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Different safety pattern of ticagrelor monotherapy following percutaneous coronary interventions related to pulse pressure levels: A sub-analysis of the GLOBAL LEADERS randomized multicenter trial

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Abstract

Aims: The relationship between pulse pressure (PP) data and clinical outcomes after contemporary percutaneous coronary intervention (PCI) is poorly defined. Therefore, we evaluated the impact of PP and different antiplatelet regimes on clinical and safety outcomes in an all-comers population.

Methods: In this sub-analysis of the GLOBAL LEADERS trial (n=15,936) we compared the experimental therapy of 23-month ticagrelor following one-month dual anti-platelet therapy (DAPT), versus standard DAPT for 12 months followed by aspirin monotherapy, in all-comers subjects who underwent PCI and were divided into two groups according to the median PP of 60 mmHg. The adjudicated primary endpoint (composite of all-cause death or new Q-wave myocardial infarction) and the composite endpoints (1) patient oriented composite endpoints (POCE), (2) secondary safety bleeding endpoint BARC types 3 or 5, and (3) net adverse clinical events (NACE) were evaluated.

Results: At 2 years, subjects in the high PP group (n=7,971) had numerically higher rates of the primary endpoint (4.3% vs. 3.9%, p=0.058), similar BARC 3 or 5 bleeding (2.5% vs. 1.7%, p=0.355) and higher rates of NACE (16.4% versus 13.7%, p=0.037), and POCE (14.9% vs. 12.7%, p=0.051), compared with the low PP group (n=7,965), respectively. There was no treatment effect of ticagrelor monotherapy compared with standard DAPT among patients with high PP levels for the studied outcomes. Among patients with arterial compliance (PP<60mmHg), the primary endpoint (3.4% vs. 4.4%, adjusted HR 0.77 [0.61-0.96], p=0.022, $p_{interaction}$=0.103) POCE (11.8% vs. 13.5%, aHR 0.86 [0.76-0.98], p=0.019, $p_{interaction}$=0.132), NACE (12.8% vs. 14.7%, aHR 0.85 [0.76-0.96], p=0.009, $p_{interaction}$=0.081) and BARC 3 or 5 (1.4 vs. 2.1%, aHR 0.69 [0.49-0.97], p=0.036; $p_{interaction}$ =0.008) were lower with the use of ticagrelor monotherapy compared with the standard DAPT.

Conclusions: After contemporary PCI subjects with high PP levels (arterial stiffness) experienced high rates of the combination of clinically relevant ischemic events and safety-related bleeding events at 2-years follow-up. In those with low PP levels, ticagrelor monotherapy led to a lower risk of bleeding events compared to standard DAPT.

Introduction

Pulse pressure (PP) is the pulsatile component of blood pressure (BP) and can predict cardiovascular outcomes (1). A rise in PP, which is mainly observed in middle-aged and elderly patients due to an increase in systolic BP (SBP) and decrease in diastolic BP (DBP), is considered a marker of underlying vascular disease, and reflects a reduction in arterial compliance (2). Specifically, in patients with coronary artery disease (CAD), aortic PP significantly predicted major adverse cardiovascular events and all-cause mortality (3). Brachial PP levels were also independently associated with all-cause mortality in CAD patients after percutaneous coronary intervention (PCI) at 5-year follow-up (4). Recently, a retrospective study has demonstrated that the combination of high SBP and low DBP – a wide PP – prior to PCI is associated with myocardial infarction and stroke at 1-year post-procedure (5). However, the relationship between PP and clinical outcomes have been poorly explored in clinical trials of large populations of patients with CAD who have undergone contemporary PCI.

Recently, the GLOBAL LEADERS trial has shown that 23-month ticagrelor monotherapy, following one-month dual anti-platelet therapy (DAPT), was not superior to standard DAPT in preventing the primary endpoint – all-cause mortality or new Q-wave myocardial infarction (MI) – among all-comers patients 2 years after PCI (6). Rates of the secondary composite endpoints (i) major bleeding (type 3 or 5 according to Bleeding Academic Research Consortium -BARC) (6), (ii) patient-oriented composite endpoints (POCE), and (iii) net adverse clinical events (NACE), which combines POCE and bleeding events (7), were also similar between the two antiplatelet strategies. Nevertheless, ticagrelor monotherapy was shown to be effective and safe (6).

In this sub-analysis of the GLOBAL LEADERS trial, which enrolled a large ‘real-life’ population we sought to evaluate: (i) the impact of PP on clinical outcomes following

contemporary PCI and (ii) the impact of different antiplatelet strategies on the 2-year clinical and safety outcomes in all-comers patients who underwent PCI stratified by low and high PP.

