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ORIGINAL RESEARCH

Ticagrelor monotherapy versus ticagrelor plus aspirin in patients with chronic coronary syndrome and high ischaemic risk: a *post hoc* analysis of the TWILIGHT trial

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ABSTRACT

BACKGROUND: Short dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy may be a valuable therapeutic option for patients with chronic coronary syndrome (CCS) and high ischaemic risk (HIR) undergoing percutaneous coronary intervention (PCI).

AIMS: We aimed to compare ticagrelor monotherapy with ticagrelor-based DAPT in CCS patients with and without HIR undergoing PCI.

METHODS: The present analysis included the CCS cohort of the TWILIGHT trial, which randomised PCI patients to ticagrelor alone or in combination with aspirin for 12 months after 3 months of ticagrelor-based DAPT. Patients were stratified into HIR and non-HIR based on the 2019 European Society of Cardiology (ESC) CCS guidelines definition. Outcomes of interest were major adverse cardiac and cerebrovascular events (MACCE), a composite of death, myocardial infarction or stroke, and Bleeding Academic Research Consortium (BARC) Type 2-5 bleeding at 1 year.

RESULTS: Of the 2,503 CCS patients who underwent randomisation, the ESC definition classified 1,264 (50.5%) as HIR and 1,239 (49.5%) as non-HIR. HIR patients displayed a higher risk of MACCE (3.9% vs 2.3%; p=0.015) and similar rates of BARC Type 2-5 bleeding (5.1% vs 5.7%; p=0.455) as compared to non-HIR patients. Ticagrelor monotherapy and ticagrelor-based DAPT were associated with similar risks of MACCE (HIR: 4.0% vs 3.8%, hazard ratio [HR] 1.06, 95% confidence interval [CI]: 0.60-1.85; non-HIR: 2.1% vs 2.6%, HR 0.80, 95% CI: 0.38-1.66, $p_{interaction}$=0.553) and bleeding (HIR: 4.7% vs 5.7%, HR 0.82, 95% CI: 0.50-1.33; non-HIR: 4.9% vs 6.7%, HR 0.71, 95% CI: 0.44-1.14; $p_{interaction}$=0.684) in both the HIR and non-HIR groups.

CONCLUSIONS: In a *post hoc* analysis of the TWILIGHT trial that included CCS patients undergoing PCI, ticagrelor monotherapy after 3 months of DAPT appeared to be safe and was not associated with increased risks of ischaemic or bleeding events, regardless of baseline HIR status, compared with standard ticagrelor-based DAPT. These findings suggest the potential to expand guideline recommendations for ticagrelor monotherapy in CCS.

KEYWORDS: chronic coronary syndrome; dual antiplatelet therapy; high ischaemic risk; percutaneous coronary intervention; ticagrelor

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In the elective patient population undergoing percutaneous coronary intervention (PCI) for chronic coronary syndrome (CCS), the optimal dual antiplatelet therapy (DAPT) is aimed to minimise stent-related thrombotic events and, at the same time, avoid excess bleeding complications[1]. Clopidogrel, in combination with aspirin, is generally the preferred antithrombotic agent, mainly because of the paucity of clinical trial data testing potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) in the CCS setting[2,3]. However, despite successful PCI, the residual risk of atherothrombotic events in CCS patients is not negligible, with cardiac death, myocardial infarction (MI) or urgent revascularisation occurring in up to 10% of patients at 1 year and 30% at 5 years[4,5]. Prolonged and/or more potent $P2Y_{12}$ inhibition might be beneficial to improve prognosis and reduce repeat hospitalisations in selected high-risk subsets[6,7]. The European Society of Cardiology (ESC) guidelines recommended considering a CCS patient at high ischaemic risk (HIR) in the presence of multivessel coronary artery disease (CAD) with at least one additional clinical risk factor among diabetes, recurrent MI, peripheral artery disease (PAD) and chronic kidney disease (CKD)[8]. Additionally, prolonged DAPT or ticagrelor-based DAPT are recommended as potential alternatives to standard clopidogrel-based DAPT in CCS patients undergoing PCI[8,9]. However, despite being effective in terms of ischaemic event reduction, standard or prolonged DAPT regimens with ticagrelor in combination with aspirin have been associated with a high risk of bleeding complications, which carry an even worse prognostic impact[10,11].

Among patients who remained event free after an initial 3-month course of ticagrelor-based DAPT, the TWILIGHT trial compared 12 months of ticagrelor monotherapy with 12 months of continued ticagrelor-based DAPT, showing a reduction in Bleeding Academic Research Consortium (BARC) Type 2-5 bleeding without an associated increase in death, MI or stroke[12]. In a prespecified subgroup analysis, ticagrelor monotherapy was associated with similar ischaemic event rates compared with ticagrelor plus aspirin in patients with either acute coronary syndrome (ACS) or CCS, while the bleeding risk reduction with ticagrelor monotherapy was significant only in the ACS subgroup[13]. The aim of the present analysis was to compare ticagrelor monotherapy and ticagrelor-based DAPT after PCI in CCS patients with or without HIR according to the 2019 ESC guidelines definition[8].

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Impact on daily practice

A consistent proportion of patients undergoing percutaneous coronary intervention (PCI) for chronic coronary syndrome (CCS) have a high risk of recurrent ischaemic events, for which guidelines recommend a prolonged dual antiplatelet therapy (DAPT) course and/or potent $P2Y_{12}$ inhibition; despite being effective, such strategies might increase bleeding and worsen patients' prognosis. In this analysis, we focused on CCS patients enrolled in the TWILIGHT trial and applied the European Society of Cardiology guidelines definition to identify those at high ischaemic risk (HIR). As compared to 12-month ticagrelor-based DAPT, ticagrelor monotherapy after a 3-month DAPT course was associated with a similar incidence of major adverse cardiac and cerebrovascular events and bleeding at 1 year regardless of the HIR status, thereby supporting its use in patients with CCS and HIR undergoing PCI.

Methods

TRIAL DESIGN AND STUDY POPULATION

This was a *post hoc* analysis of the TWILIGHT trial, whose design and principal results have been published previously[12,14]. In brief, TWILIGHT was a multicentre randomised, double-blind, placebo-controlled trial with 187 enrolling institutions across 11 countries. The study enrolled patients undergoing PCI with drug-eluting stent (DES) implantation and who met at least one clinical and one angiographic feature of high ischaemic and/or bleeding risk. Clinical features included age ≥65 years, female sex, troponin-positive ACS, vascular disease (including previous MI, previous coronary revascularisation or PAD), diabetes mellitus requiring medication, and stage ≥3 CKD (estimated glomerular filtration rate <60 ml/min). Angiographic features were multivessel CAD, total stent length >30 mm, thrombotic target lesion, bifurcation lesion treated with two stents, obstructive left main (LM; ≥50% stenosis) or proximal left anterior descending artery (LAD; ≥70% stenosis) disease, and calcified target lesion requiring atherectomy. Key exclusion criteria were ST-segment elevation MI presentation, cardiogenic shock, prior stroke, end-stage CKD on permanent dialysis and chronic anticoagulation. Patients with ACS or with missing data on the indication for PCI were also excluded from the present analysis.

