Ticagrelor monotherapy beyond one month after PCI in ACS or stable CAD in elderly patients: a pre-specified analysis of the GLOBAL LEADERS trial

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00699

KEYWORDS

- ACS/NSTE-ACS
- adjunctive pharmacotherapy
- bleeding
- elderly (>75)
- stable angina

Abstract

Aims: Antiplatelet treatment in the elderly post percutaneous coronary interventions (PCI) remains a complex issue. Here we report the results of the pre-specified subgroup analysis of the GLOBAL LEADERS trial evaluating the long-term safety and cardiovascular efficacy of ticagrelor monotherapy among patients categorised according to the pre-specified cut-off value of 75 years of age.

Methods and results: This was a pre-specified analysis of the randomised GLOBAL LEADERS trial (n=15,991), comparing 23-month ticagrelor monotherapy (after one month of DAPT) with the reference treatment (12-month DAPT followed by 12 months of aspirin). Among elderly patients (>75 years; n=2,565), the primary endpoint (two-year all-cause mortality or new Q-wave core lab-adjudicated myocardial infarction [MI]) occurred in 7.2% and 9.4% of patients in the ticagrelor monotherapy and the reference group, respectively (hazard ratio [HR] 0.75, 95% confidence interval [CI]: 0.58-0.99, p=0.041; p_{int}=0.23); BARC-defined bleeding type 3/5 occurred in 5.2% and 4.1%, respectively (HR 1.29, 95% CI: 0.89-1.86; p=0.180; p_{int}=0.06). The elderly with stable CAD had a higher rate of BARC 3/5 type bleeding (HR 2.05, 95% CI: 1.18-3.55) with ticagrelor monotherapy versus the reference treatment (p_{int}=0.02). Elderly patients had a lower rate of definite or probable stent thrombosis (ST) with ticagrelor monotherapy (0.4% vs 1.4%, p=0.015, p_{int}=0.01), compared with the reference group.

Conclusions: In this pre-specified, exploratory analysis of the overall neutral trial, there was no differential treatment effect of ticagrelor monotherapy (after one-month dual therapy with aspirin) found in elderly patients undergoing PCI with respect to the rate of the primary endpoint of all-cause death or new Q-wave MI. The lower rate of ST in the elderly with ticagrelor monotherapy is hypothesis-generating. ClinicalTrials.gov identifier: NCT01813435

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SUBMITTED ON 30/07/2019 - REVISION RECEIVED ON 12/11/2019 - ACCEPTED ON 11/12/2019

Abbreviations

ACS	acute coronary syndromes
BARC	Bleeding Academic Research Consortium
CAD	coronary artery disease
DAPT	dual antiplatelet therapy
MI	myocardial infarction
NACE	net adverse clinical events
PCI	percutaneous coronary intervention
POCE	patient-oriented composite endpoint

Introduction

Age is associated with a high comorbidity burden and an increased risk of both ischaemic and bleeding complications[1]. The benefit–risk of antiplatelet therapies in elderly patients is complex and the current data remain inconclusive with regard to optimal potency and duration of antiplatelet regimen, compared with younger individuals[1-5].

Elderly patients above 75 years of age represent more than one third of patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS) and with an ageing society this percentage is expected to grow. Nevertheless, they still tend to be under-represented in clinical trials[6]. The remaining gap in evidence-based treatment of elderly patients, including a need to identify the most suitable antiplatelet strategies in this vulnerable patient subgroup, has been underlined by leading authorities and scientific associations[2].

Recently, aspirin-free antiplatelet protocols after PCI have been advocated to preserve their anti-ischaemic effects without the bleeding risk associated with dual antiplatelet therapy (DAPT)[7]. In GLOBAL LEADERS, ticagrelor in combination with aspirin for one month followed by ticagrelor monotherapy for 23 months was not superior to 12 months of DAPT followed by 12 months of aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction (MI) in a broad patient population undergoing PCI[8]. Nevertheless, the risks and effects of different intensity antiplatelet therapies may differ substantially between younger and elderly adults, as the latter often carry the burden of multiple risk factors and comorbidities, and have been demonstrated to present altered platelet function, compared to younger individuals[1,3].

Given this background, we report the results of the pre-specified subgroup analysis of the GLOBAL LEADERS trial evaluating the long-term safety and cardiovascular efficacy of ticagrelor monotherapy among patients categorised according to the pre-specified cut-off value for age of 75 years.

Editorial, see page 1560

Methods

STUDY DESIGN AND PATIENT POPULATION

GLOBAL LEADERS (ClinicalTrials.gov NCT01813435) was an investigator-initiated, prospective, randomised, multicentre, multinational, open-label trial that compared two strategies of antiplatelet treatment in 15,991 patients scheduled for PCI[8]. Patients with stable coronary artery disease (CAD) or ACS were randomly allocated to either an experimental strategy of one-month aspirin and ticagrelor, followed by 23 months of ticagrelor alone, or to the reference strategy with 12-month DAPT consisting of aspirin in combination with either clopidogrel (for patients with stable CAD) or ticagrelor (for patients with ACS)[7]. All types of lesions were permitted, including left main, bifurcations, chronic total occlusions, interventions on grafted vessels, etc. Detailed inclusion criteria, exclusion criteria, and study procedures have been described previously **(Supplementary Appendix 1, Supplementary Appendix 2)**[7,8]. The trial was performed in compliance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent at enrolment. An independent data and safety monitoring board (DSMB) oversaw the safety of all patients.

CLINICAL ENDPOINTS

The primary endpoint comprised a composite of all-cause death or centrally adjudicated (by ECG core lab) new Q-wave MI up to two years after the index procedure. The key secondary safety endpoint was site-reported bleeding type 3 or 5 defined according to the Bleeding Academic Research Consortium (BARC) up to two-year follow-up. Further site-reported secondary endpoints included any stroke, site-reported MI, any revascularisation, target vessel revascularisation (TVR), definite stent thrombosis (ST) and the composite of definite or probable ST, according to the Academic Research Consortium (ARC) criteria **(Supplementary Appendix 3)**. In addition, upon the request of the DSMB, data on the rates of possible ST were collected, and the composite endpoint of any ST (definite/probable/possible) was reported.

Finally, the rates of the ARC 2-defined patient-oriented composite endpoint (POCE: all-cause death, any stroke, site-reported MI and any revascularisation) and net adverse clinical events (NACE: POCE and BARC 3 or 5 type bleeding) were reported up to two years.

Landmark analyses were performed within the elderly subgroup using the pre-specified time cut-offs: at 30 days (corresponding to the planned dates of discontinuation of aspirin in the experimental group) and one year (corresponding to the planned dates of discontinuation of a $P2Y_{12}$ receptor antagonist in the reference group) after the index procedure.

The trial was monitored for event under-reporting and event definition consistency; no central adjudication of clinical events was planned[7,8].

STATISTICAL ANALYSIS

Sample size consideration and statistical analysis for the primary and secondary endpoints in GLOBAL LEADERS have been described previously[8].

Clinical endpoints were evaluated using the Mantel-Cox log-rank method up to the time point when the first of this type of event occurred, reporting hazard ratios (HR) with 95% confidence intervals (CI). Pre-specified analyses of the primary endpoint, secondary efficacy and safety endpoints were performed with tests

for treatment-by-age interaction using the predefined cut-off value of 75 years of age. All analyses were performed following the intention-to-treat definition using SPSS software, Version 25 (IBM Corp., Armonk, NY, USA). A two-sided p-value of <0.05 was considered statistically significant.

Results

STUDY POPULATION

The GLOBAL LEADERS trial recruited and randomly assigned 15,991 participants. As 23 patients subsequently withdrew consent and requested deletion of their data from the database, a total of 15,968 patients remained in the study[8]. There were 2,565 (16.1%) patients aged >75 years, further referred to as elderly patients and 13,403 aged ≤75 years, further referred to as younger patients. The baseline characteristics were balanced between the experimental and the reference arm for both age subgroups, except for a higher proportion of patients with a history of prior PCI or CABG in the experimental versus the reference arm among elderly patients **(Table 1, Supplementary Table 1)**.

CLINICAL ENDPOINTS IN THE PRE-SPECIFIED AGE SUBGROUPS

Amongst elderly patients, the primary endpoint occurred in 93 (7.2%) patients in the experimental treatment strategy group and in 120 (9.4%) patients in the reference treatment strategy group (HR 0.75, 95% CI: 0.58-0.99; p=0.041) at two years (p_{int}=0.23) **(Table 2)**.

The elderly patients in the experimental group had a lower rate of all-cause death (5.7% vs 7.9%; p=0.027), POCE (16.4% vs 19.8%, p=0.032), TVR (4.3% vs 6.1%, p=0.048), definite (0.2% vs 0.9%, p=0.043) and definite or probable ST (0.4% vs 1.4%; p=0.015) at two years, as compared with the reference arm; BARC 3 or 5 type bleedings were numerically more frequent in the experimental as compared to the reference group (5.2% vs 4.1%, p=0.180), though not statistically different between the two treatment groups (p_{int}=0.06) **(Figure 1, Figure 2, Supplementary Table 2)**.

No significant differences in clinical outcome rates were found between the two treatment strategy groups in younger patients **(Figure 2, Figure 3, Supplementary Figure 1)**.

Table 1. Baseline characteristics in pre-specified age subgroups categorised according to randomised treatment.