Methods

The trial

The present study is a sub-analysis of the GLOBAL LEADERS trial (ClinicalTrials.gov, number NCT01813435) described in detail elsewhere (6,8). In brief, the trial was a randomized, open-label, multicenter, superiority study designed to compare two antiplatelet therapy strategies in all-comers patients after PCI with a biolimus A9-eluting stent. The experimental therapy comprised aspirin (75–100 mg) daily plus ticagrelor (90 mg) twice daily for 1 month, followed by 23 months of ticagrelor monotherapy, while reference therapy was standard DAPT with aspirin (75–100 mg) daily plus either clopidogrel (75 mg) daily (for patients with stable coronary artery disease) or ticagrelor (90 mg) twice daily (for patients with acute coronary syndrome-ACS) for 12 months, followed by aspirin monotherapy for 12 months (6,8).

The trial was approved by the institutional review board at each participating institution. The study was performed in accordance with the ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki), the International Conference of Harmonization, 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.

Study population

The main study enrolled 15,991 patients between July 2013 to November 2015 in an "all-comers" design: no restriction regarding clinical presentation, complexity of the lesions or number of stents used. Since (i) 23 patients withdrew consent and requested data deletion

from the database, and (ii) 32 subjects had systolic and diastolic BP levels equal to zero (treated as mistakes in completion of the eCRF, and then excluded), a total of 15,936 subjects remained for the current analysis (99.65% of all randomized patients).

Pulse Pressure

PP was calculated by subtracting the DBP from the SBP recorded at the time of randomization by a single seated BP. Patients were then divided into two groups using the median PP of 60 mmHg as a cut-off into the low (PP <60mmHg) and high (PP≥60 mmHg) group.

Study endpoints

In this sub-analysis of the GLOBAL LEADERS trial we evaluated the impact of PP and different antiplatelet strategies on the primary endpoint – a composite of investigator-reported all-cause mortality or non-fatal, new Q-wave MI identified by an independent ECG core laboratory (6) – at 2 years in all-comers subjects who underwent PCI stratified by low or high baseline PP. Secondarily, we assessed the interaction of these anti-platelet therapies on (i) the key secondary safety endpoint – site-reported bleeding assessed according to the BARC criteria (grade 3 or 5) (9), (ii) the POCE and (iii) NACE at 2 years in PP groups. POCE was defined according to the recent Academic Research Consortium (ARC)-2 consensus as all-cause mortality, any stroke (ischemic and hemorrhagic), any MI including periprocedural or spontaneous with ST-elevation MI (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI), and any revascularization (re-PCI or coronary artery bypass graft surgery (CABG) in target or non-target vessels) (10) NACE was defined as the combination of clinically relevant ischemic events and safety-related bleeding events, POCE plus BARC type 3 or 5. The composite endpoints were analyzed according to time-to-first event analysis.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation and were compared using independent t test. Categorical variables are presented as absolute number and percentage and were compared using Chi square test. Kaplan-Meier method was used to estimate the cumulative rates of events and log-rank test was performed to examine the differences between groups. The outcomes according to PP groups were assessed in the univariate and multivariate Cox proportional hazards model. The covariates in the multivariate model were included based on clinical relevance as well as association with PP in previous studies, such as age, diabetes, sex, hypertension, peripheral vascular disease, renal failure, history of MI, history of coronary artery bypass grafting and presentation of ACS. Hazard ratio (HR) and 95% confidence intervals (CI) were calculated, and interaction test was performed to evaluate the differences in the treatment effect of antiplatelet strategies in PP groups. Association between the continuous PP levels and clinical (POCE) and safety bleeding (BARC 3 or 5) outcomes were assessed using spline function in the Cox regression analysis. All the analyses were performed according to the intention-to-treat principle of all randomized patients as time-to-first-event. A two-sided alpha of 5% was considered as statistical significance. The analyses were performed in R version 3.4.2.

Results

Baseline clinical characteristics

Out of 15,936 subjects who remained in this sub-analysis of the GLOBAL LEADERS trial, 7,965 had a low PP (PP<60 mmHg), and 7,971 had a high level (PP≥ 60 mmHg). As expected, those in the high PP group were older and more likely to be women, diabetic (and insulin users), hypertensive and hypercholesterolemic compared with their counterparts. In addition, this group with a PP≥60mmHg had a higher proportion of patients with peripheral vascular disease, renal failure, previous coronary artery bypass grafting and stable coronary

artery disease compared to patients in the low PP group. On the other hand, compared with those with a PP≥60mmHg, patients with in the low PP group were more commonly smokers, and more likely to present with a NSTEMI or STEMI (Table 1).

