.41)	0.14	271 (8.5)	277 (8.8)	-0.3 (-1.6 to 1.1)	366	0.97 (0.81-1.15)	0.71	0.13
Stroke	3 (0.8)	6 (1.6)	-0.7 (-2.1 to 0.7)	150	0.50 (0.13-2.01)	0.32	10 (0.3)	10 (0.3)	-0.0 (-0.3 to 0.3)	31 939	0.99 (0.41-2.38)	0.98	0.41
BARC Type 3 or 5	8 (2.1)	27 (6.7)	-4.4 (-7.1 to -1.7)	23	0.30 (0.13-0.66)	0.0015	47 (1.5)	71 (2.3)	-0.8 (-1.4 to -0.1)	130	0.65 (0.45-0.95)	0.023	0.073
Composite of surgical access site repair or blood products transfusion	5 (1.6)	18 (4.5)	-3.0 (-5.2 to -0.8)	33	0.28 (0.10-0.75)	0.0072	31 (1.0)	50 (1.6)	-0.6 (-1.2 to -0.1)	165	0.61 (0.39-0.96)	0.031	0.15

Data are expressed as no. (%) unless otherwise indicated. BARC, bleeding academic research consortium; CI, confidence interval; KC, Killip class; OHCA, out of hospital cardiac arrest; MI, myocardial infarction; NNT/NNH, number needed to treat/harm; TVR, target vessel revascularization; UFH, unfractionated heparin; VP, hemodynamic/electrical vulnerable patients.

Outcome	Rate Ratio (95% CI)	Risk difference (95% CI)	Needed to treat	P for interaction
Co−primary composite endpoint of all−cause mortality, MI or stroke				0.77
VP	0.89 (0.64−1.25)	−1.6 (−6.3 to 3.1)	63	
non−VP	0.85 (0.72−0.99)	−1.4 (−2.6 to −0.1)	73	
Co−primary composite endpoint of all−cause mortality, MI, stroke, or BARC 3 or 5				0.89
VP	0.82 (0.59−1.13)	−3.1 (−7.9 to 1.8)	33	
non−VP	0.84 (0.72−0.97)	−1.6 (−3.0 to −0.3)	62	
All−cause mortality				0.55
VP	0.80 (0.51−1.25)	−1.7 (−5.3 to 1.8)	57	
non−VP	0.66 (0.42−1.04)	−0.4 (−0.9 to 0.0)	233	
Myocardial infarction				0.46
VP	1.07 (0.66−1.73)	0.6 (−2.8 to 4.0)	−170	
non−VP	0.88 (0.74−1.05)	−0.9 (−2.1 to 0.3)	113	
Stroke				0.69
VP	1.25 (0.34−4.66)	0.2 (−1.0 to 1.5)	−426	
non−VP	0.91 (0.40−2.07)	−0.0 (−0.3 to 0.2)	3735	
Bleeding BARC 3 or 5				0.30
VP	0.47 (0.24−0.95)	−2.7 (−5.2 to −0.2)	37	
non−VP	0.71 (0.50−1.01)	−0.6 (−1.1 to 0.0)	178	



Outcome	Rate Ratio (95% CI)	Risk difference (95% CI)	Needed to treat	P for interaction
Co−primary composite endpoint of all−cause mortality, MI or stroke				0.43
VP	0.84 (0.59−1.19)	−2.6 (−7.7 to 2.5)	38	
non−VP	0.98 (0.83−1.15)	−0.2 (−1.7 to 1.3)	520	
Co−primary composite endpoint of all−cause mortality, MI, stroke, or BARC 3 or 5				0.17
VP	0.73 (0.52−1.02)	−5.2 (−10.5 to 0.1)	19	
non−VP	0.94 (0.81−1.10)	−0.6 (−2.1 to 0.9)	164	
All−cause mortality				0.056
VP	0.51 (0.31−0.84)	−5.3 (−9.2 to −1.5)	19	
non−VP	0.99 (0.62−1.58)	−0.0 (−0.5 to 0.5)	9125	
Myocardial infarction				0.13
VP	1.46 (0.88−2.41)	3.2 (−0.6 to 7.0)	−31	
non−VP	0.97 (0.81−1.15)	−0.3 (−1.6 to 1.1)	366	
Stroke				0.41
VP	0.50 (0.13−2.01)	−0.7 (−2.1 to 0.7)	150	
non−VP	0.99 (0.41−2.38)	−0.0 (−0.3 to 0.3)	31939	
Bleeding BARC 3 or 5				0.073
VP	0.30 (0.13−0.66)	−4.4 (−7.1 to −1.7)	23	
non−VP	0.65 (0.45−0.95)	−0.8 (−1.4 to −0.1)	130	



Choice of access site and type of anticoagulant in acute coronary syndromes with advanced Killip class or out of hospital cardiac arrest.

SUPPLEMENTARY DATA CONTENT

Supplementary Table 1 Baseline characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized access site

Supplementary Table 2 Procedural characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized access site

Supplementary Table 3 Baseline characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized antithrombin type

Supplementary Table 4 Procedural characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized antithrombin type

Supplementary Table 5 Clinical outcomes at 30 days in patients with or without hemodynamic or electrical vulnerability

Supplementary Table 6 Clinical outcomes at 30 days of TRA vs TFA in patients with or without hemodynamic or electrical vulnerability

Supplementary Table 7 Clinical outcomes at 30 days of bivalirudin vs unfractionated heparin in patients with or without hemodynamic or electrical vulnerability

Supplementary Table 8 Sensitivity analysis of main clinical outcomes at 30 days analysed with Cox regression analysis and competing risk for both TRA vs TFA and bivalirudin vs unfractionated heparin in patients with or without hemodynamic or electrical vulnerability

Supplementary Figure 1 Coprimary composite access-related outcomes at 30 days in VP and non-VP

Supplementary Figure 2 Components of coprimary composite access-related outcomes at 30 days in VP and non-VP

Supplementary Figure 3 Coprimary composite antithrombin-related outcomes at 30 days in VP and non-VP

Supplementary Figure 4 Components of coprimary composite antithrombin-related outcomes at 30 days in VP and non-VP

Supplementary Table 1. Baseline characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized access site

	VP			Non-VP			
	Radial Access	**Femoral Access**	***P***	**Radial Access**	**Femoral Access**	***P***	***P* for interaction**
Number of patients	**462**	**472**		**3735**	**3735**		
Age (years)	69.1 ± 11.9	69.9 ± 11.3	.26	65.2 ± 11.8	65.4 ± 11.8	.40	.44
≥ 75 years	176 (38.1)	191 (40.5)	.46	897 (24.0)	918 (24.6)	.57	.63
Men	321 (69.5)	316 (66.9)	.41	2805 (75.1)	2730 (73.1)	.048	.94
BMI (kg/m²)	27.3 ± 4.8	27.0 ± 4.5	.28	27.1 ± 4.1	27.1 ± 4.1	.74	.22
Diabetes mellitus	156 (33.8)	144 (30.5)	.29	803 (21.5)	800 (21.4)	.93	.34
Insulin-dependent	44 (9.5)	50 (10.6)	.59	165 (4.4)	207 (5.5)	.025	.62
Current smoker	161 (34.8)	129 (27.3)	.013	1298 (34.8)	1299 (34.8)	.98	.019
Hypercholesterolemia	189 (40.9)	201 (42.6)	.60	1610 (43.1)	1691 (45.3)	.059	.89
Hypertension	325 (70.3)	325 (68.9)	.62	2300 (61.6)	2361 (63.2)	.15	.35
Previous myocardial infarction	89 (19.3)	101 (21.4)	.42	496 (13.3)	517 (13.8)	.48	.63
Previous PCI	77 (16.7)	89 (18.9)	.38	533 (14.3)	496 (13.3)	.21	.21
Previous CABG	20 (4.3)	24 (5.1)	.59	91 (2.4)	122 (3.3)	.031	.70
Previous TIA or stroke	25 (5.4)	42 (8.9)	.039	170 (4.6)	188 (5.0)	.33	.13
Peripheral vascular disease	64 (13.9)	70 (14.8)	.67	277 (7.4)	302 (8.1)	.28	.95
Renal failure	19 (4.1)	22 (4.7)	.68	27 (0.7)	37 (1.0)	.21	.65
Dialysis	1 (0.2)	1 (0.2)	1.00	3 (0.1)	3 (0.1)	1.00	.99
ST-segment elevation myocardial infarction	275 (59.5)	242 (51.3)	.011	1726 (46.2)	1767 (47.3)	.34	.0068
NSTE-ACS	275 (59.5)	242 (51.3)	.011	1726 (46.2)	1767 (47.3)	.34	.0068
NSTE-ACS, troponin positive	174 (37.7)	210 (44.5)	.034	1780 (47.7)	1722 (46.1)	.18	.015
Left ventricular ejection fraction (%)	44.8 ± 11.3	44.0 ± 11.6	.31	52.1 ± 9.0	51.7 ± 9.1	.091	.53
Systolic arterial pressure	130.6 ± 31.0	132.3 ± 30.3	.43	139.5 ± 24.6	139.7 ± 24.9	.73	.43
Heart rate	82.5 ± 21.4	82.0 ± 20.6	.72	75.5 ± 15.7	75.3 ± 16.1	.44	.86
eGFR	75.1 ± 27.6	73.5 ± 26.6	.39	85.3 ± 24.9	84.6 ± 25.1	.21	.65
eGFR<60 ml/min	151 (33.2)	154 (32.9)	.93	549 (14.8)	561 (15.1)	.68	.80

Data are expressed as no. (%) or mean ± standard deviation

Abbreviations: BMI,body mass index; CABG,coronary artery bypass graft; eGFR,estimated glomerular filtration rate; HF,heart failure; NSTE-ACS,non-ST-segment elevation acute coronary syndrome; OHCA,out of hospital cardiac arrest; PCI,percutaneous coronary intervention; TIA,transient ischemic attach; VP,hemodynamic/electrical vulnerable patients; KC,Killip class.