All included patients received DAPT with open-label ticagrelor (90 mg bid) and enteric-coated aspirin (81 or 100 mg daily) for up to 3 months following the index PCI. Patients who were adherent to DAPT and free from major bleeding or ischaemic events (BARC Type ≥3b bleeding, stroke, MI or coronary revascularisation) were randomised in a 1:1 double-blind fashion to aspirin or matching placebo for a further 12 months, in combination with open-label

Abbreviations

ACS	acute coronary syndrome	**HIR**	high ischaemic risk
BARC	Bleeding Academic Research Consortium	**LAD**	left anterior descending artery
CAD	coronary artery disease	**LM**	left main
CCS	chronic coronary syndrome	**MACCE**	major adverse cardiac and cerebrovascular events
CKD	chronic kidney disease	**MI**	myocardial infarction
DAPT	dual antiplatelet therapy	**PAD**	peripheral artery disease
DES	drug-eluting stent	**PCI**	percutaneous coronary intervention

ticagrelor. Clinical follow-up was performed via telephone call at 1 month and in-person visits at 6 and 12 months following randomisation. The study protocol was approved by national regulatory agencies, institutional review boards and ethics committees at the enrolling institutions.

ENDPOINTS

Outcomes of interest for the present analysis included BARC Type 2-5 bleeding and major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death, MI or stroke. All additional endpoints were defined as previously reported[12]. All clinical endpoints were adjudicated by an independent external committee that was blinded to treatment allocation.

STATISTICAL ANALYSIS

The 2019 ESC guidelines definition was applied to stratify the study population into two groups, defined as HIR and non-HIR[8]. Accordingly, patients were identified as HIR if they had multivessel CAD and at least one concomitant condition among diabetes mellitus, prior MI, CKD and PAD. **Supplementary Table 1** details the definitions of the ESC HIR criteria in the TWILIGHT trial protocol.

Baseline demographic, clinical, and procedural characteristics were reported as mean and standard deviation for continuous variables and absolute number and frequency for categorical variables and were compared using the Student's t-test or the chi-square test, respectively. An UpSet plot was created to quantitatively display the most frequent combinations (i.e., exclusive intersections) of the clinical and angiographic study inclusion criteria, excluding troponin-positive ACS and thrombotic target lesion, in the CCS population.

The cumulative incidence of each study endpoint in the intention-to-treat population was estimated using the Kaplan-Meier method. According to the trial protocol, patients without a BARC Type 2-5 bleeding event between randomisation and 1 year were censored at the time of death, last known contact, or at 365 days, whichever occurred first. Cox proportional hazards models were used to generate hazard ratios (HRs) with 95% confidence intervals (CIs), with formal interaction testing between the main exposure of treatment allocation (placebo vs aspirin) and HIR status (HIR vs non-HIR) to assess effect modification. Univariate Cox proportional hazards regression analyses evaluating the predictors of MACCE occurrence in the study population were conducted to explore the consistency with the HIR parameters reported by the ESC definition. Additionally, a sensitivity analysis compared the treatment effects of ticagrelor monotherapy versus DAPT in patients with and without high thrombotic risk. High thrombotic risk was defined as meeting the criteria for HIR or undergoing complex PCI, based on the definition by Giustino et al[15].

A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using Stata version 16.0 (StataCorp).

Results

PREVALENCE OF CLINICAL AND ANGIOGRAPHIC INCLUSION CRITERIA IN THE CCS POPULATION

A total of 2,503 CCS patients were randomised in the TWILIGHT trial and included in this analysis. Multivessel CAD (71.7%), LM or proximal LAD involvement (59.8%) and stent length >30 mm (57.0%) were the most prevalent angiographic inclusion criteria, while vascular disease (69.5%), age ≥65 years (56.3%) and diabetes (40.2%) were the most common clinical features **(Figure 1, Supplementary Table 2)**. The most frequent intersection of criteria was the combination of vascular disease, multivessel CAD, LM or proximal LAD involvement and stent length >30 mm **(Supplementary Figure 1)**.

PATIENT CHARACTERISTICS

The ESC definition classified 50.5% of patients as HIR (N=1,264) and 49.5% as non-HIR (N=1,239) **(Central illustration). Table 1** and **Table 2** show the baseline clinical and procedural characteristics of the study population. There were no significant differences between treatment arms in the HIR and non-HIR strata. Overall, as compared to non-HIR patients, those classified as HIR were more commonly male, had a higher prevalence of cardiovascular risk factors, and more frequently had a history of atherosclerotic coronary or peripheral artery disease. Consistently, HIR patients were more likely to have multiple vessels and lesions treated during the index PCI.

PREVALENCE AND CLINICAL IMPACT OF A HIGH ISCHAEMIC RISK STATUS

At 12 months after randomisation, HIR patients had a higher cumulative incidence of MACCE as compared with non-HIR patients (3.9% vs 2.3%; p=0.015). Conversely, the incidence of BARC Type 2-5 bleeding was not significantly different between the two groups (5.1% vs 5.7%; p=0.455) **(Supplementary Figure 2)**.

CLINICAL OUTCOMES ACCORDING TO RANDOMISED TREATMENT ALLOCATION IN PATIENTS WITH AND WITHOUT HIR

The effect of ticagrelor monotherapy versus DAPT on MACCE was similar in HIR (4.0% vs 3.8%, HR 1.06, 95% CI: 0.60-1.85) and non-HIR patients (2.1% vs 2.6%, HR 0.80, 95% CI: 0.38-1.66; $p_{interaction}$=0.553) **(Table 3, Figure 2, Central illustration)**. Similarly, BARC Type 2-5 bleeding rates were not significantly different between the ticagrelor monotherapy and DAPT arms, regardless of HIR status (HIR: 4.7% vs 5.7%, HR 0.82, 95% CI: 0.50-1.33; non-HIR: 4.9% vs 6.7%, HR 0.71, 95% CI: 0.44-1.14; $p_{interaction}$=0.684) **(Table 3, Figure 2, Central illustration)**. No significant interactions between HIR status and the effect of randomised antiplatelet strategy were detected for any of the exploratory secondary endpoints **(Table 3)**.

Such results were consistent when stratifying patients into high (N=1,565) versus non-high thrombotic risk (N=938) **(Supplementary Table 3)**.