Impact of pulse pressure levels on clinical outcomes

As shown in table 2 in the univariate model, at 2 years, rates of primary endpoint – the composite of all-cause mortality or non-fatal new Q-wave MI – were similar between the PP groups, whereas POCE, NACE and BARC 3 or 5 occurred more frequently in group with PP≥60mmHg. Multivariate analyses revealed that subjects with high PP levels had significantly higher rates of NACE, although POCE and the primary endpoint were numerically higher without reaching statistical significance, compared with the group with low PP levels. In the multivariate model rates of BARC 3 or 5 bleeding were similar between the PP groups (Table 2). Spline representation of the hazard ratios for POCE and BARC 3 or 5 are shown in **Figure 1.**

Impact of antiplatelet strategies on clinical and safety outcomes

No treatment effect of ticagrelor monotherapy compared with standard DAPT was observed among patients with a high PP for the studied outcomes. On the other hand, subjects with a low PP treated with ticagrelor had a lower risk of the clinical and safety outcomes assessed in this sub-analysis – the primary endpoint, POCE, NACE and BARC 3 or 5 – compared with standard DAPT (Table 3). Interaction testing revealed differences in the treatment effect of antiplatelet strategies between PP groups with regards to the secondary safety outcome only – BARC 3 or 5 bleeding events – $p_{interaction} = 0.008$ (Table 3). Time to first event curves for the secondary endpoints and interaction with the antiplatelet treatment strategy are shown in **Figure 2**.

Discussion

The main findings of this sub-analysis of the GLOBAL LEADERS trial are (1) at two years follow-up, regardless of confounders, patients with high PP have significantly higher rates of NACE compared to those with low PP; and (2) a significant difference in 2-year-safety outcomes was observed between the antiplatelet strategies and PP groups: the experimental therapy of ticagrelor monotherapy was superior to standard DAPT in lowering the risk of BARC 3 or 5 bleeding in subjects with low PP, whilst no difference was observed among those with high PP. Given the trial design, our study is the first to examine the interaction between PP and antiplatelet scheme on ischemic and safety outcomes in an all-comers population after contemporary PCI.

Studies have clearly pointed out that cardiovascular risk is related not only to an increase in systolic but also to a decrease in diastolic BP. Since both components of BP tend to diverge after the age of 55 (11), PP has emerged as an important risk factor for predicting cardiovascular events (1,12). PP increases along with age, body mass index, cholesterol, and risk of diabetes, but independent of these risk factors, it has been shown to be a strong predictor of death from cardiovascular disease with an increased risk of 10% in individuals 46 to 77 years of age, per 10 mmHg increment in PP (13). Rises in PP, which reflect a reduction in arterial compliance, have been identified as a simple marker of underlying vascular disease (2). As PP has been reported to be a good indicator of arterial stiffness, especially in older people, it may be considered an accurate assessment of vascular bed compliance (11,14).

Adverse outcomes in patients with CAD have been associated with elevated PP. Ascending aortic PP normalized to the mean BP correlated to the extent of coronary atherosclerosis irrespectively of the presence of hypertension (15), as well as being able to predict the risk of major adverse cardiovascular events and all-cause mortality (3) in individuals with angiographically proven CAD. Specifically in CAD patients following PCI,

mean BP-normalized PP was a powerful predictor of restenosis 3 months after the procedure [Odds Ratio = 33.5 (95% CI, 2.04 to 550.6) for the highest, compared with the lowest, tertile of PP] (16). Brachial PP levels were also independently associated with total mortality [Relative Risk=1.08 (95%CI, 1.01 to 1.15, per 10 mmHg increment in PP] in coronary patients followed for 5 years after revascularization (4). Further, increased noninvasive heart rate-corrected aortic amplification index, which assess arterial stiffness (17,18), predicted the occurrence of the combination of death, MI, and clinical restenosis in CAD patients within 2 years of their PCI (19). Most recently, a large retrospective analysis associated pre-procedural PP (high systolic combined with low diastolic BP) with a higher incidence of MI and stroke at 1 year after PCI (5). Our findings are in part consistent with those previous studies. We found that after adjusting for several confounders, subjects with high baseline PP who underwent PCI were at an increased risk (9% risk increase along the 2 years) of having the combination of clinically relevant ischemic events and safety-related bleeding events, namely NACE. Of the components of NACE, safety-related bleeding (BARC 3 or 5) has previously been poorly explored in relation to an association with baseline PP in subjects undergoing PCI. Our study supports the prognostic importance of PP– that reflect increased arterial stiffness – on subsequent cardiovascular outcomes and bleeding events in patients after PCI.

