Journal Pre-proof

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Ana Paula de Faria, PhD, Rodrigo Modolo, MD, Ply Chichareon, MD, Chun-Chin Chang, MD, Norihiro Kogame, MD, Mariusz Tomaniak, MD, Kuniaki Takahashi, MD, Tessa Rademaker-Havinga, MSc, Joanna Wykrzykowska, MD, PhD, Rob J. de Winter, MD, PhD, Rui C. Ferreira, MD, Amanda Sousa, MD, PhD, Pedro A. Lemos, MD, PhD, Scot Garg, MBChB, PhD, Christian Hamm, MD, Peter Juni, MD, PhD, Pascal Vranckx, MD, PhD, Marco Valgimigli, MD, PhD, Stephan Windecker, MD, Yoshinobu Onuma, MD, PhD, Philippe Gabriel Steg, MD, PhD, Patrick W. Serruys, MD, PhD

PII: S0828-282X(19)31350-9

DOI: https://doi.org/10.1016/j.cjca.2019.10.015

Reference: CJCA 3481

To appear in: *Canadian Journal of Cardiology*

Received Date: 21 August 2019

Revised Date: 8 October 2019

Accepted Date: 14 October 2019

Please cite this article as: Paula de Faria A, Modolo R, Chichareon P, Chang C-C, Kogame N, Tomaniak M, Takahashi K, Rademaker-Havinga T, Wykrzykowska J, de Winter RJ, Ferreira RC, Sousa A, Lemos PA, Garg S, Hamm C, Juni P, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Steg PG, Serruys PW, Association of pulse pressure with clinical outcomes in patients under different antiplatelet strategies following PCI: Analysis of GLOBAL LEADERS, *Canadian Journal of Cardiology* (2019), doi: https://doi.org/10.1016/j.cjca.2019.10.015.

Association of pulse pressure with clinical outcomes in patients under different antiplatelet strategies following PCI: Analysis of GLOBAL LEADERS

Ana Paula de Faria*, PhD[a]; Rodrigo Modolo*, MD[b,c]; Ply Chichareon*, MD[b,d]; Chun-Chin Chang, MD[e]; Norihiro Kogame, MD[b]; Mariusz Tomaniak MD[e,f]; Kuniaki Takahashi, MD[b]; Tessa Rademaker-Havinga, MSc[g]; Joanna Wykrzykowska, MD, PhD[b]; Rob J. de Winter, MD, PhD[b]; Rui C. Ferreira, MD[h]; Amanda Sousa, MD, PhD[i]; Pedro A. Lemos, MD, PhD[j]; Scot Garg, MBChB, PhD[k] Christian Hamm MD[l], Peter Juni MD, PhD[m], Pascal Vranckx, MD, PhD[n], Marco Valgimigli, MD, PhD[o], Stephan Windecker, MD[o], Yoshinobu Onuma, MD, PhD[e,g], Philippe Gabriel Steg MD, PhD[p,q], Patrick W. Serruys MD, PhD[r]

**These authors contributed equally to this manuscript*

Running title: Association of pulse pressure with clinical outcomes following contemporary PCI

Affiliations

[a]School of Medical Sciences, University of Campinas (UNICAMP), Campinas, Brazil.[b]Department of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands.[c]Department of Internal Medicine, Cardiology Division. University of Campinas (UNICAMP). Campinas, Brazil.[d]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.[e]Erasmus Medical Center, Erasmus University, Rotterdam, the Netherlands.[f]First Department of Cardiology, Medical University of Warsaw, Warsaw, Poland.[g]Cardialysis Clinical Trials Management and Core Laboratories, Westblaak 98, Rotterdam, the Netherlands.[h]Serviço de Cardiologia, Hospital de Santa Marta, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal.[i]Department of Interventional Cardiology, Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil.[j]Instituto do Coração - HCFMUSP, Universidade de São Paulo, São Paulo, Brazil.[k]East Lancashire Hospitals NHS Trust, Blackburn, Lancashire, United Kingdom.[l]Kerckhoff Heart Center, Campus University of Giessen, Bad Nauheim, Germany.[m]Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Canada.[n]Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium.[o]Department of Cardiology, Bern University Hospital, Inselspital, University of Bern, Switzerland.[p]FACT, French Alliance for Cardiovascular Trials; Hôpital Bichat, AP-HP; Université Paris-Diderot; and INSERM U-1148, all in Paris, France.[q]Royal Brompton Hospital, Imperial College, London, United Kingdom.[r]NHLI, Imperial College London, London, United Kingdom.

Address for correspondence:

Professor Patrick W. Serruys, MD, PhD.