CLINICAL AND ANGIOGRAPHIC PREDICTORS OF MACCE

Increased risk of MACCE was observed for vascular disease (HR 1.37, 95% CI: 1.02-1.85; p=0.038), diabetes mellitus (HR 1.37, 95% CI: 1.06-1.77; p=0.018) and LM or proximal LAD involvement (HR 1.38, 95% CI: 1.05-1.81; p=0.021) **(Supplementary Table 4)**. Patients with CKD had a borderline significant elevated risk of MACCE (HR 1.34, 95% CI:

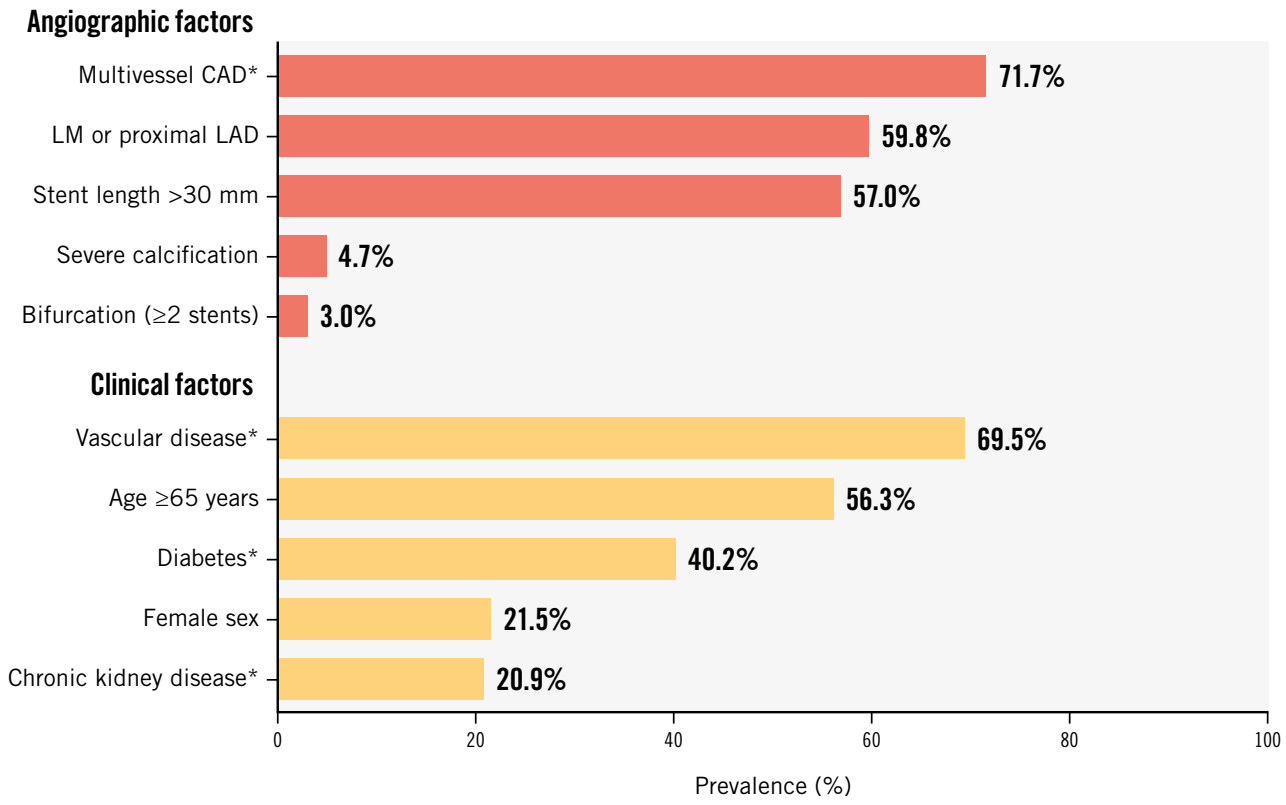


Figure 1. *Prevalence of the clinical and angiographic inclusion criteria in the CCS population of the TWILIGHT trial. *Included in the ESC definition of high ischaemic risk. CAD: coronary artery disease; CCS: chronic coronary syndrome; ESC: European Society of Cardiology; LAD: left anterior descending artery; LM: left main*

0.99-1.81; p=0.057). All other clinical and angiographic features were not significantly associated with MACCE **(Supplementary Table 4)**.

Discussion

The main findings of this analysis, which included CCS patients undergoing PCI and randomised in the TWILIGHT trial, are the following:

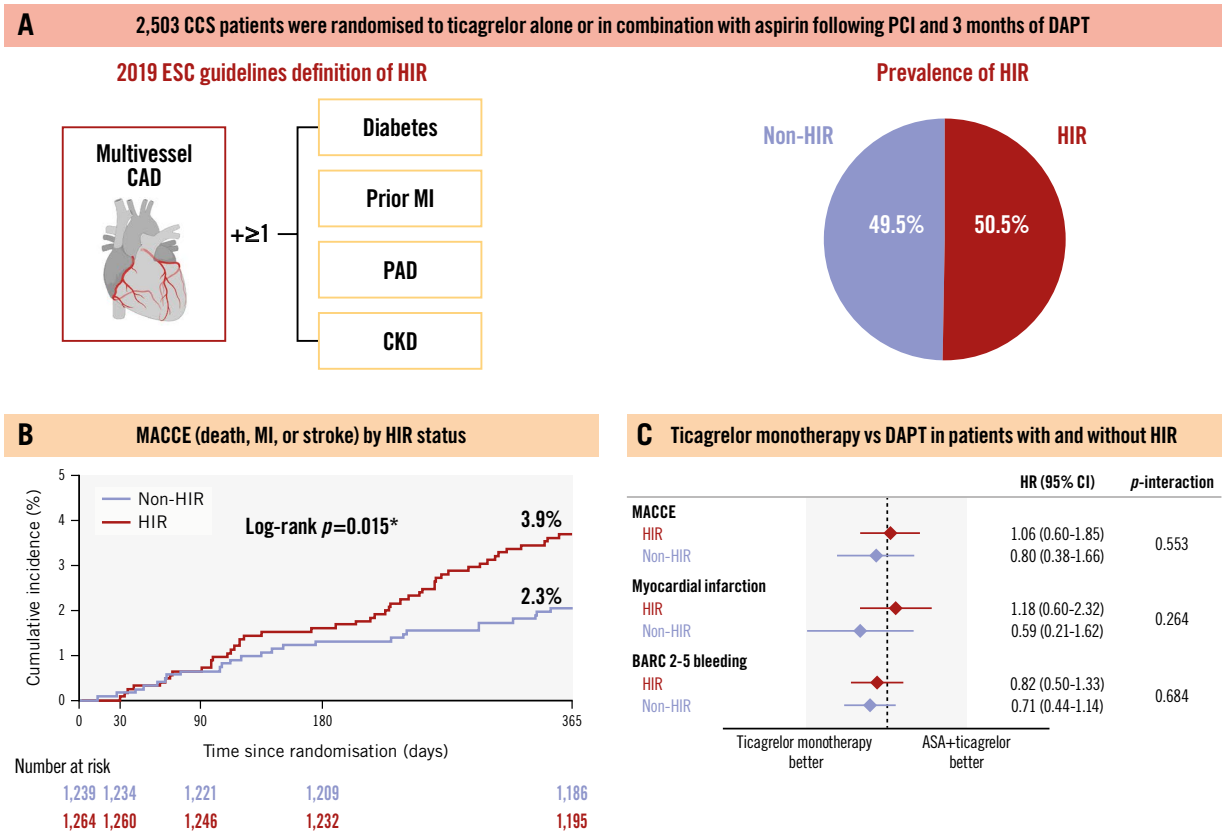
- The 2019 ESC definition classified approximately half of the patients as HIR and effectively identified those at higher risk of MACCE. Factors associated with an increased risk of MACCE in the TWILIGHT CCS population were vascular disease, diabetes, and LM or proximal LAD involvement, aligning with the criteria outlined in the ESC definition.
- Ticagrelor monotherapy, following a 3-month course of DAPT, was not associated with an increased risk of MACCE compared with standard ticagrelor-based DAPT, regardless of HIR status.