The pathophysiology of the effects of increased PP is complex. It causes increased cyclic stretch of vascular structures activating several signaling pathways ultimately leading to atherosclerotic remodeling, proinflammatory cell migration, and increases in oxidative stress (20). A bidirectional link is also present; while on the one hand elevated PP mediates progression of atherosclerosis, on the other hand, plaque formation impairs the elastic properties of the arterial wall, elevating PP, creating a vicious cycle (20-22). Pulsatile BP has been implicated as the main mechanism causing instability and rupture of atherosclerotic

plaque, and consequently acute coronary syndrome and other vascular complications (23,24). In fact, studies have suggested that cardiac events are more related to the pulsatile stress of large-artery stiffness during systole – as reflected by a rise in PP – than the steady-state stress of small-vessel resistance during diastole (as reflected in rises in both systolic and diastolic BP) (25). Rises in aortic stiffness have also supported the link between cardiac performance and myocardial perfusion. It has been shown that among patients undergoing PCI, compared to those with compliant aortas, those with stiffer aortas had a lower hyperemic coronary blood flow response to adenosine, and also a smaller improvement in hyperemic coronary blood flow after a successful PCI (26). These data demonstrate that, because the arterial wall continuously interacts with hemodynamic forces, the PP, reflecting increased arterial stiffness, might in part, be the mechanical component underlying adverse cardiovascular and bleeding events.

The most interesting finding and the novelty of this sub-analysis of GLOBAL LEADERS trial was that prolonged ticagrelor monotherapy was beneficial in reducing the risk of bleeding events compared to conventional DAPT followed by aspirin alone in subjects who had low PP, although no different effect was observed between the therapies in those with high PP. Since the relevant PLATO (The Study of Platelet Inhibition and Patient Outcomes) trial (27) revealed the superiority of ticagrelor over clopidogrel with regard to the primary efficacy endpoint without an increase in the rate of major bleeding in patients with ACS, protective effects of ticagrelor have been extensively explored in the literature (28,29). These pleiotropic effects – mainly reported due to increasing adenosine levels (30-32) – have been associated with (i) improvements in endothelial function when compared with clopidogrel (28,29), and (ii) increases in circulating endothelial progenitor cell levels (EPC) and decreases in proinflammatory cytokines compared with prasugrel (33). In fact, studies have suggested that increasing circulating EPC in ACS subjects is critical to improve

vascular healing and regenerate endothelial homeostasis (34). In addition, by reducing acute systemic inflammation, ticagrelor may modulate arterial stiffness (35). Beyond its potency in inhibiting platelet aggregation, ticagrelor seems to have additional vascular protective properties. In light of these data, our study demonstrated that subjects who underwent PCI and had a low PP –reflecting a healthier profile of arterial compliance – were the target group who, possibly due to ticagrelor-related pleiotropic effects, have a reduced risk of bleeding from ticagrelor compared to DAPT. On the other hand, no effect of ticagrelor on cardiovascular and bleeding events was noticeable in the group with high PP, which probably reflects their more advanced arterial stiffness. Although ticagrelor was not found to be more effective than DAPT in reducing cardiovascular outcomes (p values for interaction were not significant), its safety profile after PCI with low PP is of particular importance.

Accordingly, anti-platelet therapy in individuals with high BP, who presented either with cardiovascular or cerebrovascular disease, has been associated with an increased risk for hemorrhagic stroke (36-38). Nevertheless, recent guidelines for the management of arterial hypertension (39), based mainly on a Cochrane systematic review (40), state that for secondary prevention the benefit of aspirin in patients with elevated BP is many times greater than the harm (an absolute reduction in vascular events of 4.1% compared with placebo). However, antiplatelet agents such as ticlopidine, clopidogrel, and newer prasugrel and ticagrelor have not been sufficiently evaluated in these hypertensive patients (39). Although our findings showed similar rates of clinical and safety outcomes in taking either ticagrelor or DAPT at 2 year-follow up in subjects with high PP, future research is necessary to delineate this relationship more precisely.