Supplementary Table 2. Procedural characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized access site.

	VP			Non-VP			
	Radial Access	**Femoral Access**	***P***	**Radial Access**	**Femoral Access**	***P***	***P* for interaction**
Number of patients	**462**	**472**		**3735**	**3735**		
Only radial access site	428 (92.6)	0 (0.0)	< .0001	3585 (96.0)	7 (0.2)	< .0001	-
Only femoral access site	0 (0.0)	455 (96.4)	< .0001	1 (0.0)	3641 (97.5)	< .0001	-
Both radial and femoral access site	34 (7.4)	17 (3.6)	.012	147 (3.9)	82 (2.2)	< .0001	.65
Other access site	0 (0.0)	0 (0.0)	-	2 (0.1)	5 (0.1)	.45	-
Crossover	34 (7.4)	17 (3.6)	.012	149 (4.0)	83 (2.2)	< .0001	.65
Coronary angiography completed	462 (100.0)	472 (100.0)	-	3733 (99.9)	3728 (99.8)	.18	-
Medications in the catheterization laboratory							
Aspirin	25 (5.4)	27 (5.7)	.84	197 (5.3)	232 (6.2)	.082	.70
Clopidogrel	32 (6.9)	38 (8.1)	.51	237 (6.3)	216 (5.8)	.31	.33
Prasugrel	38 (8.2)	21 (4.4)	.018	297 (8.0)	270 (7.2)	.24	.060
Ticagrelor	49 (10.6)	43 (9.1)	.44	332 (8.9)	352 (9.4)	.42	.32
Unfractionated heparin	225 (48.7)	214 (45.3)	.30	1807 (48.4)	1650 (44.2)	.00027	.81
Glycoprotein IIb/IIIa inhibitor (GPI)	77 (16.7)	73 (15.5)	.62	496 (13.3)	449 (12.0)	.10	.90
Planned GPI	52 (11.3)	53 (11.2)	.99	363 (9.7)	315 (8.4)	.053	.49
Bailout GPI	25 (5.4)	20 (4.2)	.40	133 (3.6)	134 (3.6)	.95	.42
Bivalirudin	196 (42.4)	177 (37.5)	.12	1507 (40.3)	1547 (41.4)	.35	.078
Post-PCI Bivalirudin	92 (19.9)	89 (18.9)	.68	769 (20.6)	775 (20.7)	.86	.66
Intra-aortic balloon pump	41 (10.8)	40 (11.1)	.88	30 (1.0)	45 (1.5)	.084	.27
CABG after coronary angiography	20 (4.3)	28 (5.9)	.27	135 (3.6)	127 (3.4)	.62	.23
Completed PCI after coronary angiography	381 (82.5)	360 (76.3)	.019	2986 (79.9)	2997 (80.2)	.75	.021
At least one planned staged procedure	87 (18.8)	81 (17.2)	.51	680 (18.2)	660 (17.7)	.55	.67
Treated vessel(s)							
Left main coronary artery	57 (15.0)	27 (7.5)	.0014	94 (3.1)	91 (3.0)	.80	.010
Left anterior descending artery	222 (58.3)	177 (49.2)	.013	1454 (48.7)	1461 (48.7)	.97	.019
Left circumflex artery	99 (26.0)	102 (28.3)	.47	798 (26.7)	801 (26.7)	1.00	.50
Right coronary artery	90 (23.6)	127 (35.3)	.00049	1016 (34.0)	982 (32.8)	.30	.00030
Bypass graft	4 (1.0)	6 (1.7)	.54	16 (0.5)	29 (1.0)	.071	.86
≥2 vessels treated	85 (22.3)	68 (18.9)	.25	364 (12.2)	369 (12.3)	.89	.27
Overall stent length (mm)	35.3 ± 20.9	34.0 ± 23.1	.48	31.4 ± 19.1	31.1 ± 19.1	.63	.55
Duration of procedure, min	58.1 ± 28.6	58.4 ± 28.5	.89	55.0 ± 28.5	53.4 ± 27.8	.025	.38

Data are expressed as no. (%) or mean ± standard deviation. CABG,coronary artery bypass graft; HF,heart failure; KC,Killip class; OHCA,out of hospital cardiac arrest; PCI,percutaneous coronary intervention; VP,hemodynamic/electrical vulnerable patients.

Supplementary Table 3. Baseline characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized antithrombin type.

	VP			Non-VP			
	Bivalirudin	**UFH**	***P***	**Bivalirudin**	**UFH**	***P***	***P* for interaction**
Number of patients	**397**	**422**		**3213**	**3181**		
Age (years)	68.5 ± 12.1	70.0 ± 11.3	.067	65.1 ± 11.8	64.9 ± 11.8	.36	.043
≥75 years	145 (36.5)	171 (40.5)	.24	763 (23.7)	740 (23.3)	.65	.21
Men	283 (71.3)	290 (68.7)	.42	2448 (76.2)	2474 (77.8)	.13	.20
BMI (kg/m²)	27.5 ± 4.9	26.7 ± 4.1	.013	27.1 ± 4.1	27.1 ± 4.1	.67	.014
Diabetes mellitus	125 (31.5)	127 (30.1)	.67	699 (21.8)	666 (20.9)	.42	.92
Insulin-dependent	36 (9.1)	41 (9.7)	.75	165 (5.1)	149 (4.7)	.40	.52
Current Smoker	139 (35.0)	119 (28.2)	.036	1168 (36.4)	1183 (37.2)	.49	.027
Hypercholesterolemia	161 (40.6)	177 (41.9)	.69	1435 (44.7)	1381 (43.4)	.31	.47
Hypertension	277 (69.8)	283 (67.1)	.40	1987 (61.8)	1939 (61.0)	.47	.58
Previous myocardial infarction	74 (18.6)	91 (21.6)	.30	456 (14.2)	410 (12.9)	.13	.12
Previous PCI	66 (16.6)	83 (19.7)	.26	470 (14.6)	421 (13.2)	.11	.10
Previous CABG	20 (5.0)	20 (4.7)	.84	107 (3.3)	75 (2.4)	.019	.42
Previous TIA or stroke	26 (6.5)	30 (7.1)	.75	155 (4.8)	155 (4.9)	.93	.80
Peripheral vascular disease	52 (13.1)	65 (15.4)	.35	244 (7.6)	219 (6.9)	.27	.19
Renal failure	17 (4.3)	20 (4.7)	.75	31 (1.0)	27 (0.8)	.62	.58
Dialysis	1 (0.3)	0 (0.0)	.48	4 (0.1)	2 (0.1)	.69	-
ST-segment elevation myocardial infarction	249 (62.7)	268 (63.5)	.82	1763 (54.9)	1730 (54.4)	.70	.73
NSTE-ACS	148 (37.3)	154 (36.5)	.82	1450 (45.1)	1451 (45.6)	.70	.73
NSTE-ACS, troponin positive	134 (33.8)	143 (33.9)	.97	1300 (40.5)	1300 (40.9)	.74	.94
Left ventricular ejection fraction (%)	44.0 ± 11.3	44.5 ± 11.5	.57	51.3 ± 9.0	51.8 ± 8.9	.031	.97
Systolic arterial pressure	131.1 ± 30.7	130.0 ± 30.8	.61	139.5 ± 25.2	139.3 ± 24.9	.70	.65
Heart rate	81.9 ± 22.2	81.9 ± 20.0	.99	75.5 ± 15.9	75.0 ± 15.7	.17	.67
eGFR	75.4 ± 26.7	73.9 ± 27.8	.41	84.6 ± 24.7	85.8 ± 25.1	.051	.14
eGFR<60 ml/min	117 (29.8)	144 (34.4)	.16	472 (14.8)	444 (14.1)	.42	.11

Data are expressed as no. (%) or mean ± standard deviation

Abbreviations: BMI,body mass index; CABG,coronary artery bypass graft; eGFR,estimated glomerular filtration rate; HF,heart failure; NSTE-ACS,non-ST-segment elevation acute coronary syndrome; OHCA,out of hospital cardiac arrest; PCI,percutaneous coronary intervention; TIA,transient ischemic attach; VP,hemodynamic/electrical vulnerable patients; KC,Killip class.