	Age ≤75 years (n=13,403)				*p*-value	Age >75 years (n=2,565)			
	Reference (n=6,715)		Experimental (n=6,688)			Reference (n=1,273)		Experimental (n=1,292)	
	N	%	N	%		N	%	N	%
Age (±SD)	61.7	±8.4	61.6	±8.5	0.491	79.8	±3.2	79.7	±3.2
Weight (±SD)	84.1	±16.2	83.8	±16	0.197	76.1	±12.5	76.4	±13.2
Sex (female)	1,415	21.1%	1,419	21.2%	0.837	434	34.1%	446	34.5%
Stable CAD	3,526	52.5%	3,496	52.3%	0.784	725	57.0%	734	56.8%
UA	861	12.8%	837	12.5%	0.593	157	12.3%	167	12.9%
NSTEMI	1,411	21.0%	1,433	21.4%	0.558	278	21.8%	251	19.4%
STEMI	917	13.7%	922	13.8%	0.827	113	8.9%	140	10.8%
Diabetes	1,626	24.2%	1,649	24.7%	0.552	363	28.5%	400	31.0%
Diabetes on insulin	499	7.4%	478	7.1%	0.636	118	9.3%	128	9.9%
Hypertension	4,796	71.7%	4,793	71.9%	0.753	1,037	81.8%	1,089	84.5%
Hypercholesterolaemia	4,571	70.2%	4,482	69.3%	0.289	852	69.0%	863	68.9%
Currently smoking	2,013	30.0%	1,970	29.5%	0.509	90	7.1%	96	7.4%
Peripheral vascular disease	407	6.1%	355	5.4%	0.060	122	9.7%	121	9.5%
COPD	320	4.8%	320	4.8%	0.974	97	7.6%	84	6.5%
Previous major bleeding	36	0.5%	35	0.5%	0.918	16	1.3%	11	0.9%
Impaired renal function	664	9.9%	697	10.4%	0.307	412	32.4%	417	32.3%
Previous stroke	162	2.4%	158	2.4%	0.848	49	3.9%	52	4.0%
Previous MI	1,562	23.3%	1,547	23.2%	0.858	317	25.0%	284	22.1%
Previous PCI	2,130	31.7%	2,170	32.5%	0.381	482	37.9%	439	34.1%
Previous CABG	352	5.2%	341	5.1%	0.705	143	11.3%	107	8.3%
Complex PCI*	1,884	28.9%	1,867	28.9%	0.987	403	33.1%	416	33.1%

*PCI was defined as complex PCI when at least one of the following features was met: multivessel PCI, ≥3 stents implanted, ≥3 lesions treated, bifurcation PCI with ≥2 stents, and total stent length >60 mm. These five high-risk features of complex PCI for ischaemic events have been described previously [12]. Multivessel PCI was defined as PCI performed to treat two or three separate major coronary territories. An isolated left main lesion was classified as two-vessel disease in the presence of right dominance and three-vessel disease in the presence of left dominance. To calculate the total stent length, the sum of the nominal stent lengths was used as per patient. CABG: coronary artery bypass grafting; CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

Table 2. Two-year clinical outcomes in patients ≤75 years and >75 years of age in the two treatment strategy groups.

	Age ≤75 years (n=13,403)						Age >75 years (n=2,565)						
	Reference (n=6,715)		Experimental (n=6,688)		HR (95% CI)	*p*-value	Reference (n=1,273)		Experimental (n=1,292)		HR (95% CI)	*p*-value	p_{int}
	N	%	N	%			N	%	N	%			
Primary endpoint	229	3.4%	211	3.2%	0.92 (0.77-1.11)	0.403	120	9.4%	93	7.2%	0.75 (0.58-0.99)	0.041	0.230
All-cause death	153	2.3%	151	2.3%	0.99 (0.79-1.24)	0.938	100	7.9%	73	5.7%	0.71 (0.53-0.96)	0.027	0.084
New Q-wave MI	81	1.2%	60	0.9%	0.74 (0.53-1.04)	0.081	22	1.8%	23	1.9%	1.02 (0.57-1.83)	0.954	0.356
MI (site reported)	199	3.0%	204	3.1%	1.03 (0.85-1.26)	0.734	51	4.2%	44	3.5%	0.85 (0.57-1.27)	0.434	0.393
Stroke*	56	0.8%	47	0.7%	0.85 (0.57-1.25)	0.398	26	2.1%	33	2.7%	1.25 (0.75-2.09)	0.393	0.233
Revascularisation	664	10.0%	630	9.6%	0.95 (0.86-1.06)	0.389	129	10.7%	109	8.9%	0.83 (0.64-1.07)	0.144	0.317
Target vessel revascularisation	368	5.6%	336	5.1%	0.92 (0.79-1.06)	0.256	74	6.1%	53	4.3%	0.70 (0.49-1.00)	0.048	0.166
Definite ST	53	0.8%	61	0.9%	1.16 (0.80-1.68)	0.430	11	0.9%	3	0.2%	0.27 (0.07-0.96)	0.043	0.031
Definite/probable ST	65	1.0%	77	1.2%	1.19 (0.86-1.66)	0.294	17	1.4%	5	0.4%	0.29 (0.11-0.78)	0.015	0.008
Definite/probable/ possible ST	100	1.5%	116	1.8%	1.17 (0.90-1.53)	0.251	44	3.6%	23	1.9%	0.51 (0.31-0.85)	0.010	0.005
BARC 3	113	1.7%	92	1.4%	0.82 (0.62-1.08)	0.155	46	3.8%	58	4.7%	1.25 (0.85-1.84)	0.262	0.081
BARC 5	14	0.2%	10	0.2%	0.72 (0.32-1.62)	0.427	10	0.8%	12	1.0%	1.18 (0.51-2.74)	0.696	0.406
BARC 3 or 5	119	1.8%	98	1.5%	0.83 (0.63-1.08)	0.167	50	4.1%	65	5.2%	1.29 (0.89-1.86)	0.180	0.057
POCE	883	13.2%	843	12.7%	0.96 (0.87-1.05)	0.381	248	19.8%	207	16.4%	0.82 (0.68-0.98)	0.032	0.134
NACE	961	14.4%	900	13.6%	0.94 (0.86-1.03)	0.169	276	22.0%	245	19.4%	0.88 (0.74-1.04)	0.128	0.487

*Not including transient ischaemic attack. n/N and Kaplan-Meier estimates are reported. Primary endpoint: a composite of two-year all-cause mortality or new Q-wave myocardial infarction (MI). Patient-oriented composite endpoint (POCE): all-cause mortality or any MI, revascularisation or stroke. Net adverse clinical events (NACE): POCE, BARC 3/5 type bleeding. HR: hazard ratio; ST: stent thrombosis; 95% CI: 95% confidence interval

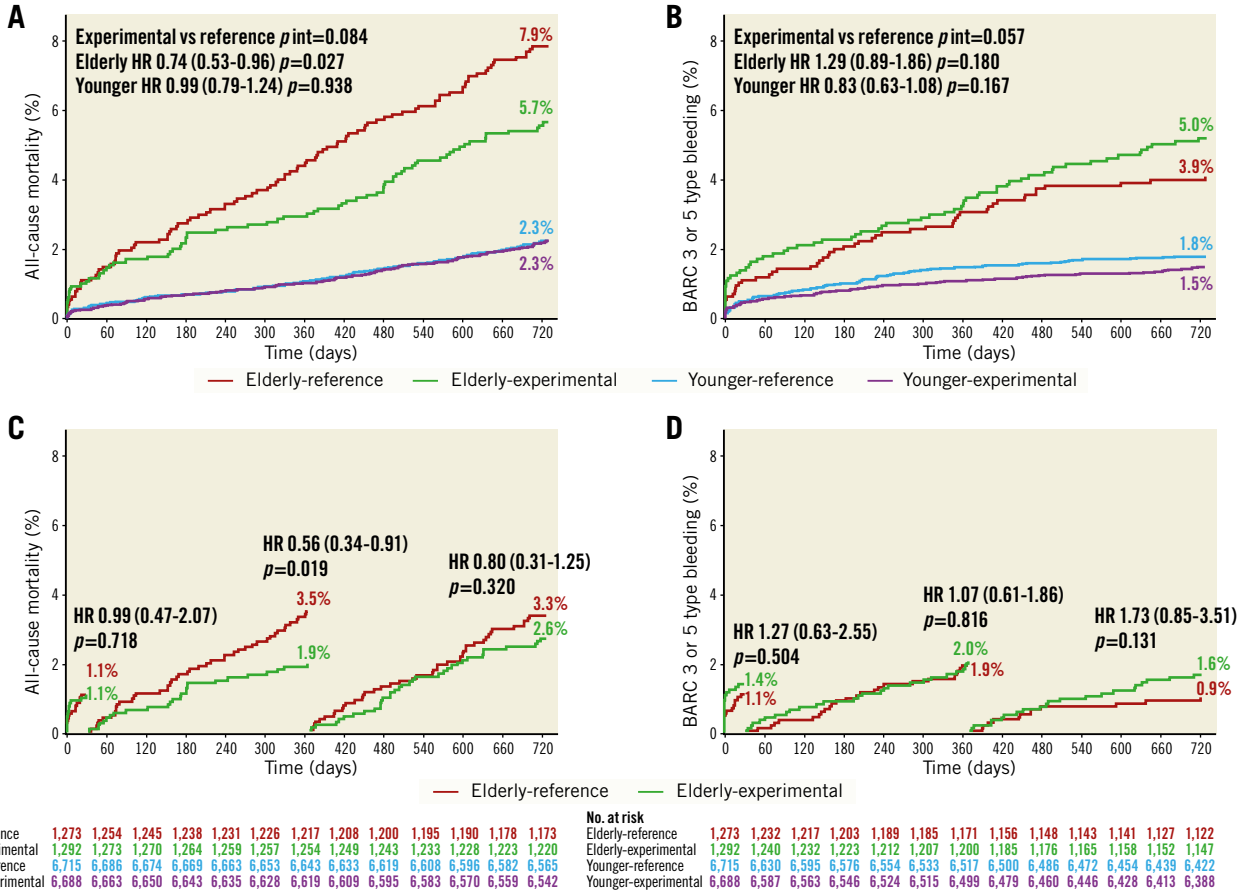

Figure 1. *Kaplan-Meier curves for all-cause mortality and BARC 3 or 5 type bleeding. All-cause mortality (A) and BARC 3 or 5 type bleeding (B) at two years categorised according to age and randomised treatment (n=15,968). Landmark analyses at 30 days, 31-365 days and 366-730 days in elderly patients (n=2,565) for all-cause mortality (C) and BARC 3 or 5 type bleeding (D).*