Limitations

The main limitation is our sub-analysis is exploratory and was not a prespecified analysis of the GLOBAL LEADERS trial, therefore, the results should be considered as hypothesis-generating. The trial did not have a clinical adjudication committee for serious adverse events due to limited financial resources. An exception of primary endpoint – all-cause death and new Q wave MI – assessed by an independent ECG core lab, the endpoints were site-reported. However, the trial was monitored for consistency and reporting of events and on-site monitoring visits were regularly performed. As we based our analyses on single office PP, it would be more accurate and precise by using the mean of multiple BP readings or ambulatory monitoring. Central PP is shown to predict cardiovascular events (41) and associate with coronary atherosclerosis (42) more strongly than peripheral measurements, but aortic measurements are not assessed in the trial. On the other hand, the difference between central and peripheral PP observed in younger individuals is not as evident as in the elderly population (43) – which favours our findings on brachial PP evaluation since the population included in the GLOBAL LEADERS trial had a mean of 64.5 years of age (6). Nonetheless, a meta-analysis has supported that central PP does not offer a significant increase in predictive ability for clinical events over peripheral PP (44).

Conclusions

Subjects with high PP experienced higher rates of the combination of clinically relevant ischemic events and safety-related bleeding events (NACE) at two years after PCI compared to those at low level. In addition, ticagrelor monotherapy was favorable to standard DAPT strategy in providing a lower risk of bleeding events (BARC 3 or 5) in patients with low PP.

Perspectives

Following the advantages ticagrelor has demonstrated over traditional antiplatelet therapy (27,45,46), our findings suggest that patients undergoing PCI with a low PP – thus reflecting more compliant arteries – may benefit from ticagrelor monotherapy compared to DAPT due to the lower risk of bleeding events. Although ticagrelor was not found to be more effective than DAPT in reducing clinical outcomes, its safety pattern in patients with low PP is of great importance in clinical practice. Since the population we studied reflects modern clinical practice, PP – easily assessed in routine practice – can help stratify and guide, after PCI, patients who can benefit from different antiplatelet therapies. The results should be interpreted as hypothesis-generating, therefore prospective confirmation of our results is needed.

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Table 1: Baseline clinical characteristics according to pulse pressure groups

	PP < 60 (n=7965)	PP ≥ 60 (n=7971)	p-value
Age, mean (SD)	62.08 (10.29)	66.99 (9.73)	<0.001
BMI, mean (SD)	28.16 (4.54)	28.22 (4.65)	0.422
Diabetes mellitus	1736 (21.8)	2294 (28.8)	<0.001
Insulin-dependent diabetes mellitus	481 (6.1)	740 (9.3)	<0.001
Male	6427 (80.7)	5799 (72.8)	<0.001
Hypertension	5375 (67.7)	6322 (79.5)	<0.001
Hypercholesterolemia	5263 (68.3)	5490 (71.1)	<0.001
Smoking history	2397 (30.1)	1765 (22.1)	<0.001
Peripheral vascular disease	392 (5.0)	608 (7.7)	<0.001
COPD	392 (4.9)	429 (5.4)	0.197
History of bleeding	50 (0.6)	48 (0.6)	0.921
Renal failure	895 (11.3)	1272 (16.0)	<0.001
Previous stroke	197 (2.5)	224 (2.8)	0.200
Previous MI	1937 (24.4)	1764 (22.2)	0.001
Previous PCI	2565 (32.2)	2640 (33.2)	0.219
Previous CABG	405 (5.1)	533 (6.7)	<0.001
Clinical presentation			
Stable CAD	3866 (48.5)	4592 (57.6)	<0.001
Unstable angina	1026 (12.9)	994 (12.5)	0.450
NSTEMI	1818 (22.8)	1549 (19.4)	<0.001
STEMI	1255 (15.8)	836 (10.5)	<0.001

Data shown are n (%), unless otherwise indicated. SD: standard deviation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; CAD: coronary artery disease; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

Table 2: Clinical and safety outcomes at 2 years according to pulse pressure groups

Outcomes at 2 years	PP < 60 (n=7965)	PP ≥ 60 (n=7971)	Unadjusted HR (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
Death/Q-wave MI	309 (3.9)	342 (4.3)	1.11 (0.95-1.29)	0.190	0.86 (0.73-1.01)	0.058
POCE	1001 (12.7)	1172 (14.9)	1.19 (1.09-1.29)	<0.001	1.09 (1.00-1.19)	0.051
BARC 3 or 5	136 (1.7)	195 (2.5)	1.44 (1.16-1.79)	0.001	1.11 (0.89-1.40)	0.355
NACE	1083 (13.7)	1290 (16.4)	1.21 (1.12-1.31)	<0.001	1.09 (1.01-1.19)	0.037

Data shown are number of events (Kaplan-Meier estimates).