Supplementary Table 4. Procedural characteristics in patients with or without hemodynamic or electrical vulnerability and according to the randomized antithrombin type

	VP			Non-VP			
	Bivalirudin	**UFH**	***P***	**Bivalirudin**	**UFH**	***P***	***P* for interaction**
Number of patients	**397**	**422**		**3213**	**3181**		
Only radial access site	188 (47.4)	189 (44.8)	.46	1516 (47.2)	1526 (48.0)	.53	.36
Only femoral access site	182 (45.8)	208 (49.3)	.32	1585 (49.3)	1546 (48.6)	.56	.26
Both radial and femoral access site	27 (6.8)	25 (5.9)	.61	109 (3.4)	107 (3.4)	.95	.66
Other access site	0 (0.0)	0 (0.0)	-	3 (0.1)	2 (0.1)	1.00	-
Coronary angiography completed	397 (100.0)	422 (100.0)	-	3210 (99.9)	3178 (99.9)	1.00	-
Medications in the catheterization laboratory							
Aspirin	22 (5.5)	31 (7.3)	.29	210 (6.5)	222 (7.0)	.48	.45
Clopidogrel	31 (7.8)	42 (10.0)	.28	210 (6.5)	247 (7.8)	.056	.76
Prasugrel	30 (7.6)	29 (6.9)	.70	283 (8.8)	284 (8.9)	.87	.68
Ticagrelor	40 (10.1)	52 (12.3)	.31	360 (11.2)	325 (10.2)	.20	.16
Unfractionated heparin	31 (7.8)	400 (94.8)	< .0001	216 (6.7)	3073 (96.6)	< .0001	.051
Glycoprotein IIb/IIIa inhibitor (GPI)	22 (5.5)	129 (30.6)	< .0001	141 (4.4)	805 (25.3)	< .0001	.95
Planned GPI	0 (0.0)	105 (24.9)	< .0001	0 (0.0)	676 (21.3)	< .0001	-
Bailout GPI	22 (5.5)	24 (5.7)	.93	141 (4.4)	129 (4.1)	0.51	.74
Bivalirudin	375 (94.5)	5 (1.2)	< .0001	3068 (95.5)	9 (0.3)	< .0001	.0064
Post-PCI Bivalirudin	183 (46.1)	1 (0.2)	< .0001	1554 (48.4)	2 (0.1)	< .0001	.25
Intra-aortic balloon pump	38 (10.6)	43 (11.2)	.79	38 (1.3)	37 (1.2)	.94	.81
CABG after coronary angiography	6 (1.5)	3 (0.7)	.33	18 (0.6)	14 (0.4)	.50	.51
Completed PCI after coronary angiography	367 (92.4)	397 (94.1)	.35	3032 (94.4)	3012 (94.7)	.57	.51
At least one planned staged procedure	73 (18.4)	71 (16.8)	.56	659 (20.5)	614 (19.3)	.23	.87
Treated vessel(s)							
Left main coronary artery	44 (12.3)	39 (10.2)	.36	99 (3.3)	86 (2.9)	.37	.78
Left anterior descending artery	209 (58.4)	190 (49.6)	.017	1477 (49.2)	1438 (48.3)	.53	.041
Left circumflex artery	84 (23.5)	116 (30.3)	.037	814 (27.1)	785 (26.4)	.54	.030
Right coronary artery	100 (27.9)	117 (30.5)	.43	997 (33.2)	999 (33.6)	.74	.53
Bypass graft	4 (1.1)	6 (1.6)	.75	28 (0.9)	17 (0.6)	.11	.25
≥2 vessels treated	74 (20.7)	78 (20.4)	.92	380 (12.6)	353 (11.9)	.36	.79
Overall stent length (mm)	33.4 ± 20.8	36.0 ± 23.0	.12	31.3 ± 19.8	31.2 ± 18.5	.84	.36
Duration of procedure, min	55.8 ± 25.8	60.5 ± 30.6	.025	54.4 ± 27.5	53.9 ± 28.8	.51	.99

Data are expressed as no. (%) or mean ± standard deviation. Abbreviations: CABG,coronary artery bypass graft; HF,heart failure; KC,Killip class; OHCA,out of hospital cardiac arrest; PCI,percutaneous coronary intervention; VP,hemodynamic/electrical vulnerable patients.

Supplementary Table 5. Clinical outcomes at 30 days in patients with or without hemodynamic or electrical vulnerability.

	VP (HF and/or OHCA)	HF (KC > 1)	OHCA	Non-VP	Rate Ratio (95% CI)*	*P* *
Number of patients	**934**	**808**	**168**	**7470**		
Co-primary composite endpoint of all-cause mortality, MI or stroke	147 (15.7)	140 (17.3)	15 (8.9)	651 (8.8)	1.87 (1.55-2.25)	< .0001
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	162 (17.3)	153 (18.9)	18 (10.7)	734 (9.9)	1.84 (1.54-2.19)	< .0001
Composite of all-cause mortality, MI, stroke, urgent TVR, definite stent thrombosis	163 (17.5)	154 (19.1)	18 (10.7)	747 (10.1)	1.82 (1.52-2.17)	< .0001
All-cause mortality	79 (8.5)	78 (9.7)	6 (3.6)	78 (1.1)	8.51 (6.21-11.66)	< .0001
Cardiovascular death	76 (8.1)	75 (9.3)	6 (3.6)	67 (0.9)	9.51 (6.83-13.24)	< .0001
Non-cardiovascular death	2 (0.2)	2 (0.3)	0 (0.0)	5 (0.1)	3.40 (0.66-17.50)	.1201
Myocardial infarction	70 (7.7)	64 (8.2)	9 (5.5)	559 (7.5)	1.03 (0.80-1.33)	.8299
Stroke	9 (1.0)	9 (1.2)	1 (0.6)	23 (0.3)	3.27 (1.51-7.04)	.0014
Ischemic	7 (0.8)	7 (0.9)	0 (0.0)	16 (0.2)	3.66 (1.51-8.88)	.0021
Haemorrhagic	2 (0.2)	2 (0.3)	1 (0.6)	6 (0.1)	2.77 (0.56-13.63)	.1906
Uncertain origin	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2.66 (0.11-65.25)	1.0000
Transient ischemic attack	6 (0.7)	6 (0.8)	0 (0.0)	12 (0.2)	4.13 (1.55-10.97)	.0020
Urgent target vessel revascularisation	18 (2.0)	13 (1.7)	8 (4.9)	71 (1.0)	2.12 (1.26-3.56)	.0037
Definite stent thrombosis	15 (1.7)	11 (1.4)	5 (3.1)	42 (0.6)	2.97 (1.65-5.36)	.0001
Acute definite stent thrombosis	7 (0.8)	5 (0.6)	2 (1.2)	26 (0.3)	2.21 (0.96-5.10)	.0562
Subacute definite stent thrombosis	9 (1.0)	7 (0.9)	3 (1.8)	16 (0.2)	4.75 (2.10-10.78)	< .0001
Definite or probable stent thrombosis	24 (2.7)	20 (2.6)	5 (3.1)	56 (0.8)	3.58 (2.22-5.78)	< .0001
Acute definite or probable stent thrombosis	10 (1.1)	8 (1.0)	2 (1.2)	28 (0.4)	2.93 (1.42-6.05)	.0022
Subacute definite or probable stent thrombosis	16 (1.8)	14 (1.9)	3 (1.8)	28 (0.4)	4.85 (2.62-8.97)	< .0001
Bleeding	147 (16.2)	128 (16.4)	27 (16.4)	814 (11.0)	1.53 (1.28-1.84)	< .0001
Type 1	60 (6.7)	47 (6.1)	16 (9.7)	414 (5.6)	1.20 (0.91-1.58)	.1918
Type 2	52 (5.7)	47 (6.0)	8 (4.8)	290 (3.9)	1.50 (1.11-2.02)	.0076
Type 3abc	25 (2.8)	23 (3.0)	5 (3.0)	111 (1.5)	1.88 (1.22-2.91)	.0038
Type 3a	18 (2.0)	17 (2.2)	2 (1.2)	53 (0.7)	2.84 (1.66-4.86)	.0001
Type 3b	6 (0.7)	5 (0.6)	2 (1.2)	54 (0.7)	0.92 (0.40-2.14)	.8485
Type 3c	1 (0.1)	1 (0.1)	1 (0.6)	5 (0.1)	1.66 (0.20-14.15)	.6373
Type 4	2 (0.2)	2 (0.3)	0 (0.0)	9 (0.1)	1.87 (0.40-8.68)	.4149
Type 5ab	12 (1.3)	12 (1.6)	0 (0.0)	17 (0.2)	5.89 (2.81-12.35)	< .0001
Type 5a	10 (1.1)	10 (1.3)	0 (0.0)	10 (0.1)	8.37 (3.48-20.11)	< .0001