Patients with CCS undergoing PCI are generally perceived to be at lower ischaemic risk compared to those treated for MI. However, a significant proportion of CCS patients undergoing PCI present with clinical and/or angiographic complexity, which contributes to a substantial risk of recurrent ischaemic events[16]. Notably, diabetic patients, who account for up to 40% of patients undergoing PCI for CCS, have double the risk of cardiac death or MI in the first years after PCI compared with non-diabetic patients[17,18]. Similarly, CKD heightens susceptibility to ischaemic events following stent implantation, which is due not only to associated comorbidities but also to factors such as inflammation, vascular calcifications, and endothelial dysfunction[19]. Additionally, patients with extensive atherosclerosis or prior atherosclerotic cardiovascular events are more likely to experience recurrent cardiac events[20].

In 2019, the ESC guidelines on CCS introduced a multiparametric definition of HIR to identify patients who might benefit most from prolonged DAPT and/or potent $P2Y_{12}$ inhibitors[8]. This was largely based on findings from the PEGASUS-TIMI 54 trial, which demonstrated a significant reduction in ischaemic events with prolonged ticagrelor-based DAPT compared with aspirin monotherapy in patients with prior MI, with consistent benefits observed in those with multivessel CAD[6,21]. However, prolonged DAPT with aspirin and ticagrelor was also associated with an increased risk of Thrombolysis in Myocardial Infarction (TIMI) major bleeding, potentially offsetting the ischaemic protection[6]. Furthermore, the time from PCI to randomisation in the PEGASUS-TIMI 54 trial ranged from 1 to 3 years, making its findings less generalisable for decision-making immediately post-PCI.

The HIR criteria defined by the 2019 ESC guidelines were consistent with the main correlates of MACCE in the present study, including LM or proximal LAD involvement, diabetes, vascular disease (including PAD and prior MI), and CKD. The specific design of the TWILIGHT trial – wherein high-risk patients were treated with ticagrelor-based DAPT for 3 months after PCI and subsequently randomised only if they remained

The TWILIGHT-CCS study.



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*The TWILIGHT-CCS study included 2,503 patients with CCS undergoing PCI, randomised to ticagrelor alone or ticagrelor plus aspirin after completing 3 months of ticagrelor-based DAPT. Patients were stratified as HIR or non-HIR using the 2019 ESC guidelines definition, with 50.5% classified as HIR (A). At 1 year after randomisation, HIR patients had a significantly higher incidence of MACCE, including death, myocardial infarction, and stroke, compared to non-HIR patients (B). However, risks of both ischaemic and bleeding events at 1 year were similar between ticagrelor monotherapy and ticagrelor-based DAPT, regardless of HIR status (C). *p-value <0.05. ASA: aspirin; BARC: Bleeding Academic Research Consortium; CAD: coronary artery disease; CCS: chronic coronary syndrome; CI: confidence interval; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; ESC: European Society of Cardiology; HIR: high ischaemic risk; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention*

free from adverse events – explains the high prevalence of HIR (50.5%) and the relatively low MACCE rate (3%) observed in the CCS population[13]. Indeed, treating CCS patients with ticagrelor was not recommended by practice guidelines at the time the trial was conducted, but the TWILIGHT inclusion criteria were in line with the subsequent 2019 ESC guidelines recommendation for ticagrelor-based DAPT in CCS (only in case of high-risk elective stenting)[8]. Nonetheless, patients who met the HIR definition experienced an almost twofold higher risk of MACCE, highlighting the critical importance of risk stratification at the time of PCI in CCS patients.

Notably, the strategy of ticagrelor monotherapy was associated with a similar risk of MACCE compared with 12 months of ticagrelor-based DAPT even in patients classified as HIR. On the other hand, we did not observe a significant bleeding risk reduction in either the HIR or non-HIR groups. This result was consistent with a previous substudy and is potentially attributable to the imbalance in baseline characteristics between CCS and ACS patients (e.g., older age and lower prevalence of female sex and Asian race in the CCS cohort), the higher rate of ticagrelor discontinuation among CCS patients, and, most importantly, the lack of statistical power in the CCS subgroup[13]. However, this finding was recently corroborated by a large individual patient-data meta-analysis showing no benefit of ticagrelor monotherapy over DAPT in terms of BARC 2-5 bleeding in approximately 6,000 CCS patients (4.5% vs 4.8%, HR 0.92, 95% CI: 0.72-1.17; p=0.478), while a significant reduction in bleeding was observed in the ACS setting[22].

Table 1. Baseline clinical characteristics.

	High ischaemic risk (N=1,264)			Non-high ischaemic risk (N=1,239)		
	Ticagrelor N=654 (51.7%)	Ticagrelor+ASA N=610 (48.3%)	*p*-value	Ticagrelor N=627 (50.6%)	Ticagrelor+ASA N=612 (49.4%)	*p*-value
Age, years	65.5±9.6	65.3±10.1	0.751	66.1±9.1	66.2±9.0	0.753
Female sex	111 (17.0)	102 (16.7)	0.905	155 (24.7)	169 (27.6)	0.247
Enrolling region			0.614			0.613
North America	336 (51.4)	300 (49.2)		265 (42.3)	271 (44.3)	
Europe	262 (40.1)	261 (42.8)		291 (46.4)	267 (43.6)	
Asia	56 (8.6)	49 (8.0)		71 (11.3)	74 (12.1)	
BMI, kg/m^2	28.4 (25.6-31.6)	28.1 (25.4-32.0)	0.794	27.6 (24.7-31.0)	27.9 (25.3-31.5)	0.260
Current smoker	98 (15.0)	109 (17.9)	0.166	100 (15.9)	91 (14.9)	0.599
Diabetes	360 (55.0)	349 (57.2)	0.438	149 (23.8)	148 (24.2)	0.863
Hypercholesterolaemia	530 (81.0)	485 (79.5)	0.494	453 (72.2)	461 (75.3)	0.218
Hypertension	547 (83.6)	519 (85.1)	0.481	498 (79.4)	478 (78.1)	0.570
Previous MI	318 (48.6)	321 (52.6)	0.155	124 (19.8)	110 (18.0)	0.418
Previous PCI	441 (67.4)	415 (68.0)	0.819	283 (45.1)	276 (45.1)	0.989
Previous CABG	123 (18.8)	94 (15.4)	0.109	38 (6.1)	55 (9.0)	0.051
Peripheral artery disease	84 (12.8)	78 (12.8)	0.976	30 (4.8)	34 (5.6)	0.540
Chronic kidney disease	173 (27.8)	161 (27.4)	0.880	71 (11.9)	67 (11.6)	0.865
Prior bleeding	7 (1.1)	8 (1.3)	0.692	3 (0.5)	7 (1.1)	0.191
Anaemia	126 (20.3)	119 (20.4)	0.958	114 (19.2)	94 (16.3)	0.189
LVEF, %	55.2±9.3	53.1±9.3	0.034	56.1±9.0	54.9±9.3	0.224

Data are n (%), mean±standard deviation, or median (interquartile range). ASA: aspirin; BMI: body mass index; CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 2. Baseline procedural characteristics.