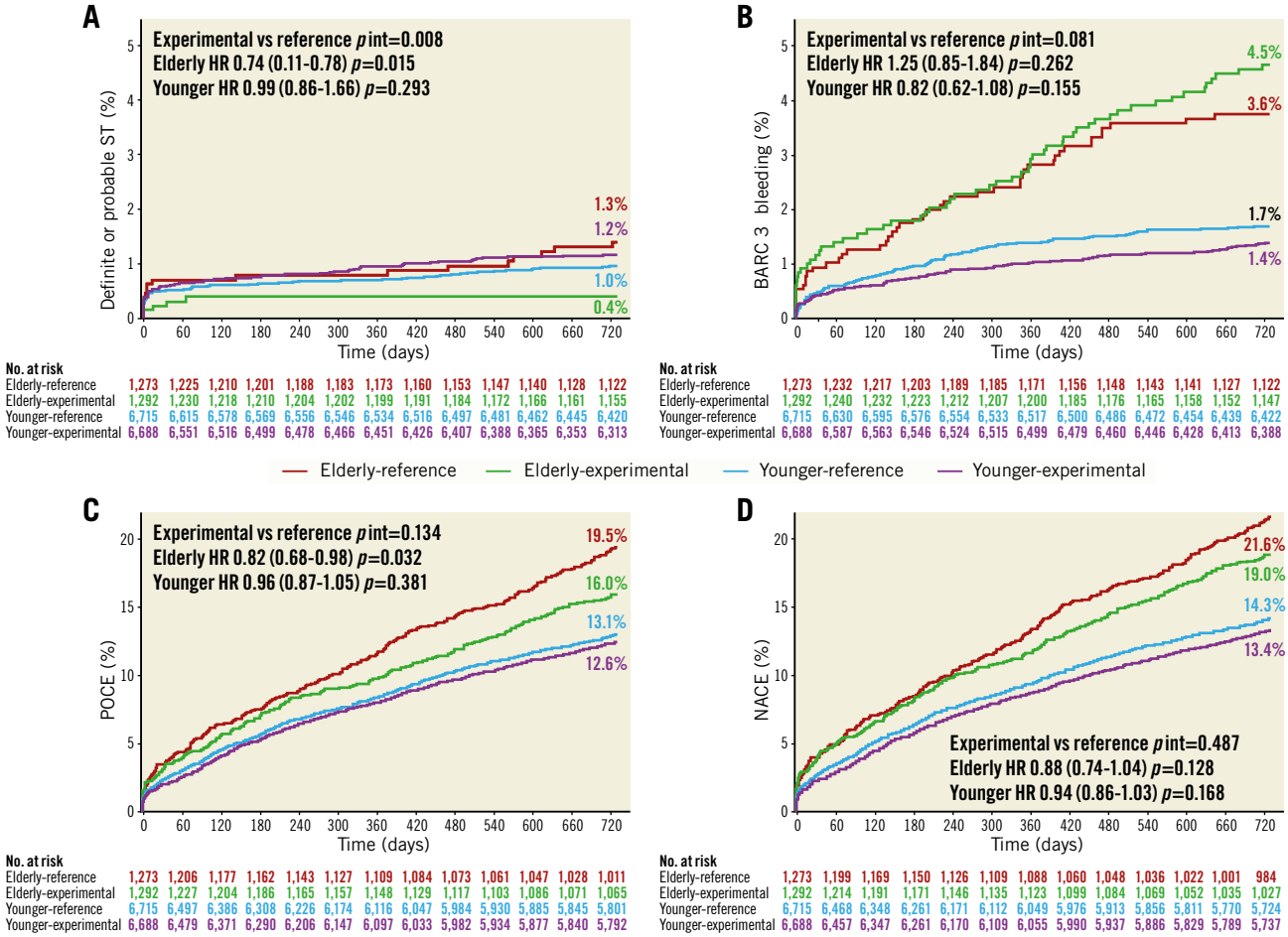

Figure 2. *Kaplan-Meier curves. Definite or probable stent thrombosis (A), BARC 3 type bleeding (B) and the composite endpoints patient-oriented composite endpoint (POCE) (C) and net adverse clinical events (NACE) (D) at two years categorised according to age and randomised treatment (n=15,968).*

A significant interaction was found between age and the treatment effects favouring the experimental strategy for definite ST (p_{int}=0.03), definite/probable ST (p_{int}=0.01) and any ST (definite/probable/possible ST) (p_{int}=0.01) risk reduction in elderly patients **(Table 2, Supplementary Table 3, Figure 2, Figure 4, Supplementary Figure 1)**. The clinical events in which ST was identified as an underlying mechanism are shown in **Figure 4** and **Supplementary Table 3**.

ONE-YEAR CLINICAL OUTCOMES

At one year, amongst elderly patients there were no differences found in the rates of the primary endpoint or the key safety endpoint of BARC 3 or 5 type bleeding; however, there was a differential treatment effect observed with regard to the rate of the composite endpoint of definite/probable/possible ST which was found to be lower in the experimental arm (p_{int}=0.03) **(Supplementary Table 4)**.

TREATMENT ADHERENCE IN THE PRE-SPECIFIED AGE SUBGROUPS

At each follow-up visit from discharge up to 24-month follow-up, the elderly presented lower treatment adherence, compared to younger patients **(Supplementary Table 5)**. From the three-month follow-up visit onwards, the adherence rates were lower in the experimental than in the reference arm, both among the elderly and among younger patients **(Supplementary Table 6)**.

LANDMARK ANALYSES

By landmark analyses at 30 days and one year, in elderly patients, the difference in all-cause mortality rates between treatment groups was found to be driven by lower mortality in the experimental arm, occurring mainly between 30 days and one year **(Figure 1)**. The rates of BARC 3 or 5 type bleedings at each time point did not differ significantly in either treatment group, though they were numerically higher between one and two years in the experimental group **(Figure 1)**.

EXPLORATORY ANALYSES IN THE ELDERLY CATEGORISED ACCORDING TO CLINICAL PRESENTATION: ACS VERSUS STABLE CAD

Exploratory analyses in elderly patients categorised according to clinical presentation did not demonstrate any differences in the rates

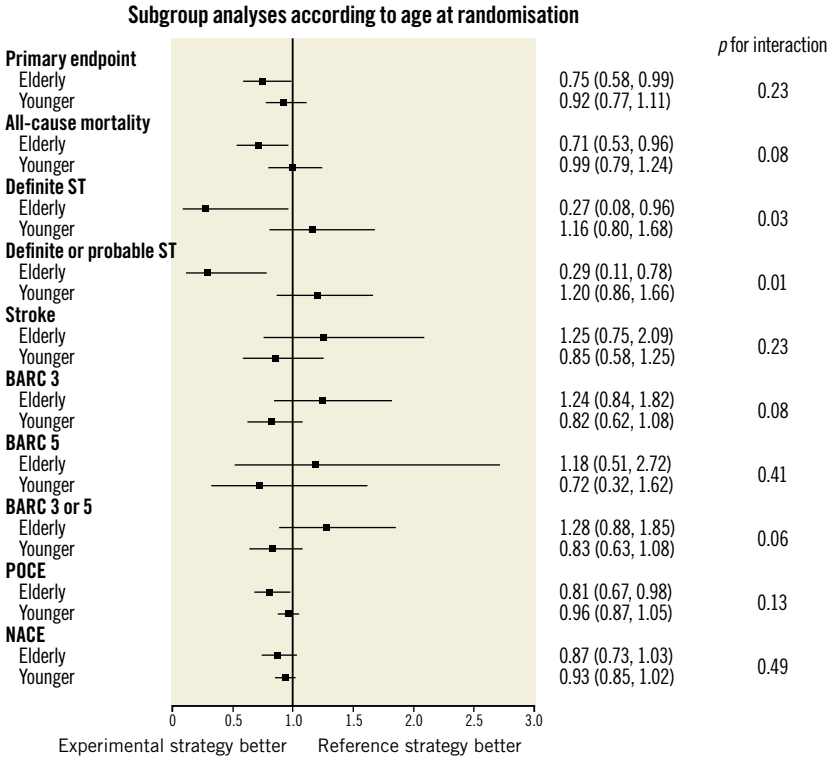

Figure 3. *Subgroup analyses of clinical outcomes categorised according to the pre-specified age cut-off of 75 years and the randomised treatment.*

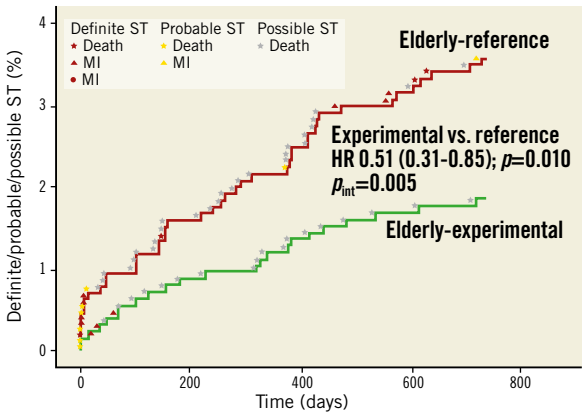

Figure 4. *Cumulative incidence of definite/probable/possible stent thrombosis in elderly patients (according to ARC definition). Shown are definite ST (red), probable ST (yellow) and possible ST (grey) among the elderly in the experimental and the reference group, along with the worst hierarchical clinical outcome, over 730 days of follow-up.*

of the primary endpoint in either treatment group **(Supplementary Table 7, Supplementary Table 8)**. However, there was a differential effect of the experimental treatment strategy found with regard to risk of bleeding BARC 3 type and BARC 3 or 5 type **(Supplementary Table 7, Supplementary Figure 2, Supplementary Figure 3)**. Amongst the elderly presenting with stable CAD who had been allocated to the experimental treatment group, there was a higher risk of BARC 3 (HR 2.06, 95% CI: 1.15-3.67, p=0.015, p_{int}=0.016) and BARC 3 or 5 type bleeding (HR 2.05, 95% CI: 1.18-3.55, p=0.012, p_{int}=0.018).

Discussion

The elderly subgroup analysis from the GLOBAL LEADERS trial represents the first study dedicated to evaluating the long-term safety and efficacy of ticagrelor monotherapy following PCI in relation to age. The main findings of the present study can be summarised as follows:

i) In the GLOBAL LEADERS trial, there was no experimental treatment effect modification by age of either all-cause mortality or new Q-wave MI.

ii) In elderly patients, ticagrelor monotherapy, compared with the reference treatment, was associated with lower rates of the primary endpoint, all-cause mortality, POCE and TVR, although there was no significant differential treatment effect observed in the elderly versus younger patients.

iii) Landmark analyses suggest that these differences are driven by differences in all-cause mortality during the period from 30 days to one year (i.e., ticagrelor monotherapy vs DAPT), while there is no clear excess bleeding risk during the same period.

Contrary to some studies that excluded very old patients[4], GLOBAL LEADERS included patients at a more varied and advanced age on admission – 1,169 (7.3%) were octogenarians, of whom 237 were at least 85 years old (1.5%).