Type 5b	2 (0.2)	2 (0.3)	0 (0.0)	7 (0.1)	2.37 (0.49-11.44)	.2676
Type 3 or 5	37 (4.1)	35 (4.5)	5 (3.0)	127 (1.7)	2.44 (1.69-3.52)	< .0001
Type 3 or 5 related to access site	11 (1.2)	10 (1.3)	2 (1.2)	48 (0.7)	1.90 (0.98-3.66)	.0517
Type 3 or 5 not related to access site	26 (2.9)	25 (3.2)	3 (1.8)	79 (1.1)	2.76 (1.77-4.29)	< .0001
Type 2, 3 or 5	89 (9.8)	82 (10.5)	13 (7.9)	412 (5.6)	1.83 (1.45-2.31)	< .0001
Type 2, 3 or 5 related to access site	37 (4.1)	33 (4.2)	6 (3.6)	229 (3.1)	1.34 (0.94-1.90)	.1014
Type 2, 3 or 5 not related to access site	55 (6.1)	51 (6.6)	8 (4.9)	186 (2.5)	2.50 (1.85-3.38)	< .0001
Major bleeding	13 (1.4)	12 (1.6)	3 (1.8)	51 (0.7)	2.12 (1.15-3.91)	.0133
Minor bleeding	16 (1.8)	15 (1.9)	2 (1.2)	41 (0.6)	3.27 (1.83-5.85)	< .0001
Major or minor bleeding	29 (3.2)	27 (3.5)	5 (3.0)	92 (1.3)	2.65 (1.74-4.03)	< .0001
Severe bleeding	12 (1.3)	11 (1.4)	3 (1.8)	40 (0.5)	2.49 (1.31-4.75)	.0041
Moderate bleeding	14 (1.6)	14 (1.8)	0 (0.0)	45 (0.6)	2.60 (1.42-4.73)	.0012
Mild bleeding	120 (13.3)	102 (13.1)	24 (14.6)	734 (9.9)	1.38 (1.13-1.68)	.0014
Severe or moderate bleeding	26 (2.9)	25 (3.3)	3 (1.8)	85 (1.2)	2.55 (1.64-3.96)	< .0001
Composite of surgical access site repair or blood products transfusion	26 (3.0)	23 (3.1)	4 (2.4)	89 (1.2)	2.44 (1.58-3.78)	< .0001
Surgical access site repair	2 (0.2)	1 (0.1)	1 (0.6)	17 (0.2)	0.98 (0.23-4.23)	.9742
Blood products transfusion	25 (2.9)	22 (3.0)	4 (2.4)	80 (1.1)	2.61 (1.67-4.10)	< .0001

Data are expressed as no. (%) unless otherwise indicated.

*Rate Ratio and *P* for comparison of VP versus non-VP.

Abbreviations: BARC,bleeding academic research consortium; CI,confidence interval; KC,Killip class; OHCA,out of hospital cardiac arrest; MI,myocardial infarction; TVR,target vessel revascularization; VP,hemodynamic/electrical vulnerable patients.

Supplementary Table 6. Clinical outcomes at 30 days of TRA vs TFA in patients with or without hemodynamic or electrical vulnerability

	VP						Non-VP						
	Radial Access	Femoral Access	Risk difference (%)	NNT/NNH	Rate Ratio (95% CI)	*P*	Radial Access	Femoral Access	Risk difference (%)	NNT/NNH	Rate Ratio (95% CI)	*P*	*P* for interaction
Number of patients	**462**	**472**					**3735**	**3735**					
Co-primary composite endpoint of all-cause mortality, MI or stroke	69 (14.9)	78 (16.5)	-1.6 (-6.3 to 3.1)	63	0.89 (0.64-1.25)	.51	300 (8.1)	351 (9.5)	-1.4 (-2.6 to -0.1)	73	0.85 (0.72-0.99)	.039	.77
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	73 (15.8)	89 (18.9)	-3.1 (-7.9 to 1.8)	33	0.82 (0.59-1.13)	.22	337 (9.0)	397 (10.7)	-1.6 (-3.0 to -0.3)	62	0.84 (0.72-0.97)	.022	.89
Composite of all-cause mortality, MI, stroke, urgent TVR, definite stent thrombosis	74 (16.0)	89 (18.9)	-2.8 (-7.7 to 2.0)	35	0.83 (0.60-1.14)	.25	345 (9.3)	402 (10.9)	-1.5 (-2.9 to -0.2)	66	0.85 (0.73-0.98)	.030	.91
All-cause mortality	35 (7.6)	44 (9.3)	-1.7 (-5.3 to 1.8)	57	0.80 (0.51-1.25)	.32	31 (0.8)	47 (1.3)	-0.4 (-0.9 to 0.0)	233	0.66 (0.42-1.04)	.068	.55
Cardiovascular death	34 (7.4)	42 (8.9)	-1.5 (-5.0 to 2.0)	65	0.81 (0.51-1.28)	.37	26 (0.7)	41 (1.1)	-0.4 (-0.8 to 0.0)	249	0.63 (0.39-1.03)	.065	.46
Myocardial infarction	36 (7.8)	34 (7.2)	0.6 (-2.8 to 4.0)	-170	1.07 (0.66-1.73)	.78	263 (7.1)	296 (7.9)	-0.9 (-2.1 to 0.3)	113	0.88 (0.74-1.05)	.15	.46
Stroke	5 (1.1)	4 (0.9)	0.2 (-1.0 to 1.5)	-426	1.25 (0.34-4.66)	.74	11 (0.3)	12 (0.3)	-0.0 (-0.3 to 0.2)	3735	0.91 (0.40-2.07)	.83	.69
Transient ischemic attack	2 (0.5)	4 (0.9)	-0.4 (-1.4 to 0.6)	241	0.50 (0.09-2.72)	.41	3 (0.1)	9 (0.2)	-0.2 (-0.3 to 0.0)	623	0.33 (0.09-1.23)	.083	.71
Urgent target vessel revascularisation	11 (2.4)	7 (1.6)	0.9 (-0.9 to 2.7)	-111	1.59 (0.61-4.11)	.34	38 (1.0)	33 (0.9)	0.1 (-0.3 to 0.6)	-747	1.15 (0.72-1.84)	.55	.55
Definite stent thrombosis	8 (1.8)	7 (1.6)	0.2 (-1.4 to 1.9)	-402	1.15 (0.42-3.18)	.79	22 (0.6)	20 (0.5)	0.1 (-0.3 to 0.4)	-1868	1.10 (0.60-2.02)	.76	.94
Acute definite stent thrombosis	5 (1.1)	2 (0.4)	0.7 (-0.5 to 1.8)	-152	2.52 (0.49-13.08)	.25	16 (0.4)	10 (0.3)	0.2 (-0.1 to 0.4)	-623	1.60 (0.73-3.54)	.24	.62
Subacute definite stent thrombosis	4 (0.9)	5 (1.1)	-0.2 (-1.4 to 1.1)	517	0.80 (0.21-2.99)	.74	6 (0.2)	10 (0.3)	-0.1 (-0.3 to 0.1)	934	0.60 (0.22-1.65)	.31	.73
Definite or probable stent thrombosis	14 (3.1)	10 (2.2)	0.9 (-1.1 to 2.9)	-110	1.41 (0.62-3.17)	.41	28 (0.8)	28 (0.8)	0.0 (-0.4 to 0.4)	.	1.00 (0.59-1.69)	1.00	.49
Acute definite or probable stent thrombosis	7 (1.5)	3 (0.7)	0.9 (-0.4 to 2.2)	-114	2.36 (0.61-9.18)	.20	17 (0.5)	11 (0.3)	0.2 (-0.1 to 0.4)	-623	1.55 (0.72-3.31)	.26	.59
Subacute definite or probable stent thrombosis	9 (2.0)	7 (1.6)	0.5 (-1.2 to 2.1)	-215	1.28 (0.48-3.45)	.62	11 (0.3)	17 (0.5)	-0.2 (-0.4 to 0.1)	623	0.64 (0.30-1.38)	.25	.28
Bleeding	59 (13.1)	88 (19.3)	-5.9 (-10.5 to -1.2)	17	0.64 (0.46-0.90)	.010	292 (7.9)	522 (14.1)	-6.2 (-7.6 to -4.8)	16	0.54 (0.46-0.62)	< .0001	.35
Type 1	26 (5.8)	34 (7.5)	-1.6 (-4.7 to 1.6)	63	0.76 (0.45-1.27)	.29	142 (3.8)	272 (7.4)	-3.5 (-4.5 to -2.4)	29	0.51 (0.42-0.63)	< .0001	.16
Type 2	22 (4.9)	30 (6.5)	-1.6 (-4.5 to 1.3)	63	0.72 (0.41-1.27)	.26	105 (2.8)	185 (5.0)	-2.1 (-3.0 to -1.3)	47	0.56 (0.44-0.71)	< .0001	.41
Type 3abc	8 (1.8)	17 (3.8)	-1.9 (-3.9 to 0.2)	53	0.47 (0.20-1.08)	.069	45 (1.2)	66 (1.8)	-0.6 (-1.1 to -0.0)	178	0.68 (0.46-0.99)	.044	.43
Type 3a	7 (1.6)	11 (2.4)	-0.8 (-2.6 to 0.9)	123	0.63 (0.24-1.64)	.34	21 (0.6)	32 (0.9)	-0.3 (-0.7 to 0.1)	340	0.65 (0.38-1.13)	.13	.96
Type 3b	1 (0.2)	5 (1.1)	-0.8 (-1.9 to 0.2)	119	0.20 (0.02-1.71)	.10	22 (0.6)	32 (0.9)	-0.3 (-0.7 to 0.1)	373	0.69 (0.40-1.18)	.17	.25
Type 3c	0 (0.0)	1 (0.2)	-0.2 (-0.6 to 0.2)	472	0.34 (0.01-8.32)	1.00	2 (0.1)	3 (0.1)	-0.0 (-0.1 to 0.1)	3735	0.67 (0.11-3.98)	.65	.44
Type 4	1 (0.2)	1 (0.2)	0.0 (-0.6 to 0.6)	-21806	1.00 (0.06-16.11)	1.00	4 (0.1)	5 (0.1)	-0.0 (-0.2 to 0.1)	3735	0.80 (0.21-2.97)	.74	.89
Type 5ab	4 (0.9)	8 (1.8)	-0.8 (-2.3 to 0.6)	121	0.50 (0.15-1.67)	.25	9 (0.2)	8 (0.2)	0.0 (-0.2 to 0.2)	-3735	1.12 (0.43-2.91)	.81	.30
Type 5a	3 (0.7)	7 (1.6)	-0.8 (-2.1 to 0.5)	120	0.43 (0.11-1.66)	.21	6 (0.2)	4 (0.1)	0.1 (-0.1 to 0.2)	-1868	1.50 (0.42-5.31)	.53	.18
Type 5b	1 (0.2)	1 (0.2)	0.0 (-0.6 to 0.6)	-21806	1.01 (0.06-16.18)	1.00	3 (0.1)	4 (0.1)	-0.0 (-0.2 to 0.1)	3735	0.75 (0.17-3.34)	.70	.85
Type 3 or 5	12 (2.7)	25 (5.5)	-2.7 (-5.2 to -0.2)	37	0.47 (0.24-0.95)	.031	53 (1.4)	74 (2.0)	-0.6 (-1.1 to 0.0)	178	0.71 (0.50-1.01)	.059	.30
Type 3 or 5 related to access site	2 (0.4)	9 (2.0)	-1.5 (-2.8 to -0.1)	68	0.22 (0.05-1.03)	.035	14 (0.4)	34 (0.9)	-0.5 (-0.9 to -0.2)	187	0.41 (0.22-0.76)	.0038	.46
Type 3 or 5 not related to access site	10 (2.2)	16 (3.6)	-1.2 (-3.3 to 0.9)	82	0.62 (0.28-1.38)	.24	39 (1.1)	40 (1.1)	-0.0 (-0.5 to 0.4)	3735	0.97 (0.63-1.51)	.90	.33