	High ischaemic risk (N=1,264)			Non-high ischaemic risk (N=1,239)		
	Ticagrelor N=654 (51.7%)	Ticagrelor+ASA N=610 (48.3%)	*p*-value	Ticagrelor N=627 (50.6%)	Ticagrelor+ASA N=612 (49.4%)	*p*-value
Radial access	415 (63.5)	384 (63.0)	0.852	441 (70.3)	415 (67.8)	0.336
Multivessel CAD	654 (100)	610 (100)	-	209 (33.3)	192 (31.4)	0.461
Target vessel						
Left main	32 (4.9)	44 (7.2)	0.083	17 (2.7)	23 (3.8)	0.297
Left anterior descending	300 (45.9)	276 (45.2)	0.823	382 (60.9)	365 (59.6)	0.644
Left circumflex	265 (40.5)	250 (41.0)	0.867	143 (22.8)	125 (20.4)	0.309
Right coronary artery	270 (41.3)	264 (43.3)	0.473	178 (28.4)	198 (32.4)	0.129
Venous bypass graft	22 (3.4)	15 (2.5)	0.340	3 (0.5)	7 (1.1)	0.191
No. of vessels treated			0.328			0.784
1	456 (69.7)	411 (67.4)		546 (87.1)	526 (85.9)	
2	183 (28.0)	177 (29.0)		70 (11.2)	76 (12.4)	
≥3	15 (2.3)	22 (3.6)		11 (1.8)	10 (1.6)	
No. of lesions treated			0.519			0.340
1	341 (52.1)	333 (54.6)		419 (66.8)	386 (63.1)	
2	241 (36.9)	206 (33.8)		155 (24.7)	173 (28.3)	
≥3	72 (11.0)	71 (11.6)		53 (8.5)	53 (8.7)	
Moderate/severe calcification	114 (17.4)	111 (18.2)	0.722	112 (17.9)	99 (16.2)	0.430
Bifurcation	72 (11.0)	67 (11.0)	0.988	77 (12.3)	70 (11.4)	0.646
Chronic total occlusion	51 (7.8)	38 (6.2)	0.276	43 (6.9)	43 (7.0)	0.907
Total stent length, mm	33.0 (20.0-51.0)	32.0 (19.0-52.0)	0.565	34.0 (23.0-51.0)	36.0 (23.0-52.0)	0.698

Data are n (%) or median (interquartile range). ASA: aspirin; CAD: coronary artery disease

Table 3. Adverse events at 1 year, stratified by randomised treatment allocation, in patients with and without high ischaemic risk.

Outcomes	High ischaemic risk (N=1,264)				Non-high ischaemic risk (N=1,239)				Interaction p-value‡
	Ticagrelor monotherapy (N=654)	Ticagrelor +ASA (N=610)	Hazard ratio (95% CI)	p-value	Ticagrelor monotherapy (N=627)	Ticagrelor +ASA (N=612)	Hazard ratio (95% CI)	p-value	
MACCE	26 (4.0)	23 (3.8)	1.06 (0.60-1.85)	0.851	13 (2.1)	16 (2.6)	0.80 (0.38-1.66)	0.545	0.553
Cardiovascular death, MI or ischaemic stroke	25 (3.9)	21 (3.5)	1.11 (0.62-1.98)	0.727	11 (1.8)	14 (2.3)	0.77 (0.35-1.70)	0.520	0.469
All-cause death	6 (0.9)	8 (1.3)	0.70 (0.24-2.02)	0.510	6 (1.0)	6 (1.0)	0.98 (0.32-3.03)	0.969	0.672
Cardiovascular death	5 (0.8)	6 (1.0)	0.78 (0.24-2.55)	0.680	4 (0.6)	4 (0.7)	0.99 (0.25-3.94)	0.983	0.799
MI	19 (3.0)	15 (2.5)	1.18 (0.60-2.32)	0.634	6 (1.0)	10 (1.6)	0.59 (0.21-1.62)	0.305	0.264
Ischaemic stroke	3 (0.5)	2 (0.3)	1.40 (0.23-8.39)	0.711	2 (0.3)	0 (0.0)	N/A	N/A	0.992
Stent thrombosis	6 (0.9)	3 (0.5)	1.87 (0.47-7.48)	0.376	0 (0.0)	3 (0.5)	N/A	N/A	0.989
BARC 2, 3 or 5 bleeding	30 (4.7)	34 (5.7)	0.82 (0.50-1.33)	0.419	30 (4.9)	41 (6.7)	0.71 (0.44-1.14)	0.153	0.684
BARC 3 or 5 bleeding	10 (1.6)	13 (2.2)	0.71 (0.31-1.63)	0.421	7 (1.1)	7 (1.2)	0.99 (0.35-2.82)	0.982	0.631
TIMI major bleeding	2 (0.3)	8 (1.3)	0.23 (0.05-1.09)	0.065	3 (0.5)	3 (0.5)	0.99 (0.20-4.89)	0.987	0.203
GUSTO moderate or severe bleeding	7 (1.1)	8 (1.3)	0.81 (0.29-2.24)	0.689	6 (1.0)	5 (0.8)	1.18 (0.36-3.88)	0.780	0.636
ISTH major bleeding	11 (1.7)	14 (2.3)	0.73 (0.33-1.60)	0.430	8 (1.3)	7 (1.2)	1.13 (0.41-3.12)	0.813	0.502

Data are number of events (%), unless otherwise indicated. The percentages mentioned above represent Kaplan-Meier rates at 12 months after the index procedure. ‡P-value is obtained from the interaction test between HIR status and randomised treatment allocation. ASA: aspirin; BARC: Bleeding Academic Research Consortium; CI: confidence interval; GUSTO: Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded arteries; ISTH: International Society on Thrombosis and Haemostasis; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; N/A: not applicable; TIMI: Thrombolysis in Myocardial Infarction