The finding of no differential treatment effect of the experimental strategy with regard to the primary endpoint among elderly patients appears reassuring. There was a borderline significant increase in major bleeding risk (p_{int}=0.06) found in the elderly treated with experimental treatment, that was mainly related to the higher bleeding rates observed in elderly patients presenting with stable CAD. Interestingly, higher bleeding rates in the experimental arm amongst the elderly with stable CAD were observed, despite lower PRECISE DAPT and PARIS score-defined bleeding risk in the stable CAD subgroup, as compared with ACS individuals. It has to be noted that previous studies documented a higher rate of bleeding events after ACS in the elderly, in particular within the first months after it[9,10]. Nevertheless, it should be underlined that GLOBAL LEADERS did not compare two drugs, but assessed two treatment strategies, and the reference treatment strategy was different in patients presenting with ACS (ticagrelor and aspirin for 12 months), compared to patients presenting with stable CAD (clopidogrel and aspirin for 12 months)[11]. As a consequence, in the experimental group stable CAD patients – representing 53% of the overall study – received ticagrelor monotherapy and were therefore (as stable patients) unduly exposed to potent platelet inhibitors, guideline-recommended primarily for ACS.

An intriguing observation from this study is the low rate of definite or probable ST (0.4%) in the experimental strategy arm among elderly patients, which contrasts with a higher proportion of ST (2.5%) within elderly patients (>75 years) in the LEADERS FREE trial[5]. These patients were treated with the polymer-free drug-coated stent and one-month DAPT post PCI, although followed by aspirin rather than ticagrelor monotherapy[5].

As our study was not powered for evaluation of an ST clinical endpoint, which occurred in a low number of patients in this cohort, we cannot exclude that this finding could have arisen from chance alone. With the caveat of the inherent limitations related to subgroup analyses, the observed difference in ST rates between two treatment groups among the elderly may also point towards some potentially age-dependent effects of the experimental strategy[1,2,4]. Interestingly, ADP-mediated platelet aggregation has been demonstrated to increase with age, whereas no difference was observed for aspirin response[3]. This could explain some differences in the efficacy of the experimental treatment strategy, including ticagrelor instead of aspirin monotherapy, in elderly versus younger patients. ST represents a mechanistic explanation for clinically relevant adverse events **(Supplementary Table 3)**. All-cause death, POCE and TVR were all consistently lower among the elderly in the experimental arm versus the reference arm, though no significant interaction terms were found for age effects, with a borderline effect for all-cause mortality (p_{int}=0.08) **(Figure 4)**.

WHO COULD ULTIMATELY BENEFIT FROM POTENT $P2Y_{12}$ ANTAGONIST MONOTHERAPY AMONG THE ELDERLY?

Although any simplified definition of complex PCI cannot fully account for the vast spectrum of PCI complexity encountered in daily clinical practice[12,13], complex PCIs were more frequent among the elderly compared with younger patients in this cohort **(Supplementary Table 1)**.

Notably, patients who underwent complex PCI treated with the experimental treatment strategy had a significant reduction in the risk of the primary endpoint as well as POCE, while maintaining a similar risk of bleeding, thereby resulting in a net clinical benefit at two years in the overall GLOBAL LEADERS trial population[12,13]. A clinically oriented interpretation may suggest that patients at increased risk of both ischaemic and bleeding events, as expressed by high-risk clinical characteristics (such as advanced age) and high-risk procedural features, might represent the target group for potent $P2Y_{12}$ monotherapy; in GLOBAL LEADERS the elderly presenting with ACS benefitted from the anti-ischaemic effect of the drug without an excess in bleeding associated with DAPT up to one year after PCI, having a potential reduction in definite and probable stent thrombosis. Indeed, age and complex procedural features also represented enrichment criteria in the protocol of TWILIGHT – a trial that recently showed reduction of the BARC 2, 3 or 5 type bleeding with ticagrelor monotherapy following a three-month event-free period of DAPT after PCI and non-inferiority of such a strategy with regard to the composite of all-cause death, non-fatal MI, or stroke, compared with a standard DAPT regimen[14]. However, the electronic case report form in GLOBAL LEADERS did not include information on rotational atherectomy or other tools used to modify calcified stenoses. As severely calcified lesions are relatively frequent among the elderly, the safety of novel antiplatelet regimens still remains to be evaluated more specifically among patients requiring advanced lesion preparation. This clinically oriented interpretation would need to be formally confirmed in a dedicated trial.

Limitations

Since the superiority criteria for the primary endpoint were not met in the overall trial, no formal procedure was planned to account for multiple testing and the present study did not have sufficient power to reach statistical significance in comparisons between treatment groups, all reported findings should be considered strictly as hypothesis-generating and exploratory. Secondly, some imbalance may exist between the treatment groups within elderly patients, as the randomisation was not stratified by age. No central adjudication was planned to ascertain secondary outcomes. However, GLOBAL LEADERS was monitored for event underreporting and consistency of event definitions[8]. Finally, adherence to randomised treatment was lower in the experimental arm, in particular amongst the elderly – a finding in line with previous reports[15]. Nevertheless, discontinuation rates were comparable to previous trials investigating ticagrelor[16]. According to protocol, ticagrelor monotherapy was used at the dose of 90 mg twice daily. A lower dose, 60 mg twice daily, may be better tolerated while retaining a high level of platelet inhibition[16,17] and could be preferred in future studies. Given that patients who take any medication twice a day are more likely to have reduced compliance, it could also appear justified to consider testing prasugrel – a $P2Y_{12}$

inhibitor administered once daily – in monotherapy, as a means to improve adherence amongst the elderly. Nevertheless, among patients at a more advanced age, the use of prasugrel remains controversial: TRITON TIMI-38, TRILOGY ACS and Elderly ACS 2 demonstrated no net clinical benefit of prasugrel over clopidogrel amongst the elderly, although prasugrel was evaluated in these trials as part of dual, not single, antiplatelet therapy. Recently, in an ACS population, ISAR-REACT 5 showed a significantly lower incidence of death, MI, or stroke with prasugrel, as compared with ticagrelor, with no significantly different incidence of major bleeding (bleeding BARC 3, 4 or 5 type) between groups; however, the outcomes specifically among elderly patients have not been reported[18].

Conclusions

In this pre-specified, exploratory analysis of the overall neutral trial, there was no differential treatment effect of ticagrelor monotherapy (after one-month dual therapy with aspirin) in elderly patients with respect to the rate of the primary endpoint of all-cause death or new Q-wave MI after PCI, but the elderly had a borderline excess in bleeding risk. The elderly presented lower rates of ST with ticagrelor monotherapy; however, given the low rate of ST, this finding remains hypothesis-generating.

Impact on daily practice

The data presented on the safety profile of ticagrelor from a large-scale contemporary PCI cohort may facilitate better informed clinical decisions on newer $P2Y_{12}$ antagonist use in the elderly. Further research could establish whether the experimental strategy represents a good treatment alternative in selected elderly patients undergoing PCI for acute coronary syndromes, in whom the standard dual antiplatelet therapy is perceived by clinicians as not possible due to an expected excess in bleeding risk. The population of patients at increased risk of both ischaemic and bleeding complications, as expressed by clinical (including age) and procedural high-risk criteria, might represent the target group for ticagrelor monotherapy. In the GLOBAL LEADERS trial, the elderly presenting with ACS were able to benefit from the anti-ischaemic effect of the drug without an excess in bleeding associated with DAPT up to one year after PCI, having a potential reduction in definite and probable stent thrombosis.

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Guest Editor

This paper was guest edited by William Wijns, MD, PhD; National University of Ireland Galway, Lambe Institute, Galway, Ireland.

Funding

This work was supported by the European Clinical Research Institute, which received unrestricted grants from Biosensors International, AstraZeneca, and The Medicines Company.

Conflict of interest statement

M. Tomaniak acknowledges funding received as the Laureate of the European Society of Cardiology Research and Training Programme in the form of ESC 2018 Grant. P. Chichareon has received a research grant from Biosensors. R. Modolo has received research grants from Biosensors. E. Spitzer has received institutional grants from the European Cardiovascular Research Institute. T. Geisler has received personal fees from AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, Daiichi Sankyo, Eli Lilly, The Medicines Company, MSD, Siemens Healthcare, and Spartan Bioscience. M. Sabaté has received personal fees from Abbott Vascular. P. Jüni reports being an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company. C. Hamm reports personal fees from AstraZeneca. P.G. Steg reports grants/personal fees from Bayer/Janssen, Merck, Sanofi, Amarin, Amgen, Bristol Myers Squibb, Boehringer-Ingelheim, Pfizer, Novartis, Regeneron, Lilly, AstraZeneca, and Servier. M. Valgimigli reports grants/personal fees from Abbott, Chiesi, Bayer, Daiichi Sankyo, Amgen, Terumo, Alvimedica, Medicure, AstraZeneca, Biosensors, and Idorsia.

P. Vranckx reports personal fees from AstraZeneca, The Medicines Company, Bayer HealthCare, Terumo, and Daiichi Sankyo. J. Tijssen reports personal fees from Cardialysis, for DSMB membership in the GLOBAL LEADERS trial. S. Windecker reports grants from Abbott, Amgen, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St. Jude Medical, Symetis SA, and Terumo. P.W. Serruys reports personal fees from Abbott Laboratories, AstraZeneca, Biosensors, Biotronik, Cardialysis, GLG Research, Medtronic, Micel Technologies, Qualimed, Sino Medical Sciences Technology, Société Europa Digital & Publishing, St. Jude Medical, Stentys, Svelte Medical Systems, Philips/Volcano, Xeltis, StentIt, and HeartFlow. The other authors have no conflicts of interest to declare. The Guest Editor has no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria.

Supplementary Appendix 2. Study procedures and follow-up.

Supplementary Appendix 3. Clinical endpoint definitions.

Supplementary Appendix 4. List of GLOBAL LEADERS study investigators.

Supplementary Figure 1. Kaplan-Meier curves.

Supplementary Figure 2. Two-year clinical outcomes among elderly patients categorised according to clinical presentation and randomised treatment.

Supplementary Figure 3. Exploratory (*post hoc*) analyses of two-year clinical outcomes in elderly patients categorised according to clinical presentation on admission (stable CAD vs ACS).

Supplementary Table 1. Baseline characteristics of patients categorised according to age ≤75 years and >75 years.

Supplementary Table 2. Additional composite clinical endpoints and BARC-defined bleedings, divided into subtypes.

Supplementary Table 3. Stent thrombosis (definite/probable/possible) in patients who encountered adverse clinical events in the GLOBAL LEADERS cohort.

Supplementary Table 4. One-year clinical outcomes in patients ≤75 years and >75 years of age in the two treatment strategy groups.

Supplementary Table 5. Adherence to randomised treatment in patients aged >75 years and ≤75 years.