Type 2, 3 or 5	34 (7.5)	55 (12.1)	-4.3 (-8.0 to -0.5)	23	0.60 (0.39-0.93)	.021	156 (4.2)	256 (6.9)	-2.7 (-3.7 to -1.6)	37	0.60 (0.49-0.73)	< .0001	.99
Type 2, 3 or 5 related to access site	8 (1.8)	29 (6.3)	-4.4 (-6.9 to -1.9)	23	0.27 (0.12-0.59)	.0005	61 (1.6)	168 (4.5)	-2.9 (-3.6 to -2.1)	35	0.36 (0.27-0.48)	< .0001	.51
Type 2, 3 or 5 not related to access site	26 (5.8)	29 (6.4)	-0.5 (-3.5 to 2.5)	194	0.90 (0.53-1.53)	.69	96 (2.6)	90 (2.4)	0.2 (-0.5 to 0.9)	-623	1.07 (0.80-1.42)	.67	.58
Major bleeding	4 (0.9)	9 (2.0)	-1.0 (-2.5 to 0.5)	96	0.44 (0.14-1.44)	.16	22 (0.6)	29 (0.8)	-0.2 (-0.6 to 0.2)	534	0.76 (0.43-1.32)	.32	.42
Minor bleeding	5 (1.1)	11 (2.4)	-1.2 (-2.9 to 0.4)	80	0.45 (0.16-1.31)	.13	19 (0.5)	22 (0.6)	-0.1 (-0.4 to 0.3)	1245	0.86 (0.47-1.59)	.63	.30
Major or minor bleeding	9 (2.0)	20 (4.4)	-2.3 (-4.5 to -0.1)	44	0.45 (0.20-0.98)	.040	41 (1.1)	51 (1.4)	-0.3 (-0.8 to 0.2)	373	0.80 (0.53-1.21)	.29	.19
Severe bleeding	4 (0.9)	8 (1.8)	-0.8 (-2.3 to 0.6)	121	0.50 (0.15-1.66)	.25	19 (0.5)	21 (0.6)	-0.1 (-0.4 to 0.3)	1868	0.90 (0.48-1.68)	.75	.39
Moderate bleeding	5 (1.1)	9 (2.0)	-0.8 (-2.4 to 0.7)	121	0.55 (0.18-1.65)	.28	19 (0.5)	26 (0.7)	-0.2 (-0.5 to 0.2)	534	0.73 (0.40-1.32)	.29	.66
Mild bleeding	49 (10.9)	71 (15.6)	-4.4 (-8.7 to -0.2)	23	0.67 (0.46-0.97)	.034	257 (6.9)	477 (12.9)	-5.9 (-7.2 to -4.5)	17	0.52 (0.44-0.61)	< .0001	.22
Severe or moderate bleeding	9 (2.0)	17 (3.8)	-1.7 (-3.8 to 0.4)	60	0.53 (0.23-1.18)	.11	38 (1.0)	47 (1.3)	-0.2 (-0.7 to 0.2)	415	0.81 (0.52-1.24)	.32	.36
Composite of surgical access site repair or blood products transfusion	8 (2.0)	18 (4.0)	-2.1 (-4.2 to 0.0)	48	0.44 (0.19-1.01)	.047	34 (0.9)	55 (1.5)	-0.6 (-1.1 to -0.1)	178	0.62 (0.40-0.94)	.025	.48
Surgical access site repair	0 (0.0)	2 (0.4)	-0.4 (-1.0 to 0.2)	236	0.20 (0.01-4.15)	.50	4 (0.1)	13 (0.3)	-0.2 (-0.5 to -0.0)	415	0.31 (0.10-0.94)	.029	.44
Blood products transfusion	8 (2.0)	17 (3.8)	-1.9 (-3.9 to 0.2)	53	0.47 (0.20-1.08)	.069	33 (0.9)	47 (1.3)	-0.4 (-0.8 to 0.1)	267	0.70 (0.45-1.09)	.11	.40

Data are expressed as no. (%) unless otherwise indicated.

Abbreviations: BARC,bleeding academic research consortium; CI,confidence interval; MI,myocardial infarction; NNT/NNH,number needed to treat/harm; TVR,target vessel revascularization; VP,hemodynamic/electrical vulnerable patients.

Supplementary Table 7. Clinical outcomes at 30 days of bivalirudin vs unfractionated heparin in patients with or without hemodynamic or electrical vulnerability