The potential benefits of a DAPT regimen with potent $P2Y_{12}$ inhibitors over clopidogrel in CCS patients remain a topic of debate. The ALPHEUS trial demonstrated no significant reduction in PCI-related MI and higher rates of minor bleeding at 30 days with ticagrelor compared to clopidogrel[23]. Similarly, the Intensified Loading With Prasugrel Versus Standard Loading with Clopidogrel in Invasive-treated Patients With Biomarker-Negative Angina Pectoris (SASSICAIA) trial found no additional benefit with a prasugrel loading strategy compared to standard clopidogrel loading[24]. In contrast, the PRASugrel For Japanese PatIenTs with Coronary Artery Diseases Undergoing Elective PCI (PRASFIT-Elective) study, which evaluated major cardiovascular events up to 1 year as the primary endpoint, demonstrated the superiority of prasugrel over clopidogrel in Japanese patients undergoing elective PCI[25]. More recently, promising data supporting the use of ticagrelor monotherapy over clopidogrel-based DAPT or clopidogrel monotherapy have been reported. An individual patient-data meta-analysis of six randomised clinical trials (RCTs) showed that clopidogrel monotherapy significantly reduced the risk of bleeding as compared to standard DAPT with either clopidogrel or ticagrelor, but at the cost of a 37% higher risk of death and MI, while ticagrelor monotherapy reduced bleeding without increasing ischaemic events[26]. Similarly, a network meta-analysis evaluating different antithrombotic strategies within the first year after PCI found that clopidogrel-based DAPT was associated with a higher risk of all-cause and cardiovascular mortality compared with ticagrelor monotherapy[27]. When our results are considered in light of these recent meta-analyses, it appears that short DAPT followed by ticagrelor monotherapy represents a safe and effective antithrombotic regimen for patients with CCS and HIR undergoing PCI. However, a tailored risk assessment that incorporates both ischaemic and bleeding risk scores is essential to identify patients most likely to benefit from this strategy[28].

Finally, important considerations in broadening ticagrelor use to CCS patients are the associated costs and the limited approval for reimbursement in certain countries. Ticagrelor-based DAPT has been shown to be cost-effective in high-risk CCS patients[29,30], and it is reasonable to speculate that the same might apply to ticagrelor monotherapy, particularly with the increasing availability of generic formulations. Nevertheless, dedicated cost-effectiveness analyses are warranted.

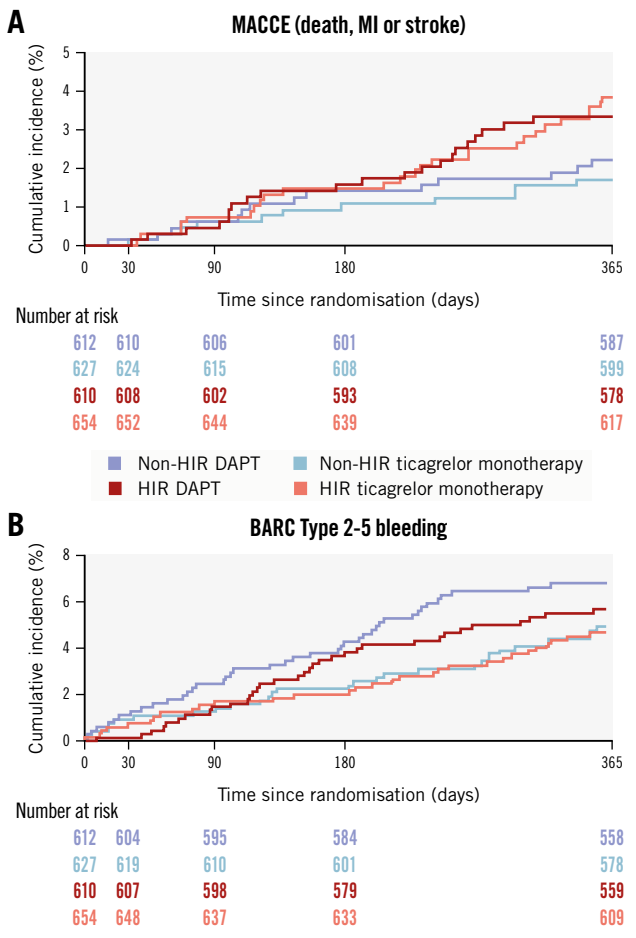

Figure 2. *Cumulative incidence of MACCE and BARC Type 2-5 bleeding by randomised treatment allocation and HIR status. The Kaplan-Meier curves show the event rates for MACCE (A) and BARC 2-5 bleeding (B) at 1 year after randomisation in HIR (red/pink curves) and non-HIR (blue/light blue curves) patients treated with ticagrelor monotherapy (light blue/pink lines) or ticagrelor-based DAPT (blue/red lines). BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; HIR: high ischaemic risk; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction*

Limitations

Firstly, the results of this *post hoc* analysis of an RCT should be regarded as hypothesis-generating, necessitating further dedicated studies for confirmation. Secondly, given the inclusion criteria of the TWILIGHT trial, the study focused on a selected high-risk population, potentially excluding patients with lower ischaemic and bleeding risks. As a result, it is likely that the proportion of HIR patients in our study may overestimate the prevalence of HIR in the general CCS population. Similarly, the absence of a comparator arm treated with clopidogrel, which is the most commonly used $P2Y_{12}$ inhibitor in patients with CCS, is an inherent limitation of the present analysis. Thirdly, the relatively small sample size in the CCS group, along with the low absolute number of events, may have increased the risk of type II error. Fourthly, while this substudy considered MACCE as the main outcome of interest, the primary endpoint of the TWILIGHT trial was BARC Type 2-5 bleeding. Fifthly, as with the main trial, these results may not be generalisable to patients who do not complete an initial 3-month DAPT run-in phase. Finally, the most updated HIR definition from the 2024 ESC guidelines on CCS, which include slightly different angiographic risk criteria, were not available at the time this analysis was designed[9].

Conclusions

In patients with CCS undergoing PCI who were randomised in the TWILIGHT trial, the ESC definition of HIR identified those at heightened risk of MACCE at 1 year. Short-term DAPT followed by ticagrelor monotherapy resulted in a similar risk of ischaemic and bleeding events compared to standard ticagrelor-based DAPT in both HIR and non-HIR patients. Although hypothesis-generating, because of the small sample size and *post hoc* design of the analysis, these findings support the potential expansion of current guideline indications for ticagrelor monotherapy in CCS patients undergoing PCI.

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Conflict of interest statement

U. Baber has received honoraria from AstraZeneca and Boston Scientific. D.J. Angiolillo has received consulting fees or

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Supplementary data

Supplementary Table 1. Definition of the 2019 ESC guidelines high ischaemic risk criteria used in the TWILIGHT trial.

Supplementary Table 2. Prevalence of the TWILIGHT inclusion criteria, according to randomised treatment allocation, within the CCS population.

Supplementary Table 3. Adverse events at 1 year, stratified by randomised treatment allocation, in patients with and without high thrombotic risk.

Supplementary Table 4. Impact of the TWILIGHT inclusion criteria on the risk of MACCE in the CCS population.

Supplementary Figure 1. UpSet plot showing the most common combinations of clinical and angiographic inclusion criteria in the CCS population of the TWILIGHT trial.

Supplementary Figure 2. Cumulative incidence of MACCE and BARC Type 2-5 bleeding by HIR status.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00973

Supplementary data

Supplementary Table 1. Definition of the 2019 ESC guidelines' high ischaemic risk criteria used in the TWILIGHT trial.