* Adjusted for age, diabetes, sex, hypertension, peripheral vascular disease, renal failure, history of myocardial infarction, history of coronary artery bypass grafting and presentation of acute coronary syndrome. Death/Q-wave MI: composite of all-cause mortality or non-fatal, new Q-wave myocardial infarction; POCE: patient oriented composite endpoints; BARC: bleeding academic research consortium; NACE: net adverse clinical events.

Table 3: Clinical and safety outcomes at 2 years according to antiplatelets therapies in pulse pressure groups

	PP<60				PP ≥ 60				
Outcomes at 2 years	**Reference (n=3928)**	**Experimental (n=4037)**	**Adjusted HR*† (95% CI)**	**p-value†**	**Reference (n=4043)**	**Experimental (n=3928)**	**Adjusted HR*‡ (95% CI)**	**p-value‡**	**p-value for interaction**
Death / Q-wave MI	173 (4.4)	136 (3.4)	0.77 (0.61-0.96)	0.022	175 (4.3)	167 (4.3)	0.98 (0.79-1.22)	0.873	0.103
POCE	528 (13.5)	473 (11.9)	0.86 (0.76-0.98)	0.019	600 (14.9)	572 (14.8)	0.99 (0.88-1.11)	0.905	0.132
BARC 3 or 5	80 (2.1)	56 (1.4)	0.69 (0.49-0.97)	0.036	89 (2.2)	106 (2.6)	1.28 (0.96-1.71)	0.085	0.008
NACE	574 (14.7)	509 (12.8)	0.85 (0.76-0.96)	0.009	660 (16.5)	630 (16.3)	0.99 (0.89-1.12)	0.975	0.081

Data shown are number of events (Kaplan-Meier estimates).

* Adjusted for age, diabetes, sex, hypertension, peripheral vascular disease, renal failure, history of myocardial infarction, history of coronary artery bypass grafting and presentation of acute coronary syndrome.

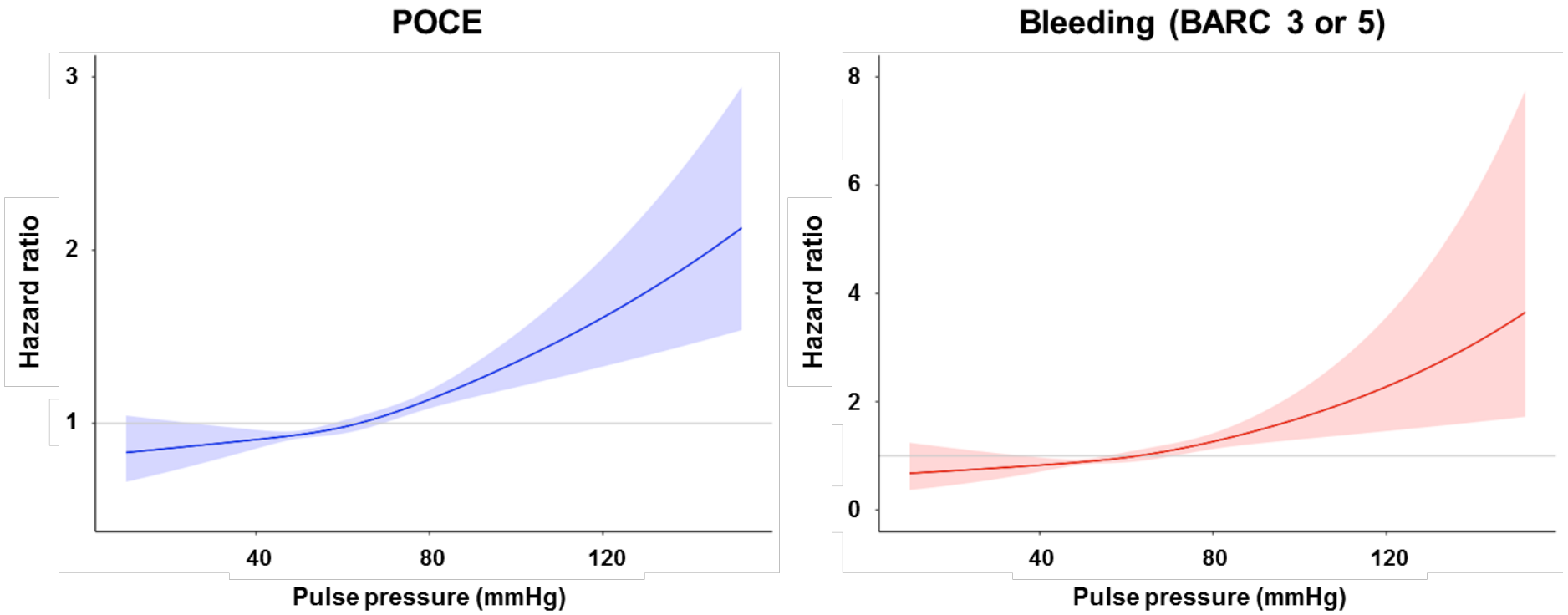
† Values calculated from the experimental versus reference antiplatelet therapy within subjects with pule pressure < 60.