Supplementary Table 6. Adherence to randomised treatment in patients aged >75 years and ≤75 years in relation to randomisation group.

Supplementary Table 7. Comparison of bleeding risk among elderly patients divided according to clinical presentation.

Supplementary Table 8. Two-year clinical outcomes in the elderly patients (>75 years of age) in the two treatment strategy groups categorised according to clinical presentation.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00699

Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria

Inclusion criteria
For inclusion in the study patients must fulfil the following criteria:

1. Age ≥18 years.
2. Patients with any clinical indication for percutaneous coronary intervention.
3. Presence of one or more coronary artery stenosis of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 millimetres.

Exclusion criteria
Drug-related

1. Known intolerance to aspirin, $P2Y_{12}$ inhibitors, bivalirudin, stainless steel or biolimus.
2. Known intake of a strong cytochrome P3A4 inhibitor (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor.
3. Use of fibrinolytic therapy within 24 hours of percutaneous coronary intervention.
4. Known severe hepatic impairment.

Treatment-related

1. Planned coronary artery bypass grafting as a staged procedure (hybrid) within 12 months of the index procedure.
2. Planned surgery within 12 months of percutaneous coronary intervention unless dual antiplatelet therapy is maintained throughout the peri-surgical period.
3. Need for oral anticoagulation therapy.
4. PCI for a priori known stent thrombosis.

Medical

1. Known overt major bleeding.
2. Known history of intracranial haemorrhage.
3. Known stroke from ischaemic or unknown cause within last 30 days.

General

1. Known pregnancy at time of randomisation.
2. Inability to provide informed consent.
3. Currently participating in another trial before reaching primary endpoint.

Supplementary Appendix 2. Study procedures and follow-up

Percutaneous coronary intervention

Oral antiplatelet therapy was started as early as possible and no later than two hours after the index procedure.

Loading and switching of $P2Y_{12}$ receptor inhibitors in the GLOBAL LEADERS trial is presented elsewhere [7]. In case of ticagrelor discontinuation due to adverse effects other than bleeding (i.e., atrioventricular block, dyspnoea), patients could be switched to a standard dose of prasugrel in both study arms. The use of clopidogrel was restricted to patients undergoing elective stenting for stable lesions (cardiac biomarker negative, no clinical signs or symptoms of ongoing myocardial ischaemia lasting more than 20 minutes). In case of definite stent thrombosis, patients were treated according to best clinical practice. Patients who required systemic oral anticoagulation after randomisation were treated according to local practice guidelines. Triple therapy was to be prescribed for the shortest necessary duration with frequent INR measurement (target INR 2–2.5) with clopidogrel as the default $P2Y_{12}$ receptor inhibitor. For patients not previously receiving aspirin, a loading dose of 325 mg is preferred (160-500 mg allowed). In the case of staged PCI or in case of unplanned reintervention (other than for definite stent thrombosis or ST-segment elevation myocardial infarction) in the study treatment arm, the 30-day treatment period with aspirin was re-started at the time of the staged procedure or reintervention.

The GLOBAL LEADERS trial protocol mandated a uniform anticoagulation with bivalirudin (The Medicines Company) (dose adjusted per local drug label) in those countries where the drug was approved for use during the procedure and uniform stent platform (Biolimus-A9™ eluting stent; Biosensors Interventional Technologies) use during the index procedure (including staged procedures) and any unplanned or inter-current repeat percutaneous coronary intervention. Balloon angioplasty and stent implantation were performed according to standard techniques; direct stenting (without previous balloon dilatation) was allowed. Staged procedures were permitted within three months after the index procedure; all the stents used were of the assigned type. Glycoprotein IIb/IIIa receptor inhibitors were to be administered only in patients who had periprocedural ischaemic complications (i.e., no reflow or giant thrombus) after stenting. The use of unfractionated heparin (up to an arbitrary set maximum of 4,000 IU) during the index diagnostic angiogram was left to the discretion of the investigator. The use of other medications was per applicable professional guidelines.

Patient follow-up

During study follow-up visits, patients were questioned about whether they had had a myocardial infarction, had been hospitalised for a subsequent cardiovascular presentation, had undergone revascularisation or cardiac testing, or had seen a cardiologist, and what medications they were taking. If a patient reported a hospitalisation that was possibly related to cardiac causes, the hospital records were reviewed. Adverse events were confirmed by means of a review of the records. If the patients or secondary contacts were unavailable, records at the presenting and neighbouring hospitals were reviewed to determine whether there had been repeat visits. Patients who withdrew consent to participate in the study were included up to the date of withdrawal, with the exception of the analysis of death from any cause, in which we included information from all the patients for whom vital status could be determined from public records at the end of the study.

Study oversight

The electronic case record form (eCRF) was built to collect detailed information on the individual components of the predefined secondary endpoints (e.g., death, any stroke, MI, revascularisation, bleeding). Moreover, textboxes allowed for free text narrative information per event.

The trial was monitored for event under-reporting (onsite and remote monitoring) and event definition consistency. The eCRF (including free text boxes: event narratives) was reviewed by independent medical monitors for consistency with the endpoint definitions and sites queried when considered necessary. In addition, there were seven on-site monitoring visits carried out at individual sites, with 20% of reported events validated against source documents, but overall no independent central event adjudication was planned.

Ethics

The study was performed in compliance with the ethical principles of the Declaration of Helsinki, the International Conference of Harmonisation, and Good Clinical Practice. All participants provided written informed consent at enrolment. An independent data and safety monitoring committee oversaw the safety of all patients. The trial was registered with the ClinicalTrials.gov number NCT01813435.

Supplementary Appendix 3. Clinical endpoint definitions

Research nurses screened for clinical endpoint events during the follow-up visits. If the patient did not appear and patients or relatives could not be contacted after the nurses had placed repeated telephone calls and mailed a letter, information on the vital status was collected through review of public health records. All-cause death was ascertained without the need for adjudication.

Investigators were instructed during the investigator meetings and site initiation visits on the outcome definitions implemented in the GLOBAL LEADERS trial. Detailed patient-based information was collected via the individual electronic case report forms to allow proper classification of all site-reported outcome events. Medical monitors (Cardialysis, Rotterdam, the Netherlands) checked the case record forms of site-reported endpoints for completeness and consistency against the following definitions.

Stroke
Stroke was defined as an acute onset of focal or global neurological deficit persisting ≥24 hours or <24 hours in case i) therapeutic intervention was required, ii) it was confirmed by neuro-imaging, or iii) patient's death. Stroke was categorised as either ischaemic, haemorrhagic or as of undetermined cause.

Myocardial infarction
Myocardial infarction was defined according to the third universal myocardial infarction definition, applicable at the time of study conduct, as study-specific myocardial infarction criteria [19].
The term acute myocardial infarction was used when there was evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria met the diagnosis for myocardial infarction:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
    - symptoms of ischaemia
    - new or presumed new significant ST-segment–T-wave (ST–T) changes or new left bundle branch block (LBBB)
    - development of pathological Q-waves on the ECG
    - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - identification of an intracoronary thrombus by angiography or autopsy

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic electrocardiographic changes or new left bundle branch block, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention-related myocardial infarction was arbitrarily defined by elevation of cardiac troponin values (>5 x the 99th percentile upper reference limit) in patients with normal baseline values (≤99th percentile of the upper reference limit) or a rise of cardiac troponin values >20% if the baseline values were elevated and were stable or falling. In addition, either:
    - symptoms suggestive of myocardial ischaemia, or

- new ischaemic electrocardiographic changes, or
- angiographic findings consistent with a procedural complication, or
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality was required

- Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile of the upper reference limit

- Coronary artery bypass grafting-related myocardial infarction is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile of the upper reference limit) in patients with normal baseline cardiac troponin values (≤99th percentile of the upper reference limit). In addition, either:
  - new pathological Q-waves or new left bundle branch block, or
  - angiographic documented new graft or new native coronary artery occlusion, or
  - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Q-wave myocardial infarction ascertainment and definition

Resting 12-lead electrocardiograms at hospital discharge, three-month, and the 24-month end-of-trial visit and any available intercurrent electrocardiograms, related to suspected ischaemic events, were inspected for quality and technical errors and analysed by an independent electrocardiography core laboratory (Cardialysis, Rotterdam, the Netherlands). Serial comparison of sequential tracings was performed to identify patients with new appearance of Q-waves (major Q-QS wave abnormalities 1-1-1 to 1-2-8 according to the Minnesota Code) [20].

Where new Q-waves, with respect to the immediately preceding electrocardiogram (first reference electrocardiogram is at discharge) were identified, an independent cardiologist confirmed or rejected the myocardial as a new Q-wave myocardial infarction and, if confirmed, also assigned a date, based on a review of the reported adverse events to the new Q-wave myocardial infarction [7]. Where no clinical correlate was identified, the date of the new silent Q-wave myocardial infarction was arbitrarily assigned to the date of the qualifying electrocardiogram. In case electrocardiograms remained missing after review of all documentation (e.g., death before two years of follow-up) it will be assumed no new Q-wave myocardial infarction occurred since the last obtained electrocardiogram.

The electrocardiogram core laboratory also identified new left bundle branch block on serial electrocardiograms. Where a new left bundle branch block was identified, the independent cardiologist determined, from electronic clinical record form extracts supplemented where necessary with additional source documents, whether a likely ischaemic event (prolonged ischaemic chest pain, significant rise in cardiac biomarkers or imaging evidence of loss of viable myocardium) occurred. A new left bundle branch block counted as a new Q-wave myocardial infarction only where a qualifying ischaemic event was identified. The new Q-wave myocardial infarction was assigned to the date of the qualifying ischaemic event.

Core laboratory staff and the independent cardiologist were unaware of the study group assignments.

Revascularisation

Revascularisation included target and non-target vessel revascularisations.

Stent thrombosis
Stent thrombosis was classified as per the Academic Research Consortium definition.

Definite stent thrombosis – was considered to have occurred by either angiographic or pathological confirmation.

The presence of thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour window. (The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms was not considered a confirmed stent thrombosis silent occlusion):

- acute onset of ischaemic symptoms at rest
- new ischaemic electrocardiographic changes that suggest acute ischaemia
- typical rise and fall in cardiac biomarkers that represent a spontaneous myocardial infarction
- non-occlusive thrombus: intracoronary thrombus defined as a (sphere-shaped, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or visible embolisation of intraluminal material downstream
- occlusive thrombus: Thrombolysis In Myocardial Infarction (TIMI) flow grading 0 or 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch)
    - evidence of recent thrombus within the stent determined at autopsy, or via examination of tissue retrieved following thrombectomy.