2019 ESC guidelines for the diagnosis and management of chronic coronary syndrome[1]	TWILIGHT Trial[2]
Multivessel or diffuse CAD	Multivessel CAD defined as significant disease in at least 2 major epicardial vessels or significant left main disease plus one major epicardial vessel. Significant CAD was defined as angiographic stenosis of at least 70% in a major epicardial vessel or at least 50% in the left main trunk. For intermediate stenosis in major epicardial vessels (50%-70%), an invasive hemodynamic assessment using fractional flow reserve with values less than or equal to 0.8 was considered significant. For intermediate left main lesions, a minimal lumen area by intravascular ultrasound less than 6.0 mm^2 was considered significant.
Diabetes mellitus requiring medication	Diabetes mellitus treated with medications (oral hypoglycemic, subcutaneous injection of insulin)
Chronic Kidney Disease with eGFR 15-59 mL/min/1.73 m^2	Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 or creatinine clearance (CrCl) < 60 ml/min. Dialysis-dependent renal failure was an exclusion criterion.
Peripheral artery disease	Documented peripheral artery disease defined as ≥1 of the following: 1) Claudication, either with exertion or at rest; 2) Prior amputation for arterial vascular insufficiency; 3) Prior vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping); 4) Documented aortic aneurysm with or without repair; 5) Positive noninvasive test (eg, ankle brachial index ≤0.9, ultrasound, magnetic resonance or computed tomography imaging of >50%

	diameter stenosis in any peripheral artery, ie, renal, subclavian, femoral, iliac)
Recurrent MI	Prior MI defined as ≥1 of the following: 1) medical record documentation of prior MI; 2) pathological Q waves with or without symptoms in the absence of nonischemic causes; 3) imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause; 4) pathological findings of prior MI.

1. Knuuti J et al. Eur Heart J. 2020 Jan 14;41(3):407-477. 2. Mehran R et al. N Engl J Med 2019;381:2032-42.

Abbreviations: CAD, coronary artery disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; MI, myocardial infarction.

Supplementary Table 2. Prevalence of the TWILIGHT inclusion criteria, according to randomised treatment allocation, within the CCS population.

	Overall (N=2503)	Ticagrelor+ASA (N=1281)	Ticagrelor (N=1222)	P-Value
Clinical inclusion criteria				
Age ≥65 years	1408 (56.3%)	680 (55.6%)	728 (56.8%)	0.551
Female sex	537 (21.5%)	271 (22.2%)	266 (20.8%)	0.390
Vascular disease*	1740 (69.5%)	849 (69.5%)	891 (69.6%)	0.966
Diabetes*	1006 (40.2%)	497 (40.7%)	509 (39.7%)	0.633
Chronic kidney disease*	498 (20.9%)	245 (21.0%)	253 (20.8%)	0.877
Angiographic inclusion criteria				
Multi-vessel CAD*	1795 (71.7%)	869 (71.1%)	926 (72.3%)	0.514
Total stent length > 30 mm	1425 (57.0%)	697 (57.1%)	728 (56.8%)	0.898
Bifurcation with at least 2 stents	75 (3.0%)	37 (3.0%)	38 (3.0%)	0.928
LM or proximal LAD treated	1498 (59.8%)	729 (59.7%)	769 (60.0%)	0.848
Calcification requiring atherectomy	117 (4.7%)	59 (4.8%)	58 (4.5%)	0.722

All variables are reported as absolute number and percentages. Vascular disease included previous myocardial infarction, previous coronary revascularization or peripheral artery disease. Acute coronary syndrome presentation and thrombotic target lesion were exclusion criteria for the current analysis.

*Included in the ESC definition of high ischemic risk.

Abbreviations: ASA, aspirin; CAD, coronary artery disease; CCS, chronic coronary syndrome; LAD, left anterior descending; LM, left main.

Supplementary Table 3. Adverse events at 1 year, stratified by randomised treatment allocation, in patients with and without high thrombotic risk.

Outcomes	High Thrombotic Risk (N=1565)				Non-High Thrombotic Risk (N=938)				Interaction p-value‡
	Ticagrelor monotherapy (N=804)	Ticagrelor + ASA (N=761)	Hazard ratio (95% CI)	p-value	Ticagrelor monotherapy (N=477)	Ticagrelor + ASA (N=461)	Hazard ratio (95% CI)	p-value	
	no. of events (%)				no. of events (%)				
MACCE	28 (3.5%)	26 (3.4%)	1.02 (0.60 - 1.74)	0.939	11 (2.3%)	13 (2.8%)	0.82 (0.37 - 1.84)	0.633	0.662
Cardiovascular death, MI or ischemic stroke	27 (3.4%)	23 (3.1%)	1.11 (0.64 - 1.94)	0.710	9 (1.9%)	12 (2.6%)	0.73 (0.31 - 1.73)	0.473	0.422
All-cause death	7 (0.9%)	10 (1.3%)	0.66 (0.25 - 1.74)	0.403	5 (1.0%)	4 (0.9%)	1.21 (0.33 - 4.52)	0.773	0.466
Cardiovascular death	6 (0.8%)	7 (0.9%)	0.81 (0.27 - 2.42)	0.710	3 (0.6%)	3 (0.7%)	0.98 (0.20 - 4.84)	0.977	0.852
MI	20 (2.5%)	16 (2.1%)	1.18 (0.61 - 2.28)	0.617	5 (1.1%)	9 (2.0%)	0.54 (0.18 - 1.61)	0.268	0.228
Ischemic stroke	3 (0.4%)	2 (0.3%)	1.42 (0.24 - 8.52)	0.699	2 (0.4%)	0 (0.0%)	N/A	N/A	0.993
Stent thrombosis	6 (0.8%)	3 (0.4%)	1.90 (0.48 - 7.60)	0.364	0 (0.0%)	3 (0.7%)	N/A	N/A	0.990
BARC 2, 3 or 5 bleeding	35 (4.4%)	43 (5.7%)	0.76 (0.49 - 1.19)	0.238	25 (5.3%)	32 (7.0%)	0.75 (0.44 - 1.27)	0.282	0.957
BARC 3 or 5 bleeding	11 (1.4%)	17 (2.3%)	0.61 (0.29 - 1.30)	0.200	6 (1.3%)	3 (0.7%)	1.96 (0.49 - 7.83)	0.342	0.146
TIMI major bleeding	2 (0.3%)	10 (1.3%)	0.19 (0.04 - 0.86)	0.031	3 (0.6%)	1 (0.2%)	2.93 (0.30 - 28.1)	0.352	0.048
GUSTO moderate or severe bleeding	8 (1.0%)	10 (1.3%)	0.76 (0.30 - 1.91)	0.555	5 (1.1%)	3 (0.7%)	1.63 (0.39 - 6.81)	0.505	0.376
ISTH major bleeding	13 (1.6%)	18 (2.4%)	0.68 (0.33 - 1.39)	0.289	6 (1.3%)	3 (0.7%)	1.96 (0.49 - 7.83)	0.342	0.182

High thrombotic risk was defined as either meeting criteria for HIR or undergoing complex PCI. The percentages mentioned above represent K-M rates at 12 months after index procedure. Abbreviations as in Table 3.