	VP						Non-VP						
	Bivalirudin	UFH	Risk difference (%)	NNT/NNH	Rate Ratio (95% CI)	*P*	Bivalirudin	UFH	Risk difference (%)	NNT/NNH	Rate Ratio (95% CI)	*P*	*P* for interaction
Number of patients	**397**	**422**					**3213**	**318)**					
Co-primary composite endpoint of all-cause mortality, MI or stroke	61 (15.4)	76 (18.0)	-2.6 (-7.7 to 2.5)	38	0.84 (0.59-1.19)	.33	313 (9.8)	316 (10.0)	-0.2 (-1.7 to 1.3)	520	0.98 (0.83-1.15)	.80	.43
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	63 (15.9)	89 (21.1)	-5.2 (-10.5 to 0.1)	19	0.73 (0.52-1.02)	.064	345 (10.8)	361 (11.4)	-0.6 (-2.1 to 0.9)	164	0.94 (0.81-1.10)	.45	.17
Composite of all-cause mortality, MI, stroke, urgent TVR, definite stent thrombosis	64 (16.1)	89 (21.1)	-5.0 (-10.3 to 0.3)	20	0.74 (0.53-1.04)	.079	351 (11.0)	367 (11.6)	-0.6 (-2.2 to 0.9)	163	0.94 (0.81-1.10)	.45	.20
All-cause mortality	24 (6.0)	48 (11.4)	-5.3 (-9.2 to -1.5)	19	0.51 (0.31-0.84)	.0070	35 (1.1)	35 (1.1)	-0.0 (-0.5 to 0.5)	9125	0.99 (0.62-1.58)	.97	.056
Cardiovascular death	23 (5.8)	47 (11.1)	-5.3 (-9.1 to -1.6)	19	0.50 (0.30-0.83)	.0063	30 (0.9)	30 (1.0)	-0.0 (-0.5 to 0.5)	10646	0.99 (0.60-1.65)	.97	.060
Myocardial infarction	39 (10.0)	28 (6.9)	3.2 (-0.6 to 7.0)	-31	1.46 (0.88-2.41)	.14	271 (8.5)	277 (8.8)	-0.3 (-1.6 to 1.1)	366	0.97 (0.81-1.15)	.71	.13
Stroke	3 (0.8)	6 (1.6)	-0.7 (-2.1 to 0.7)	150	0.50 (0.13-2.01)	.32	10 (0.3)	10 (0.3)	-0.0 (-0.3 to 0.3)	31939	0.99 (0.41-2.38)	.98	.41
Transient ischemic attack	2 (0.5)	3 (0.8)	-0.2 (-1.3 to 0.9)	483	0.68 (0.11-4.06)	.67	3 (0.1)	6 (0.2)	-0.1 (-0.3 to 0.1)	1050	0.50 (0.12-1.98)	.31	.79
Urgent target vessel revascularisation	12 (3.1)	6 (1.5)	1.6 (-0.4 to 3.6)	-62	2.07 (0.77-5.53)	.14	40 (1.3)	29 (0.9)	0.3 (-0.2 to 0.8)	-300	1.37 (0.85-2.21)	.19	.46
Definite stent thrombosis	9 (2.3)	6 (1.5)	0.8 (-1.0 to 2.7)	-118	1.54 (0.55-4.35)	.41	27 (0.8)	15 (0.5)	0.4 (-0.0 to 0.8)	-271	1.79 (0.95-3.37)	.067	.81
Acute definite stent thrombosis	4 (1.0)	3 (0.7)	0.3 (-1.0 to 1.6)	-337	1.37 (0.31-6.14)	.68	16 (0.5)	10 (0.3)	0.2 (-0.1 to 0.5)	-545	1.59 (0.72-3.51)	.25	.86
Subacute definite stent thrombosis	5 (1.3)	4 (1.0)	0.3 (-1.1 to 1.7)	-321	1.28 (0.34-4.78)	.71	11 (0.3)	5 (0.2)	0.2 (-0.1 to 0.4)	-540	2.19 (0.76-6.30)	.14	.53
Definite or probable stent thrombosis	11 (2.9)	13 (3.3)	-0.3 (-2.6 to 2.0)	323	0.87 (0.39-1.94)	.73	34 (1.1)	22 (0.7)	0.4 (-0.1 to 0.8)	-273	1.54 (0.90-2.63)	.11	.24
Acute definite or probable stent thrombosis	4 (1.0)	6 (1.5)	-0.4 (-1.9 to 1.1)	241	0.69 (0.19-2.44)	.56	18 (0.6)	10 (0.3)	0.2 (-0.1 to 0.6)	-407	1.79 (0.82-3.88)	.14	.20
Subacute definite or probable stent thrombosis	7 (1.8)	9 (2.3)	-0.4 (-2.3 to 1.5)	271	0.79 (0.29-2.13)	.64	16 (0.5)	12 (0.4)	0.1 (-0.2 to 0.4)	-828	1.32 (0.63-2.80)	.46	.41
Bleeding	57 (14.6)	80 (19.9)	-4.6 (-9.7 to 0.5)	22	0.72 (0.50-1.02)	.062	336 (10.6)	408 (12.9)	-2.4 (-3.9 to -0.8)	42	0.80 (0.69-0.93)	.0036	.56
Type 1	24 (6.2)	33 (8.3)	-1.8 (-5.2 to 1.7)	56	0.74 (0.43-1.26)	.26	172 (5.4)	213 (6.7)	-1.3 (-2.5 to -0.2)	74	0.79 (0.65-0.97)	.026	.80
Type 2	26 (6.6)	23 (5.7)	1.1 (-2.2 to 4.4)	-91	1.17 (0.66-2.07)	.59	128 (4.0)	134 (4.2)	-0.2 (-1.2 to 0.7)	437	0.94 (0.74-1.21)	.65	.50
Type 3abc	6 (1.5)	18 (4.5)	-2.8 (-5.0 to -0.5)	36	0.34 (0.13-0.85)	.015	43 (1.4)	60 (1.9)	-0.5 (-1.2 to 0.1)	183	0.71 (0.48-1.05)	.084	.14
Type 3a	3 (0.8)	14 (3.5)	-2.6 (-4.5 to -0.7)	39	0.22 (0.06-0.76)	.0083	24 (0.8)	27 (0.9)	-0.1 (-0.5 to 0.3)	982	0.88 (0.51-1.53)	.65	.035
Type 3b	2 (0.5)	4 (1.0)	-0.4 (-1.6 to 0.7)	225	0.51 (0.09-2.80)	.43	16 (0.5)	32 (1.0)	-0.5 (-0.9 to -0.1)	197	0.49 (0.27-0.90)	.019	.97
Type 3c	1 (0.3)	0 (0.0)	0.3 (-0.2 to 0.7)	-397	3.19 (0.13-78.08)	.48	3 (0.1)	2 (0.1)	0.0 (-0.1 to 0.2)	-3279	1.49 (0.25-8.90)	.66	.44
Type 4	0 (0.0)	0 (0.0)	0.0 (0.0 to 0.0)	.			1 (0.0)	3 (0.1)	-0.1 (-0.2 to 0.1)	1583	0.33 (0.03-3.18)	.31	
Type 5ab	2 (0.5)	9 (2.2)	-1.6 (-3.2 to -0.1)	61	0.23 (0.05-1.05)	.038	4 (0.1)	12 (0.4)	-0.3 (-0.5 to -0.0)	396	0.33 (0.11-1.02)	.044	.70
Type 5a	1 (0.3)	8 (2.0)	-1.6 (-3.0 to -0.3)	61	0.13 (0.02-1.02)	.021	4 (0.1)	6 (0.2)	-0.1 (-0.3 to 0.1)	1559	0.66 (0.19-2.34)	.52	.16
Type 5b	1 (0.3)	1 (0.2)	0.0 (-0.7 to 0.7)	-6701	1.02 (0.06-16.53)	.99	0 (0.0)	6 (0.2)	-0.2 (-0.3 to -0.0)	530	0.08 (0.00-1.42)	.015	.062
Type 3 or 5	8 (2.1)	27 (6.7)	-4.4 (-7.1 to -1.7)	23	0.30 (0.13-0.66)	.0015	47 (1.5)	71 (2.3)	-0.8 (-1.4 to -0.1)	130	0.65 (0.45-0.95)	.023	.073
Type 3 or 5 related to access site	2 (0.5)	9 (2.2)	-1.6 (-3.2 to -0.1)	61	0.23 (0.05-1.05)	.038	19 (0.6)	26 (0.8)	-0.2 (-0.6 to 0.2)	442	0.72 (0.40-1.31)	.28	.15

Type 3 or 5 not related to access site	6 (1.5)	18 (4.5)	-2.8 (-5.0 to -0.5)	36	0.34 (0.13-0.85)	.016	28 (0.9)	45 (1.5)	-0.5 (-1.1 to -0.0)	184	0.62 (0.38-0.99)	.042	.25
Type 2, 3 or 5	34 (8.7)	50 (12.4)	-3.3 (-7.4 to 0.8)	30	0.69 (0.44-1.07)	.098	172 (5.4)	203 (6.4)	-1.0 (-2.2 to 0.1)	97	0.83 (0.68-1.02)	.084	.44
Type 2, 3 or 5 related to access site	16 (4.1)	20 (5.0)	-0.7 (-3.5 to 2.1)	141	0.82 (0.42-1.59)	.55	89 (2.8)	117 (3.7)	-0.9 (-1.8 to -0.0)	110	0.75 (0.57-0.99)	.040	.81
Type 2, 3 or 5 not related to access site	20 (5.1)	31 (7.8)	-2.3 (-5.6 to 1.0)	43	0.66 (0.37-1.16)	.14	83 (2.6)	89 (2.8)	-0.2 (-1.0 to 0.6)	466	0.93 (0.69-1.25)	.61	.29
Major bleeding	5 (1.3)	6 (1.5)	-0.2 (-1.7 to 1.4)	616	0.85 (0.26-2.79)	.79	12 (0.4)	28 (0.9)	-0.5 (-0.9 to -0.1)	197	0.42 (0.22-0.83)	.010	.32
Minor bleeding	3 (0.8)	13 (3.3)	-2.3 (-4.2 to -0.5)	43	0.23 (0.07-0.83)	.014	17 (0.6)	23 (0.8)	-0.2 (-0.6 to 0.2)	516	0.73 (0.39-1.37)	.33	.10
Major or minor bleeding	8 (2.1)	19 (4.7)	-2.5 (-4.9 to -0.1)	40	0.43 (0.19-0.98)	.038	29 (0.9)	51 (1.6)	-0.7 (-1.2 to -0.2)	143	0.56 (0.36-0.89)	.012	.56
Severe bleeding	5 (1.3)	4 (1.0)	0.3 (-1.1 to 1.7)	-321	1.28 (0.34-4.76)	.72	12 (0.4)	25 (0.8)	-0.4 (-0.8 to -0.0)	242	0.48 (0.24-0.95)	.030	.18
Moderate bleeding	1 (0.3)	12 (3.0)	-2.6 (-4.3 to -0.9)	39	0.08 (0.01-0.65)	.0024	19 (0.6)	21 (0.7)	-0.1 (-0.5 to 0.3)	1453	0.90 (0.48-1.67)	.73	.011
Mild bleeding	51 (13.1)	63 (15.8)	-2.1 (-6.8 to 2.6)	48	0.83 (0.56-1.21)	.32	308 (9.7)	366 (11.6)	-1.9 (-3.4 to -0.4)	52	0.82 (0.70-0.96)	.014	.99
Severe or moderate bleeding	6 (1.6)	16 (4.0)	-2.3 (-4.5 to -0.1)	44	0.38 (0.15-0.97)	.035	31 (1.0)	46 (1.5)	-0.5 (-1.0 to 0.1)	208	0.67 (0.42-1.05)	.080	.28
Composite of surgical access site repair or blood products transfusion	5 (1.6)	18 (4.5)	-3.0 (-5.2 to -0.8)	33	0.28 (0.10-0.75)	.0072	31 (1.0)	50 (1.6)	-0.6 (-1.2 to -0.1)	165	0.61 (0.39-0.96)	.031	.15
Surgical access site repair	0 (0.0)	2 (0.5)	-0.5 (-1.1 to 0.2)	211	0.21 (0.01-4.36)	.50	5 (0.2)	10 (0.3)	-0.2 (-0.4 to 0.1)	630	0.50 (0.17-1.45)	.19	.34
Blood products transfusion	5 (1.6)	17 (4.3)	-2.8 (-4.9 to -0.6)	36	0.30 (0.11-0.81)	.011	26 (0.8)	47 (1.5)	-0.7 (-1.2 to -0.1)	150	0.55 (0.34-0.88)	.012	.27

Data are expressed as no. (%) unless otherwise indicated.