‡ Values calculated from experimental versus reference antiplatelet therapy within subjects with pule pressure ≥ 60.

PP: pulse pressure; Death/Q-wave MI: composite of all-cause mortality or non-fatal, new Q-wave myocardial infarction; POCE: patient oriented composite endpoints; BARC: bleeding academic research consortium; NACE: net adverse clinical events

509 **Figure 1.** Spline representation of the unadjusted hazard ratios for patient oriented composite endpoints (POCE) and major bleeding (BARC 3 or
510 5) at 2 years according to pulse pressure values.

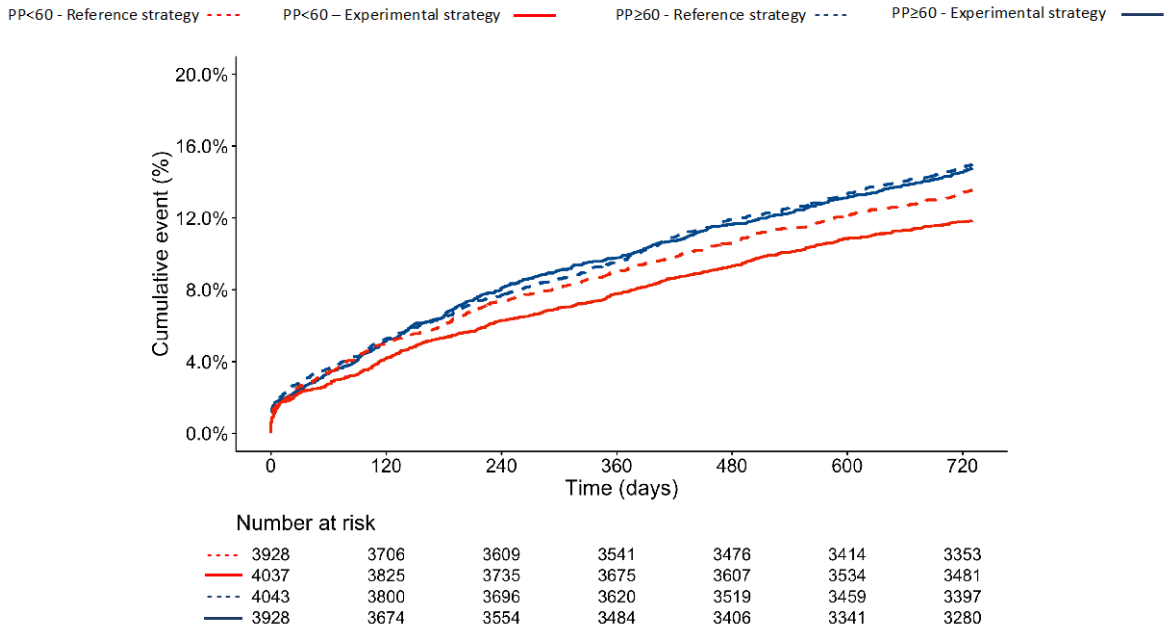
511



512

513 **Figure 2A**: Interaction of the two antiplatelet therapies on the clinical endpoint POCE in the