Bleeding
Bleeding was assessed according to the Bleeding Academic Research Consortium (BARC) definition [21]. We only considered BARC 3 or 5 for the key secondary safety endpoint. These bleedings are clinically meaningful and relatively easy to ascertain.
-Type 0: no evidence of bleeding
-Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
-Type 2: any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:

- requiring non-surgical, medical intervention by a healthcare professional,
- leading to hospitalisation or increased level of care, or
- prompting evaluation

-Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

- Type 3a:
    - overt bleeding plus haemoglobin drop of 3 to <5 g/dL (provided haemoglobin drop is related to bleed),
    - any transfusion with overt bleeding.
- Type 3b:
    - overt bleeding plus haemoglobin drop ≥5 g/dL (provided haemoglobin drop is related to bleed),

        - cardiac tamponade,
        - bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid),
        - bleeding requiring intravenous vasoactive agents.
    - Type 3c:
        - Intracranial hemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal),
        - Subcategories confirmed by autopsy or imaging or lumbar puncture,
        - Intraocular bleed compromising vision.

-Type 4: coronary artery bypass grafting-related bleeding

- Perioperative intracranial bleeding within 48 hrs.
- Reoperation after closure of sternotomy for the purpose of controlling bleeding.
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hr period.
- Chest tube output more than or equal to 2 L within a 24-hr period.

-Type 5: fatal bleeding

- Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious,
- Type 5b: definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

Supplementary Appendix 4. List of the GLOBAL LEADERS study investigators.

Country	Investigating centre	Principal investigator
Belgium	Virga Jesse	Dr. Edouard Benit
Germany	Kerckhoff Heart Center	Dr. Christoph Liebetrau
Belgium	Imelda	Dr. Luc Janssens
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Netherlands	Erasmus MC	Prof. Robert Jan van Geuns
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Austria	Wilhelminenspital	Prof. Kurt Huber
Netherlands	OLVG	Dr. Ton Slagboom
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UK	Golden Jubilee National Hospital	Prof. Keith G. Oldroyd
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Germany	Klinikum Landshut-Achdorf	Dr. med. Bernhard Zrenner
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Germany	Kliniken Maria Hilf	Prof. Dr. med. Jürgen vom Dahl

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Bulgaria	St. Anna Sofia	Dr. Vasil Velchev
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Spain	Hospital 12 Oct.	Dr. Agustin Albarran Gonzalez-Trevilla
Spain	Sant Pau i Santa Creu	Dr. Antonio Serra Peñaranda
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France	Clinique de Fontaine	Dr. Philippe Brunel
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Bulgaria	Heart Center "Pontica"	Dr. Mariana Konteva
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Switzerland	Tiefenauspital	Dr. Aris Moschovitis
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Switzerland	CHUV, Centre Hospitalier Universitaire Vaudois	Prof. Eric Eeckhout
Netherlands	Medisch Centrum Leeuwarden	Dr. Sjoerd H. Hofma
Bulgaria	"St. Ekaterina" University Hospital	Dr. Diana Trendafilova-Lazarova
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Netherlands	UMC St Radboud	Prof. Dr. Harry Suryapranata
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Portugal	Hospital de Santa Maria	Dr. Pedro Canas da Silva
Spain	Hosp Juan Ramon Jiminez	Dr. Jose Francisco Diaz
UK	New Cross Hospital	Dr. James Cotton
France	Clinique-Saint Hilaire	Dr. René Koning
Netherlands	Sint Antonius Ziekenhuis	Dr. Benno Rensing
Germany	Med. Fakult. Mannheim der Univ. Heidelberg	Prof. Dr. med. Ibrahim Akin
UK	Royal Victoria	Dr. Simon Walsh
Germany	Uniklinikum Bonn	Prof. Dr. med. Nikos Werner
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Germany	Charite, Campus Virchow	Dr. Florian Krackhardt
France	Uni. Hospital Mondor	Prof. Emmanuel Teiger
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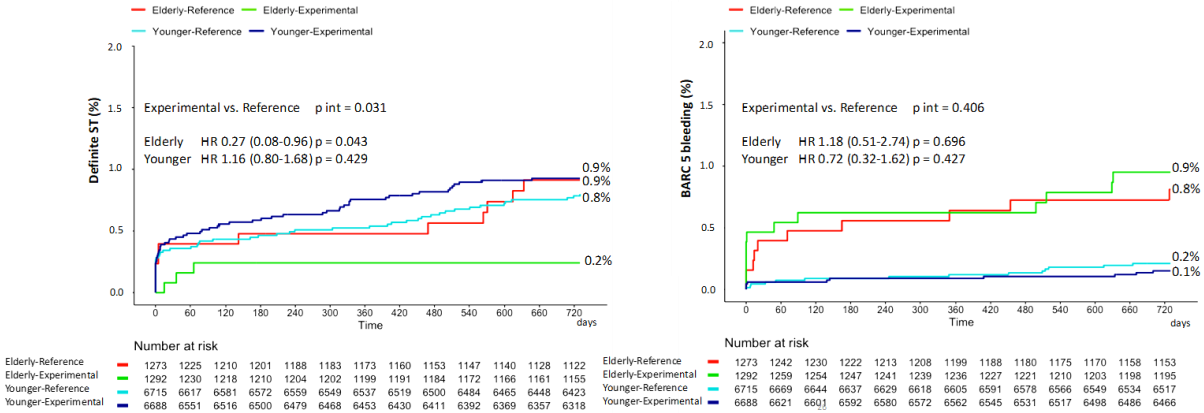
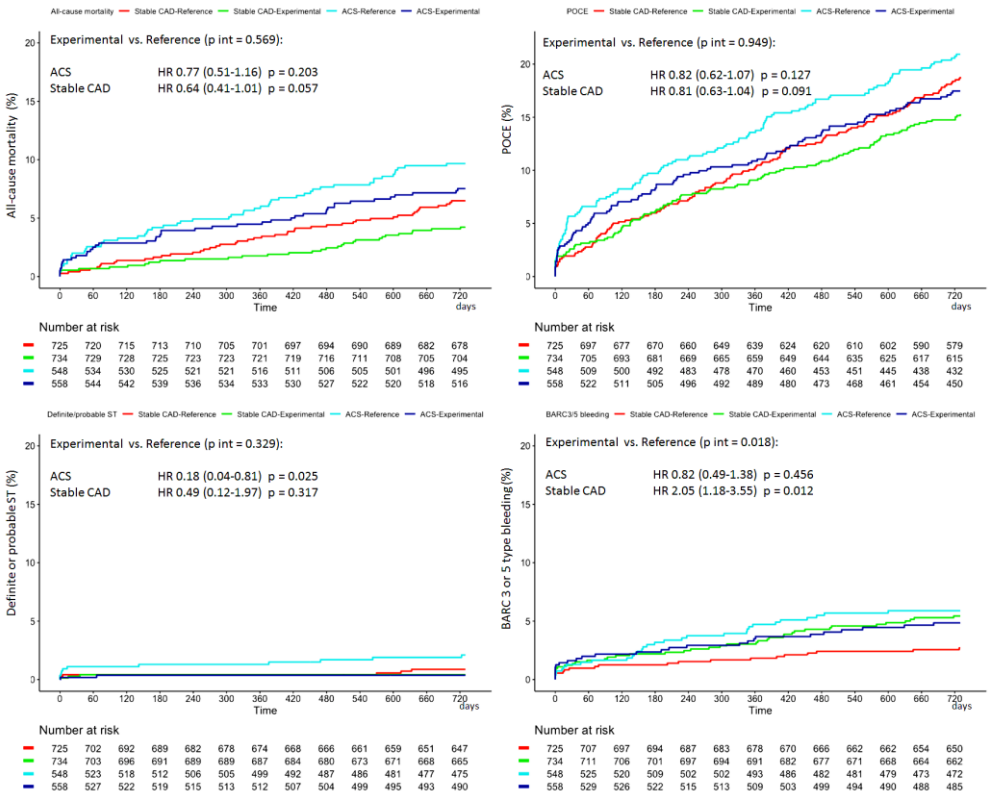
Portugal	Hospital St. Cruz Lisbon	Dr. Manuel Almeida
Hungary	Gottsegen György (National Health Institute)	Dr. Geza Fontos
France	Clinique des Domes	Dr. Pascal Barraud
France	Clinique Louis Pasteur	Dr. Michael Angioi
France	Hôpital de la Croix-Rousse	Dr. Pierre Lantelme
Portugal	Centro Hospitalar de Gaia	Dr. Vasco Gama Ribeiro
Australia	St. Vincent’s Hospital (Victoria)	Prof. Peter Barlis
Belgium	OLVZ	Dr. Emanuel Barbato
Brazil	Instituto Nacional De Cardiologia	Dr. Sergio Leandro

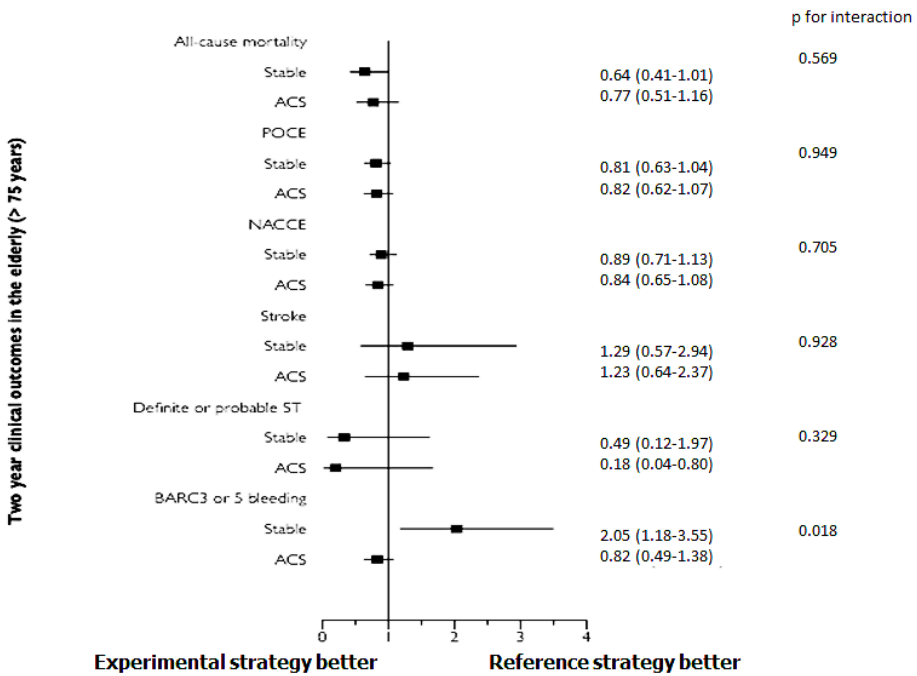


Supplementary Figure 1. Kaplan-Meier curves. Definite stent thromboses (ST) (A) and Bleeding Academic Research Consortium (BARC)-defined type 5 bleeding (B) categorised according to pre-specified cut-off of 75 years and randomised treatment strategy (n=15,968).
BARC: Bleeding Academic Research Consortium; HR: hazard ratio; 95% CI: 95% confidence interval; ST: stent thrombosis



Supplementary Figure 2. Two-year clinical outcomes among elderly patients categorised according to clinical presentation and randomised treatment.