Abbreviations: BARC,bleeding academic research consortium; CI,confidence interval; MI,myocardial infarction; NNT/NNH,number needed to treat/harm; TVR,target vessel revascularization; UFH,unfractionated heparin; VP,hemodynamic/electrical vulnerable patients.

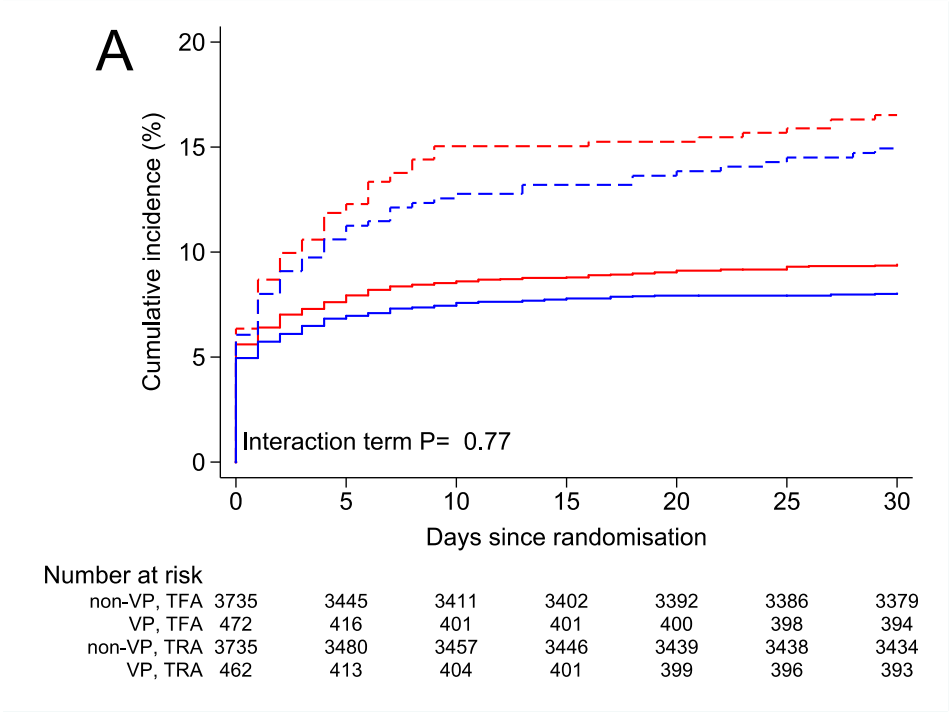
Supplementary Table 8. Sensitivity analysis of main clinical outcomes at 30 days analysed with Cox regression analysis and competing risk for both TRA vs TFA and bivalirudin vs unfractionated heparin in patients with or without hemodynamic or electrical vulnerability

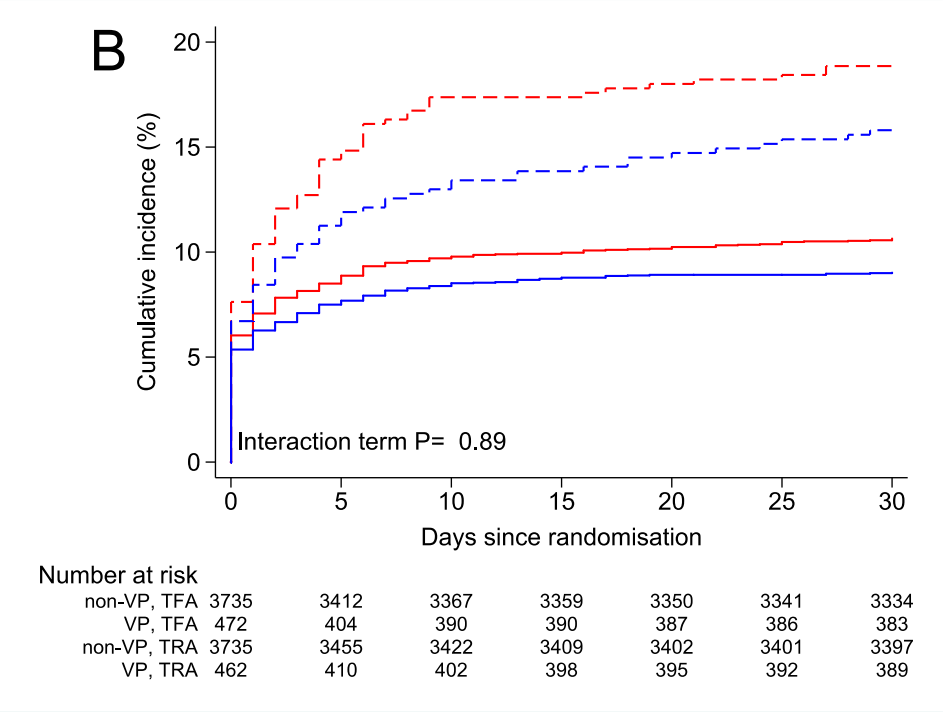
	VP		non-VP		*P* for interaction
COX REGRESSION ANALYSIS					
ACCESS SITE	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***	
Co-primary composite endpoint of all-cause mortality, MI or stroke	0.90 (0.65-1.23)	.50	0.85 (0.73-0.99)	.036	.75
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	0.82 (0.61-1.12)	.21	0.84 (0.73-0.97)	.020	.91
All-cause mortality	0.80 (0.52-1.24)	.32	0.66 (0.42-1.04)	.070	.55
ANTI-THROMBIN					
Co-primary composite endpoint of all-cause mortality, MI or stroke	0.84 (0.61-1.17)	.32	0.98 (0.84-1.14)	.80	.43
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	0.74 (0.54-1.01)	.059	0.94 (0.82-1.09)	.44	.17
All-cause mortality	0.52 (0.32-0.84)	.0076	0.99 (0.62-1.58)	.97	.057
ADJUSTED COX REGRESSION ANALYSIS*					
ACCESS SITE					
Co-primary composite endpoint of all-cause mortality, MI or stroke	0.92 (0.64-1.32)	.64	0.87 (0.74-1.02)	.078	.48
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	0.82 (0.59-1.15)	.26	0.87 (0.75-1.00)	.054	.88
All-cause mortality	0.77 (0.45-1.31)	.34	0.75 (0.45-1.23)	.25	.82
ANTI-THROMBIN					
Co-primary composite endpoint of all-cause mortality, MI or stroke	0.86 (0.61-1.22)	.40	0.96 (0.82-1.12)	.63	.69
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	0.74 (0.53-1.03)	.073	0.92 (0.80-1.07)	.30	.33
All-cause mortality	0.46 (0.26-0.80)	.0063	0.93 (0.56-1.53)	.77	.084
COMPETING RISK ANALYSIS (for death)					
ACCESS SITE	**SubHazard Ratio (95% CI)**	***P***	**SubHazard Ratio (95% CI)**	***P***	
MI	1.07 (0.67-1.70)	.78	0.89 (0.75-1.04)	.14	.45
Stroke	1.67 (0.40-6.99)	.48	0.91 (0.40-2.07)	.83	.47
BARC 3 or 5	0.50 (0.25-0.99)	.047	0.71 (0.50-1.01)	.060	.36
ANTI-THROMBIN					
MI	1.44 (0.89-2.32)	.13	0.97 (0.82-1.14)	.70	.12
Stroke	0.34 (0.07-1.66)	.18	0.99 (0.41-2.38)	.98	.25
BARC 3 or 5	0.26 (0.11-0.60)	.0016	0.65 (0.45-0.95)	.024	.048

*Multivariable adjustment included the following variables: age, sex, bmi, diabetes, smoking, hypercholesterolemia, hypertension, previous MI, previous TIA/stroke, peripheral arterial disease, renal failure, clinical presentation as STEMI, left main treated, multivessel treatment. Abbreviations: BARC, bleeding academic research consortium; CI, confidence interval; MI, myocardial infarction; VP, hemodynamic/electrical vulnerable patients.

Supplementary Figure 1. Co-primary composite access-related outcomes at 30 days in VP and non-VP

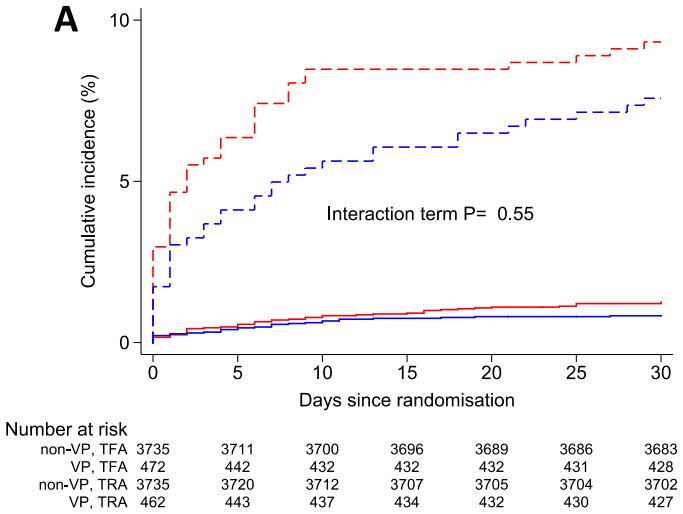
Panels A and B show the cumulative incidence of the co-primary outcome of MACE and NACE respectively. Blue indicates radial access (TRA), red indicates femoral access (TFA), continuous line indicates non-VP, dashed line indicates VP.