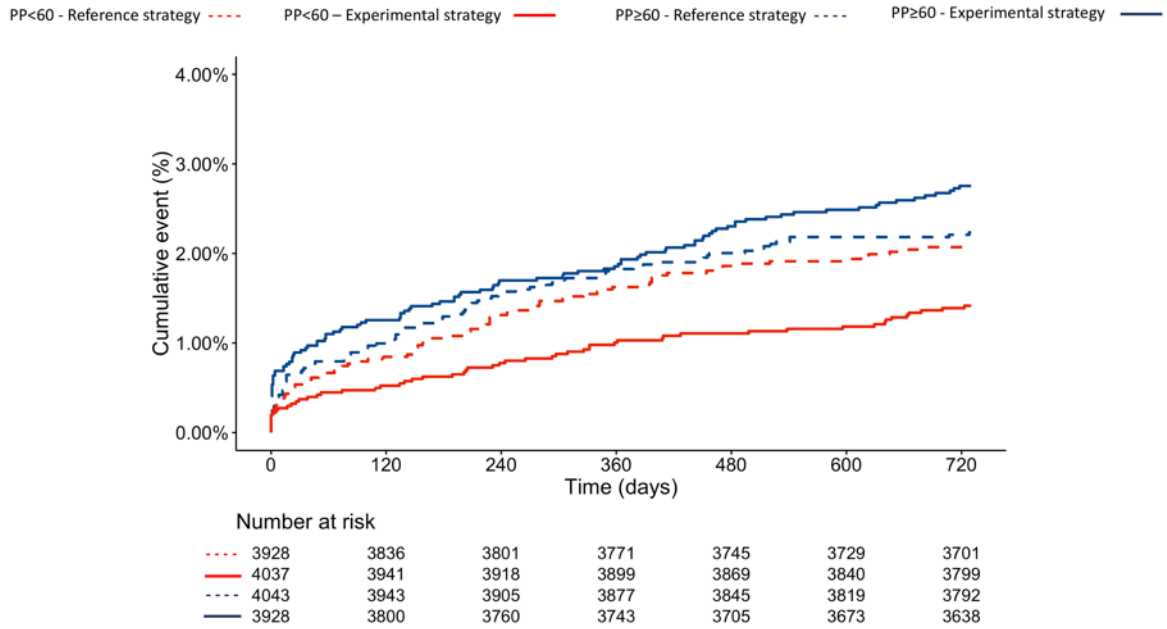
514 pulse pressure groups.



515

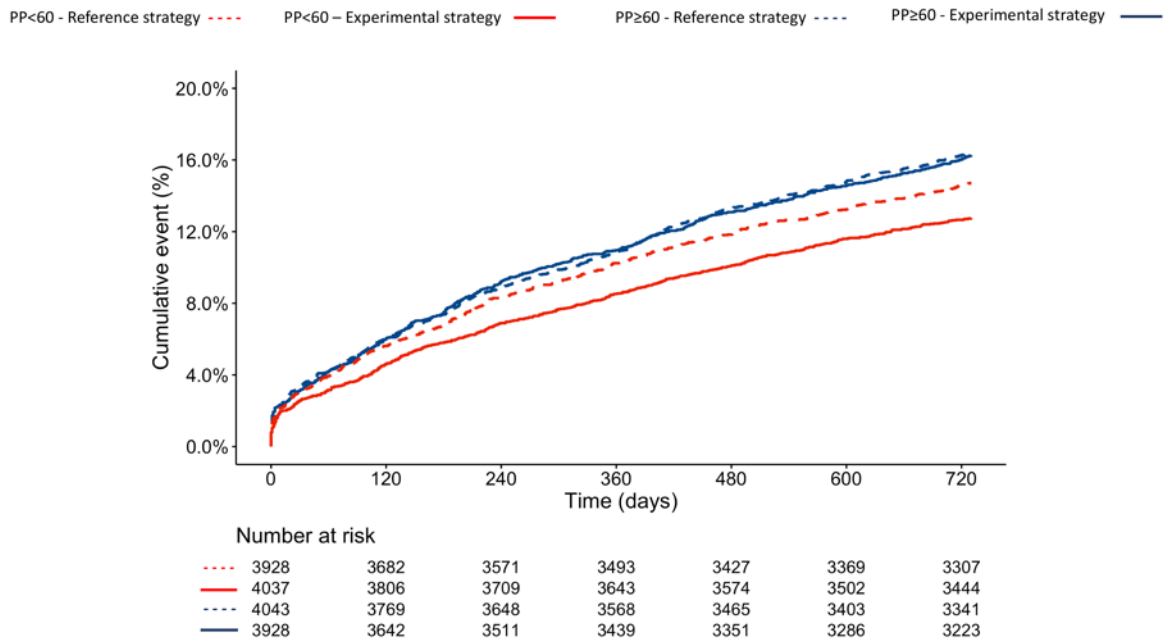
516 **Figure 2B**: Interaction of the two antiplatelet therapies on the safety endpoint BARC type 3 or

517 5 in the pulse pressure groups.



518

519 **Figure 2C**: Interaction of the two antiplatelet therapies on the combination of clinically
520 relevant and safety-related bleeding events NACE in the pulse pressure groups.



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