Two-year all-cause mortality (A), patient-oriented clinical endpoints (POCE) (B), definite or probable stent thrombosis (ST) (C) and Bleeding Academic Research Consortium (BARC)-defined bleedings type 3 or 5 (D) among elderly patients (>75 years) categorised according to clinical presentation (acute coronary syndrome or stable coronary artery disease) and randomised treatment strategy (n=2,565).



Supplementary Figure 3. Exploratory (*post hoc*) analyses of two-year clinical outcomes in elderly patients categorised according to clinical presentation on admission (stable coronary artery disease vs acute coronary syndromes).
Patient-oriented clinical outcomes (POCE) included all-cause mortality or any myocardial infarction, revascularisation or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding.
ST: stent thrombosis

Supplementary Table 1. Baseline characteristics of patients categorised according to age ≤75 years and >75 years.

	AGE ≤75 years (n=13,403)		**AGE >75 years (n=2,565)**		
	N	%	N	%	*p*-value
Age (±SD)	61.6	8.5	79.8	3.2	0.001
Weight (±SD)	84	16.1	76.3	12.8	0.001
Sex (female)	2,834	21.1%	880	34.3%	0.001
Stable CAD	7,022	52.4%	1,459	56.9%	0.001
Unstable angina	1,698	12.7%	324	12.6%	0.959
NSTEMI	2,844	21.2%	529	20.6%	0.499
STEMI	1,839	13.7%	253	9.9%	0.001
Diabetes	3,275	24.5%	763	29.8%	0.001
Diabetes on insulin	977	7.3%	246	9.6%	0.001
Hypertension	9,589	71.8%	2,126	83.2%	0.001
Hypercholesterolaemia	9,053	69.8%	1,715	69.0%	0.428
Currently smoking	3,983	29.7%	186	7.3%	0.001
Peripheral vascular disease	762	5.7%	243	9.6%	0.001
COPD	640	4.8%	181	7.1%	0.001
Previous major bleeding	71	0.5%	27	1.1%	0.001
Impaired renal function	1,361	10.2%	829	32.3%	0.001
Previous stroke	320	2.4%	101	3.9%	0.001
Previous MI	3,109	23.2%	601	23.6%	0.718
Previous PCI	4,300	32.1%	921	36.0%	0.001
Previous CABG	693	5.2%	250	9.8%	0.001
Complex PCI*	3,751	28.9%	819	33.1%	0.001

* PCI was defined as complex PCI when at least one of the following features was met: multivessel PCI, ≥3 stents implanted, ≥3 lesions treated, bifurcation PCI with ≥2 stents, and total stent length >60 mm. These five high-risk features of complex percutaneous procedure for ischaemic events have been described previously [12, 22]. Multivessel PCI was defined as PCI performed to treat two or three separate major coronary territories. An isolated left main lesion was classified as two-vessel disease in the presence of right dominance and three-vessel disease in the presence of left dominance. To calculate the total stent length, the sum of the nominal stent lengths was used as per patient.

CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation

Supplementary Table 2. Additional composite clinical endpoints and Bleeding Academic Research Consortium (BARC)-defined bleedings, divided into subtypes.

	AGE ≤75 years (N=13,403)				AGE >75 years (N=2,565)				
	Reference (n=7,988)	**Experimental (n=7,980)**	**HR (95% CI)**	***p*-value**	**Reference (n=7,988)**	**Experimental (n=7,980)**	**HR (95% CI)**	***p*-value**	***p* int**
All-cause death	153 (2.3%)	151 (2.3%)	0.99 (0.77-1.11)	0.403	100 (7.9%)	73 (5.7%)	0.71 (0.53-0.96)	0.027	0.084
Cardiac death	70 (1.0%)	70 (1.0%)	1.00 (0.72-1.40)	0.980	52 (4.1%)	36 (2.8%)	0.68 (0.44-1.03)	0.071	0.150
All-cause death, stroke or new Q-wave MI	158 (2.4%)	131 (2.0%)	0.91 (0.76-1.08)	0.266	80 (6.3%)	66 (5.1%)	0.79 (0.62-1.02)	0.066	0.380
All-cause death, stroke, MI, or BARC 3 or 5	306 (4.6%)	283 (4.2%)	0.96 (0.84-1.10)	0.547	118 (9.3%)	119 (9.2%)	0.91 (0.74-1.12)	0.365	0.658
Cardiac death, stroke or MI	197 (2.9%)	205 (3.1%)	1.00 (0.85-1.17)	0.956	70 (5.5%)	72 (5.6%)	0.90 (0.69-1.18)	0.447	0.534
BARC 2, 3, 4 or 5	**407 (6.1%)**	385 (5.8%)	0.95 (0.83-1.09)	0.474	129 (10.1%)	150 (11.6%)	1.16 (0.91-1.46)	0.229	0.160
BARC 2, 3, or 5	**404 (6.0%)**	380 (5.7%)	0.95 (0.82-1.09)	0.426	128 (10.1%)	149 (11.5%)	1.16 (0.91-1.46)	0.228	0.147

BARC 3 or 5	98 (1.5%)	73 (1.1%)	0.83 (0.63-1.08)	0.167	38 (3.0%)	44 (3.4%)	1.29 (0.89-1.86)	0.180	0.057
BARC 5	8 (0.1%)	6 (0.1%)	0.72 (0.32-1.62)	0.427	8 (0.6%)	8 (0.6%)	1.18 (0.51-2.74)	0.696	0.406
BARC 5b	4 (0.1%)	5 (0.1%)	0.78 (0.29-2.10)	0.629	7 (0.5%)	4 (0.3%)	0.87 (0.34-2.27)	0.782	0.876
BARC 5a	4 (0.1%)	1 (0.01%)	0.61 (0.15-2.53)	0.491	1 (0.1%)	4 (0.3%)	3.96 (0.44-35.42)	0.218	0.160
BARC 3	93 (1.4%)	69 (1.0%)	0.82 (0.62-1.08)	0.155	35 (2.7%)	38 (2.9%)	1.25 (0.85-1.84)	0.262	0.081
BARC 3c	11 (0.2%)	13 (0.2%)	1.06 (0.56-2.03)	0.850	5 (0.4%)	10 (0.8%)	2.26 (0.93-5.48)	0.073	0.179
BARC 3b	44 (0.7%)	31 (0.5%)	0.70 (0.46-1.07)	0.096	18 (1.4%)	12 (0.9%)	0.76 (0.40-1.43)	0.397	0.820
BARC 3a	42 (0.6%)	32 (0.5%)	0.97 (0.64-1.45)	0.863	15 (1.2%)	20 (1.5%)	1.39 (0.81-2.40)	0.236	0.288
BARC 2	250 (3.7%)	222 (3.3%)	0.98 (0.84-1.15)	0.800	74 (5.8%)	76 (5.9%)	1.09 (0.82-1.46)	0.548	0.516

The p-value for interaction for the various endpoints is derived from the dichotomised analysis with the pre-specified cut-off of 75 years.
BARC: Bleeding Academic Research Consortium; HR: hazard ratio; MI: myocardial infarction; 95% CI: 95% confidence interval

Supplementary Table 3. Stent thrombosis (definite/probable/possible) in patients who encountered adverse clinical events in the GLOBAL LEADERS cohort.

	Overall ST (n=283)		**ST in elderly (n=67)**		**ST in non-elderly (n=216)**	
	Nr of ST /total no. of events	**%**	**Nr of ST /total no. of events**	**%**	**Nr of ST /total no. of events**	**%**
All-cause mortality	161/477	**33.8%**	56/290	**32.4%**	105/304	**34.5%**

Cardiovascular mortality	152/228	**66.7%**	53/88	**60.2%**	99/140	**70.7%**
MI (site-reported)	108/498	**21.7%**	19/95	**20.0%**	89/403	**22.1%**
Revascularisation	140/1,532	**9.1%**	16/238	**6.7%**	124/1,294	**9.6%**
TVR	124/831	**14.9%**	15/127	**11.8%**	109/704	**15.5%**
POCE	200/2,181	**13.9%**	43/291	**14.8%**	157/1,152	**13.6%**

Percentages (%) indicate the rate of events in which ST was identified by investigators as an underlying mechanism.
ST was defined according to the Academic Research Consortium definition.
MI: myocardial infarction; POCE: patient-oriented composite endpoint (all-cause mortality, any stroke, MI or revascularisation); ST: stent thrombosis; TVR: target vessel revascularisation

Supplementary Table 4. One-year clinical outcomes in patients ≤75 years and >75 years of age in the two treatment strategy groups.