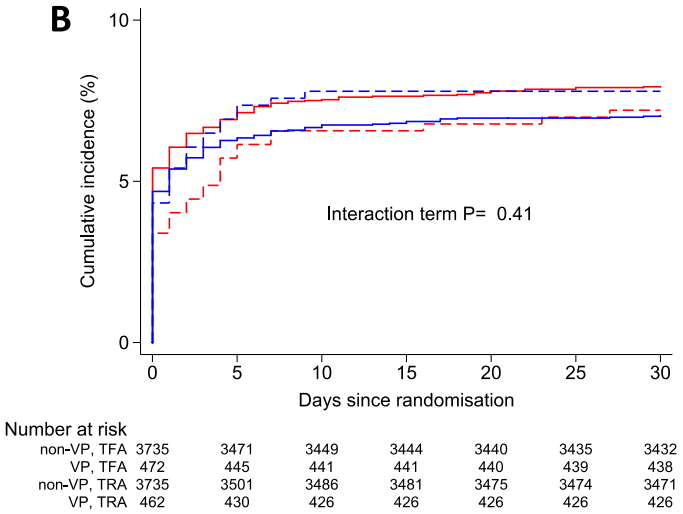


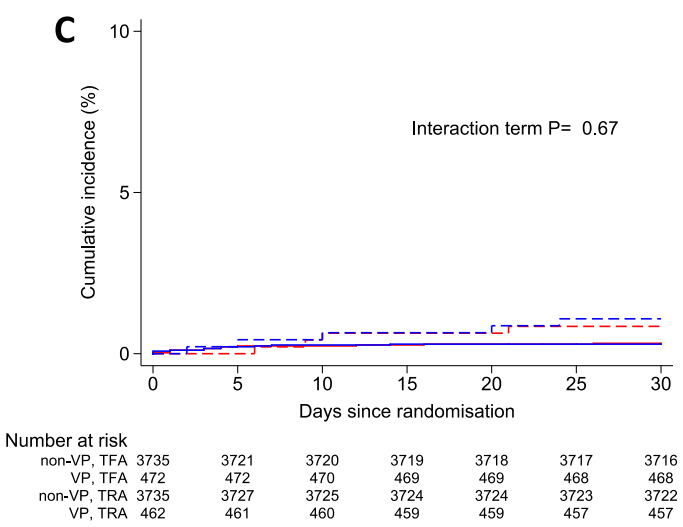


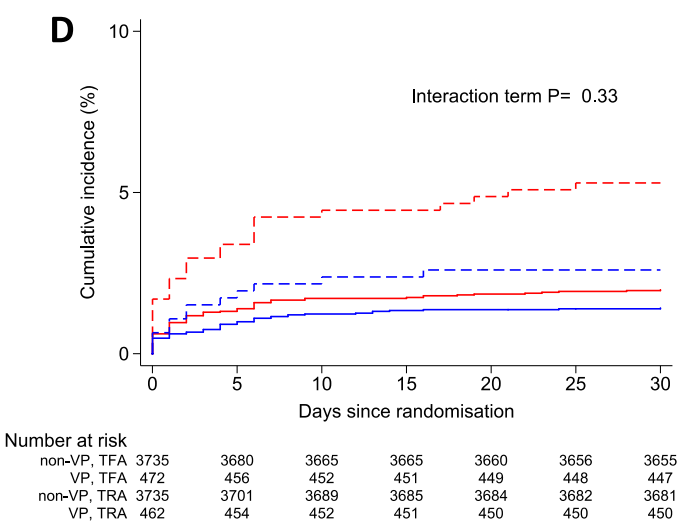
Supplementary Figure 2. Components of coprimary composite access-related outcomes at 30 days in VP and non-VP

Panels show the cumulative incidence of the coprimary outcome of all-cause death (A), myocardial infarction (B), stroke (C), and BARC 3 or 5 bleeding (D). Blue indicates radial access (TRA), red indicates femoral access (TFA), continuous line indicates non-VP, dashed line indicates VP.



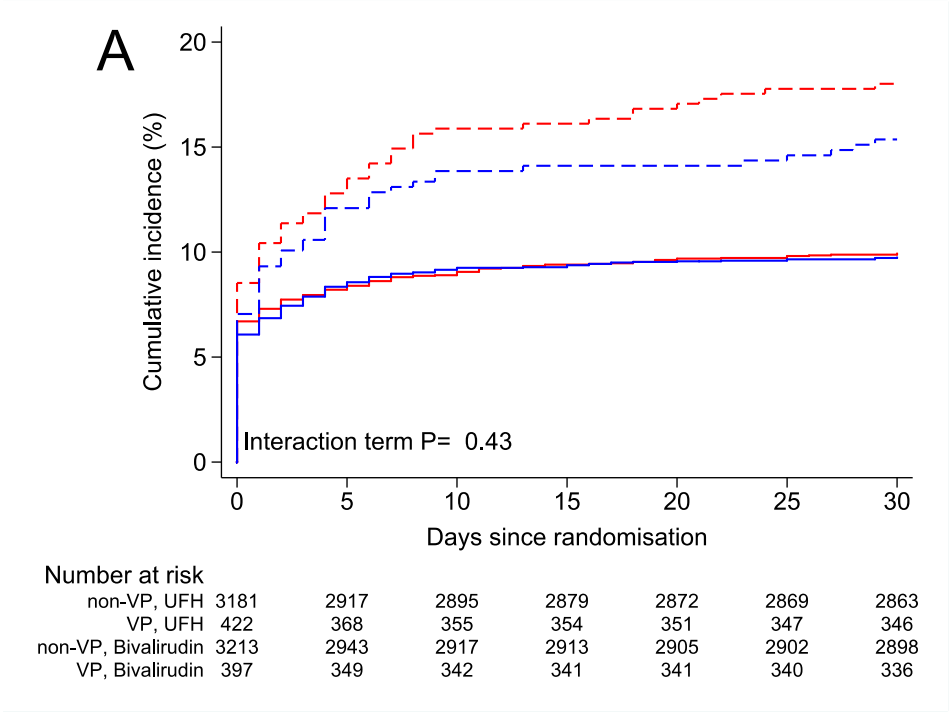


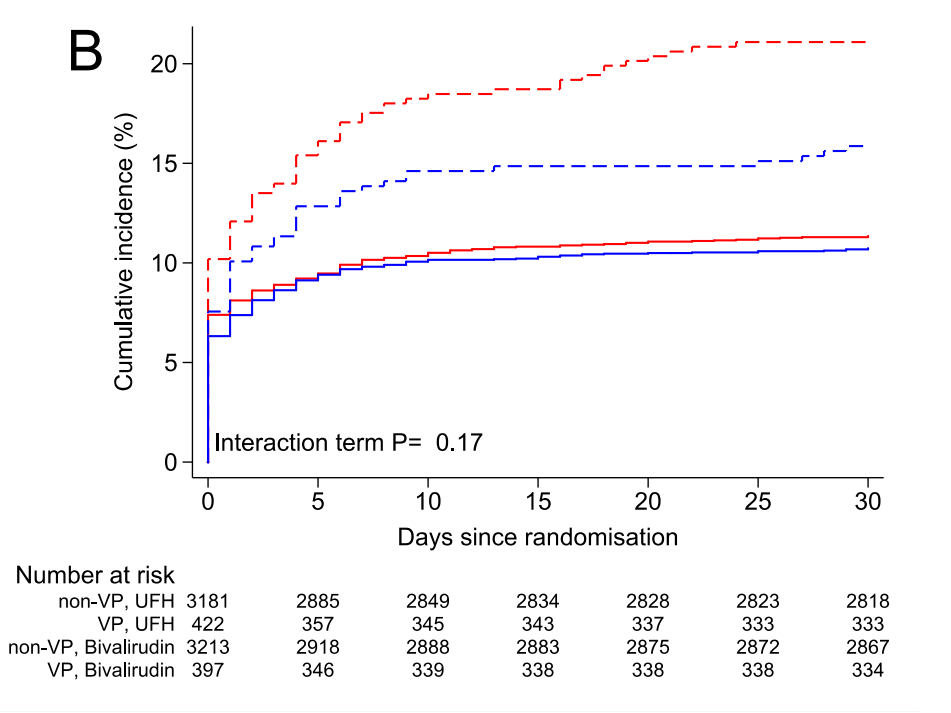




Supplementary Figure 3. Coprimary composite antithrombin-related outcomes at 30 days in VP and non- VP

Panels A and B show the cumulative incidence of the coprimary outcome of MACE and NACE respectively. Blue indicates bivalirudin, red indicates UFH, continuous line indicates non-VP, dashed line indicates VP.





Supplementary Figure 4. Components of coprimary composite antithrombin-related outcomes at 30 days in VP and non-VP

Panels show the cumulative incidence of the coprimary outcome of all-cause death (A), myocardial infarction (B), stroke (C), and BARC 3 or 5 bleeding (D). Blue indicates bivalirudin, red indicates UFH, continuous line indicates non-VP, discontinuous line indicates VP.