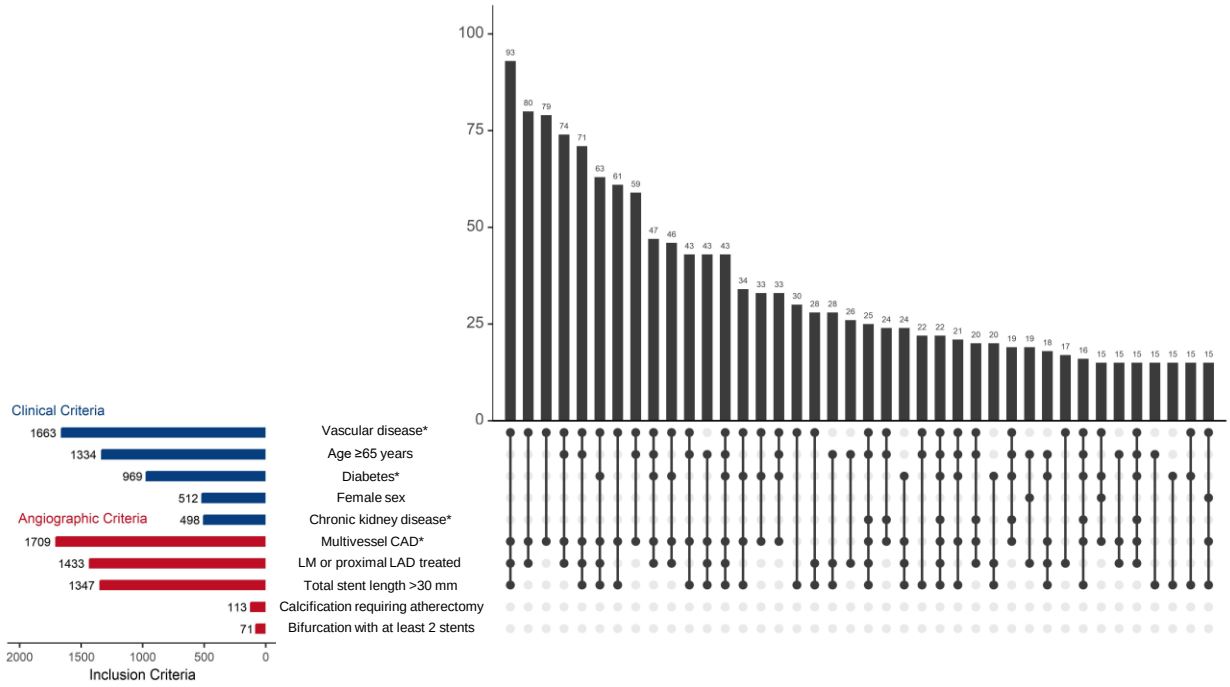
Supplementary Table 4. Impact of the TWILIGHT inclusion criteria on the risk of MACCE in the CCS population.

	Hazard ratio (95% CI)	P-value
Clinical inclusion criteria		
Age ≥ 65 years	0.81 (0.63 - 1.05)	0.109
Female sex	0.98 (0.71 - 1.34)	0.886
Vascular disease*[#]	1.37 (1.02 - 1.85)	**0.038**
Diabetes mellitus*	1.37 (1.06 - 1.77)	**0.018**
Chronic kidney disease*	1.34 (0.99 - 1.81)	0.057
Angiographic inclusion criteria		
Multi-vessel CAD*	1.25 (0.93 - 1.69)	0.146
Stent length > 30 mm	1.04 (0.80 - 1.35)	0.751
Bifurcation with at least 2 stents	1.49 (0.79 - 2.80)	0.220
LM or proximal LAD treated	1.38 (1.05 - 1.81)	**0.021**
Calcified target lesion requiring atherectomy	1.35 (0.79 - 2.32)	0.274

Vascular disease included previous myocardial infarction, previous coronary revascularization or peripheral artery disease. Acute coronary syndrome presentation and thrombotic target lesion were exclusion criteria for the current analysis. P-values <0.05 are highlighted in bold.

*Included in the ESC definition of high ischemic risk. [#]Vascular disease included previous myocardial infarction, previous coronary revascularization or peripheral artery disease.

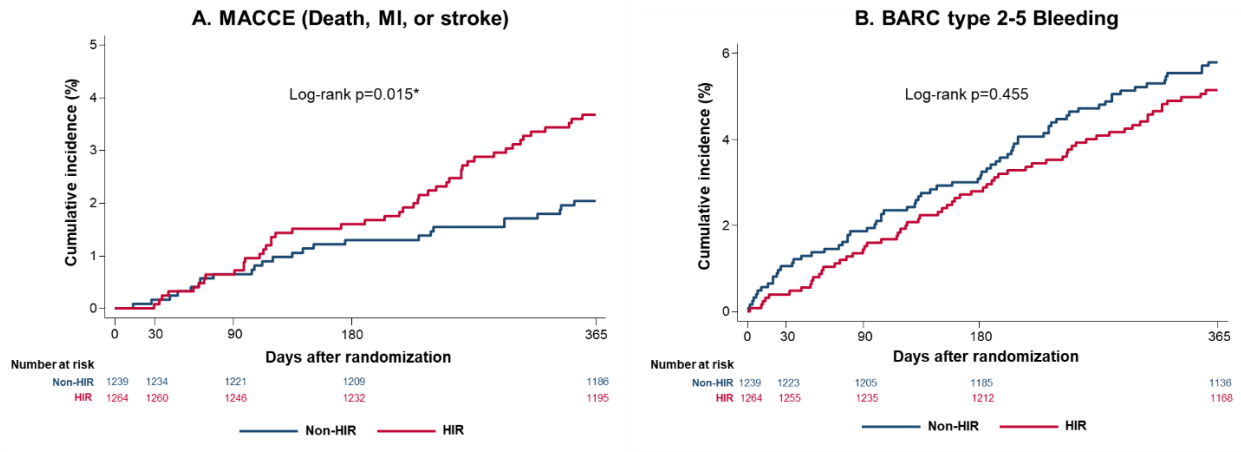
Abbreviations: CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events. Other abbreviations as in Table 1.



Supplementary Figure 1. UpSet plot showing the most common combinations of clinical and angiographic inclusion criteria in the CCS population of the TWILIGHT trial.

*Included in the ESC definition of high ischemic risk.

Abbreviations as in Figure 1.



Supplementary Figure 2. Cumulative incidence of MACCE and BARC Type 2-5 bleeding by HIR status.

The Kaplan Maier curves show the event rates for MACCE (panel A) and BARC 2-5 bleeding (panel B) at 1 year after randomization in HIR (red curves) vs. non-HIR (blue curves) patients.

Abbreviations: BARC, Bleeding Academic Research Consortium; HIR, high ischemic risk; MACCE, major adverse cardiac and cerebrovascular events. MI, myocardial infarction.