	AGE ≤75 years (N=13,403)						AGE >75 years (N=2,565)						
	Reference (n=6,715)		Experimental (n=6,688)				Reference (n=1,273)		Experimental (n=1,292)				
	N	%	N	%	HR (95% CI)	*p*-value	N	%	N	%	HR (95% CI)	*p*-value	*p* int
Primary endpoint	129	1.9%	105	1.6%	0.94 (0.75-1.16)	0.546	68	5.3%	51	3.9%	0.79 (0.58-1.08)	0.135	0.375
All-cause death	73	1.1%	69	1.0%	0.95 (0.68-1.32)	0.756	58	4.6%	39	3.0%	0.66 (0.44-0.99)	0.045	0.172
New Q-wave MI	58	0.9%	36	0.5%	0.62 (0.41-0.94)	0.025	11	0.9%	12	0.9%	1.07 (0.47-2.43)	0.871	0.247
MI (site-reported)	131	2.0%	145	2.2%	1.12 (0.88-1.41)	0.363	27	2.1%	34	2.6%	1.25 (0.75-2.07)	0.390	0.695
Stroke*	32	0.5%	30	0.4%	0.94 (0.57-1.55)	0.819	17	1.3%	22	17%	1.28 (0.68-2.41)	0.442	0.454
Revascularisation	465	6.9%	443	6.6%	0.96 (0.84-1.09)	0.506	84	6.6%	75	5.8%	0.88 (0.65-1.20)	0.422	0.629
Target vessel revascularisation	253	3.8%	230	3.4%	0.91 (0.76-1.09)	0.322	53	4.2%	38	2.9%	0.71 (0.47-1.07)	0.101	0.265
Definite ST	35	0.5%	50	0.7%	1.44 (0.93-2.22)	0.099	6	0.5%	3	0.2%	0.49 (0.12-1.98)	0.319	0.149
Definite/probable ST	47	0.7%	63	0.9%	1.35 (0.93-1.97)	0.120	10	0.8%	5	0.4%	0.49 (0.17-1.44)	0.197	0.083
Definite/probable/ possible ST	67	1.0%	82	1.2%	1.23 (0.89-1.70)	0.204	27	2.1%	15	1.2%	0.55 (0.29-1.03)	0.063	0.025
BARC 3	93	1.4%	69	1.0%	0.75 (0.55-1.02)	0.065	35	2.7%	38	2.9%	1.08 (0.68-1.70)	0.753	0.194
BARC 5	8	0.1%	6	0.1%	0.76 (0.26-2.18)	0.602	8	0.6%	8	0.6%	0.99 (0.37-2.63)	0.981	0.714
BARC 3 or 5	98	1.5%	73	1.1%	0.75 (0.55-1.01)	0.062	38	3.0%	44	3.4%	1.15 (0.74-1.77)	0.534	0.113
POCE	589	8.8%	563	8.4%	0.96 (0.86-1.08)	0.482	155	12.2%	136	10.5%	0.87 (0.69-1.09)	0.223	0.440
NACE	664	9.9%	609	9.1%	0.92 (0.82-1.03)	0.133	180	14.1%	168	13.0%	0.93 (0.75-1.14)	0.470	0.952

*Not including transient ischaemic attack.

Primary endpoint: a composite of two-year all-cause mortality or new Q-wave myocardial infarction (MI). Patient-oriented composite endpoint (POCE): all-cause mortality or any MI, revascularisation or stroke. Net adverse clinical events (NACE): POCE, BARC 3/5 type bleeding.

HR: hazard ratio; ST: stent thrombosis; 95% CI: 95% confidence interval

Supplementary Table 5. Adherence to randomised treatment in patients aged >75 years and ≤75 years.

	Age ≤75 years (n=13,403)	**Age >75 years (n=2,565)**	***p*-value**
Discharge	97.6 (13,057/13,384)	96.5 (2,451/2,540)	0.002
Follow-up 1 month	96.7 (12,662/13,100)	94.8 (2,307/2,434)	0.001
Follow-up 3 months	90.6 (11,725/12,946)	85.8 (2,042/2,380)	0.001
Follow-up 6 months	89.3 (11,480/12,859)	83.5 (1,961/2,348)	0.001
Follow-up 12 months	86.5 (11,043/12,762)	79.8 (1,853/2,321)	0.001
Follow-up 18 months	86.3 (10,838/12,552)	79.5 (1,802/2,268)	0.001
Follow-up 24 months	86.5 (10,988/12,697)	78.8 (1,803/2,289)	0.001

Data shown are % (n/N).

*p-value derived from chi-square test.

The drug counts at the one-month, one-year and two-year time points reflect patient adherence before the protocol mandated change in antiplatelet regimen. Revascularisations and per-protocol restart of DAPT allowed: i) ticagrelor and aspirin for 30 days in the experimental treatment strategy group, ii) dual antiplatelet therapy with ticagrelor and aspirin (acute coronary syndrome, stable coronary artery disease patients already on ticagrelor or prasugrel), clopidogrel and aspirin (stable coronary artery patients) for 365 days in the standard treatment strategy group.

Supplementary Table 6. Adherence to randomised treatment in patients aged >75 years and ≤75 years in relation to randomisation group.

	Age <75 years (n=13,403)					**Age >75 years (n=2,565)**				
	Reference (n=6,715)		**Experimental (n=6,688)**		***p*-value**	**Reference (n=1,273)**		**Experimental (n=1,292)**		***p*-value**
	N	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Discharge	6,532	97.4%	6,525	97.7%	0.304	1,212	96.0%	1,239	96.9%	0.212
Follow-up 1 month	6,341	96.6%	6,321	96.7%	0.662	1,149	94.6%	1,158	94.9%	0.763
Follow-up 3 months	6,106	94.1%	5,619	87.0%	0.001	1,082	91.2%	960	80.5%	0.001
Follow-up 6 months	5,956	92.4%	5,524	86.1%	0.001	1,029	88.1%	932	79.0%	0.001
Follow-up 12 months	5,745	90.0%	5,298	83.1%	0.001	979	85.2%	874	74.6%	0.001
Follow-up 18 months	5,784	92.5%	5,054	80.2%	0.001	994	89.0%	808	70.2%	0.001
Follow-up 24 months	5,972	93.8%	5,016	79.3%	0.001	1,009	89.4%	794	68.4%	0.001

Data shown are count and percentages.

*p-value derived from chi-square test.

The drug counts at the one-month, one-year and two-year time points reflect patient adherence before the protocol mandated change in antiplatelet regimen. Revascularisations and per-protocol restart of DAPT allowed: i) ticagrelor and aspirin for 30 days in the experimental treatment strategy group, ii) dual antiplatelet therapy with ticagrelor and aspirin (acute coronary syndrome, stable coronary artery disease patients already on ticagrelor or prasugrel), clopidogrel and aspirin (stable coronary artery patients) for 365 days in the standard treatment strategy group.

Supplementary Table 7. Comparison of bleeding risk among elderly patients divided according to clinical presentation. Distribution of elderly patients (aged >75 years) with stable coronary artery disease (CAD) and acute coronary syndromes (ACS) categorised according to the baseline PARIS risk score* into the subgroups of low, intermediate and high risk of ischaemia. Comparison of PRECISE DAPT scores specifically among the elderly patients with stable CAD or ACS.**

	Stable CAD (n=1,459)		ACS (n=1,106)		
	N	**%**	**N**	**%**	***p*-value**
PARIS: thrombotic risk					0.001
Low	791	55.3	272	24.8	
Intermediate	380	26.6	431	39.4	
High	260	18.2	392	35.8	
PARIS: bleeding risk					
Low	293	21.3	195	18.1	0.022
Intermediate	805	58.5	623	57.7	
High	279	20.3	262	24.3	
PRECISE DAPT	25.7	±7.7	27.4	±8.1	0.001

Data presented as count and percentages (%) or mean±standard deviation.

* Thrombotic and bleeding risk scores were assigned according to the previously validated integer risk score values [23]. Subsequently, using the same thresholds as in the PARIS population, patients were grouped into strata of low, intermediate, and high thrombotic risk (0-2, 3-4, or ≥5) and low, intermediate, and high bleeding risk (0-3, 4-7, or ≥8). Complete data on clinical characteristics for computation of the PARIS ischaemic and bleeding integers for ischaemic and bleeding risk estimation were available in 2,526 and 2,457 elderly patients, respectively.

** PRECISE-DAPT score was derived using previously described methodology based on 5 variables: age, creatinine clearance, haemoglobin, white blood cell count, and previous spontaneous bleeding [24].

Supplementary Table 8. Two-year clinical outcomes in the elderly patients (>75 years of age) in the two treatment strategy groups categorised according to clinical presentation (n=2,565).

	Stable CAD (N=1,459)						ACS (N=1,106)						
	Reference (n=725)		Experimental (n=734)				Reference (n=548)		Experimental (n=558)				
	N	%	N	%	HR (95% CI)	*p*-value	N	%	N	%	HR (95% CI)	*p*-value	*p* int
Primary endpoint	61	8.4%	42	5.7%	0.66 (0.44-0.99)	0.046	59	10.8%	51	9.1%	0.83 (0.56-1.24)	0.367	0.421
All-cause death	47	6.5%	31	4.2%	0.64 (0.41-1.01)	0.057	53	9.7%	42	7.5%	0.77 (0.51-1.16)	0.203	0.569
New Q-wave MI	15	2.1%	12	1.6%	0.79 (0.37-1.69)	0.539	7	1.3%	11	2.0%	1.55 (0.60-4.04)	0.362	0.276
POCE	134	18.5%	111	15.1%	0.81 (0.63-1.04)	0.091	114	20.8%	96	17.2%	0.82 (0.62-1.07)	0.127	0.949
Definite ST	6	0.8%	2	0.3%	0.33 (0.07-1.63)	0.173	5	0.9%	1	0.2%	0.20 (0.02-1.68)	0.137	0.705
Definite/probable ST	6	0.8%	3	0.4%	0.49 (0.12-1.97)	0.317	11	2.0%	2	0.4%	0.18 (0.04-0.80)	0.025	0.329
Definite/probable /possible ST	13	1.8%	7	1.0%	0.49 (0.24-1.02)	0.056	14	2.6%	8	1.4%	0.53 (0.26-1.08)	0.080	
Stroke	10	1.4%	13	1.8%	1.29 (0.57-2.94)	0.548	16	2.9%	20	3.6%	1.23 (0.64-2.37)	0.543	0.928
NACE	145	20.0%	133	18.1%	0.89 (0.71-1.13)	0.342	130	23.7%	112	20.1%	0.84 (0.65-1.08)	0.166	0.705
BARC 3	17	2.3%	35	4.8%	2.06 (1.15-3.67)	0.015	29	5.3%	23	4.1%	0.78 (0.4 5-1.34)	0.362	0.016
BARC 5	4	0.6%	6	0.8%	1.49 (0.42-5.25)	0.543	6	1.1%	6	1.1%	0.98 (0.32-3.04)	0.971	0.629
BARC 3 or 5	19	2.6%	39	5.3%	2.05 (1.18-3.55)	0.012	31	5.7%	26	4.7%	0.82 (0.49-1.38)	0.456	0.018

*Not including TIA.

ACS: acute coronary syndromes; CAD: coronary artery disease. The primary endpoint was a composite of two-year all-cause mortality or non-fatal, centrally adjudicated, new Q-wave myocardial infarction (MI). Patient-oriented clinical endpoint (POCE) included all-cause mortality or any MI, revascularisation or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding.

ST: stent thrombosis