Professor of Medicine (em) - Erasmus University Medical Center, Rotterdam, The Netherlands.

Professor of Cardiology (hon) - Imperial College London, London, The United Kingdom

P.O. Box 2125, 3000 CC Rotterdam, the Netherlands

E-mail: patrick.w.j.c.serruys@gmail.com

Number of figures: 3, Number of tables: 2

Word count: 4,755

Twitter: @AP_deFaria / @R_Modolo / @chichareon

Abstract

Background: We evaluated the association of pulse pressure (PP) and different antiplatelet regimes with clinical and safety outcomes in an all-comers percutaneous coronary intervention (PCI) population.

Methods: In this analysis of GLOBAL LEADERS (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 subjects who underwent PCI divided into two groups according to the median PP (60 mmHg). The primary endpoint (all-cause death or new Q-wave myocardial infarction) and the composite endpoints (1)patient oriented composite endpoints (POCE), (2) Bleeding Academic Research Consortium types 3 or 5 (BARC 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 similar rates of the primary endpoint (4.3%vs.3.9%,p=0.058), POCE (14.9%vs.12.7%,p=0.051) and BARC 3 or 5 (2.5%vs. 1.7%,p=0.355), and higher rates of NACE (16.4% versus 13.7%,p=0.037), compared with the low PP group (n=7,965). Among patients with PP<60mmHg, the primary endpoint (3.4% vs. 4.4%, aHR 0.77 [0.61-0.96]), POCE (11.8% vs. 13.5%, aHR 0.86 [0.76-0.98]), NACE (12.8% vs. 14.7%, aHR 0.85 [0.76-0.96]) and BARC 3 or 5 (1.4 vs. 2.1%, aHR 0.69 [0.49-0.97]) were lower with ticagrelor monotherapy compared with DAPT. The only significant interaction was for BARC 3 or 5 (p=0.008).

Conclusions: After contemporary PCI, subjects with high PP levels experienced high rates of NACE at 2-years. In those with low PP, ticagrelor monotherapy led to a lower risk of bleeding events compared to standard DAPT.

Keywords: ticagrelor, antiplatelet therapy, pulse pressure, percutaneous coronary intervention.

Brief Summary:

In this analysis of the GLOBAL LEADERS trial (n=15,936) we assessed the association of pulse pressure and its interaction with different antiplatelet strategies (ticagrelor monotherapy versus standard DAPT) with clinical outcomes following PCI. At 2 years, patients with PP≥60 mmHg had similar rates of the primary outcome, POCE and BARC 3 or 5, and higher rates of NACE, compared with the low PP group. Among patients with PP<60mmHg, the clinical outcomes were lower with ticagrelor.

Abbreviations

ACS = acute coronary syndrome;

BARC = Bleeding Academic Research Consortium;

BP = blood pressure;

CAD = coronary artery disease;

DAPT = dual antiplatelet therapy;

DBP = diastolic blood pressure;

MI = myocardial infarction;

NACE = net adverse clinical events

NSTEMI = non-ST elevation myocardial infarction;

PCI = percutaneous coronary intervention;

POCE = patient-oriented composite endpoints;

PP = pulse pressure;

SBP = systolic blood pressure;

STEMI = ST elevation myocardial infarction.

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 predicted major adverse cardiovascular events and all-cause mortality (3) and provides additional prognostic information beyond mean BP (4). Brachial PP levels were also independently associated with all-cause mortality in CAD patients after percutaneous coronary intervention (PCI) at 5-year follow-up (5). 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 (6). Although previous studies have reported PP predicting poor clinical outcomes after PCI, they were mainly conducted in registries with an outdated PCI approach (either balloon angioplasty or bare metal stents implantation) in selected PCI population. Thus, PP association with outcomes in clinical trials including a large all-comers population with CAD, who have undergone contemporary PCI is lacking.

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 (7). Rates of the secondary composite endpoints (i) major bleeding (type 3 or 5 according to Bleeding Academic Research Consortium -BARC) (7), (ii) patient-oriented composite endpoints (POCE), and (iii) net adverse clinical events (NACE), which combines POCE and bleeding

events (8), were also similar between the two antiplatelet strategies. Nevertheless, ticagrelor monotherapy was shown to be effective and safe (7).

In this analysis of the GLOBAL LEADERS trial, which enrolled a large 'real-life' population we sought to evaluate: (i) the association of PP with 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 (7,9). 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 (7,9).

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 association of PP and different antiplatelet strategies with 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 (7) – 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, detailed in Supplementary Table S1) (10), (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) (11) 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 Fisher's exact test if dichotomous or Chi-square test if > 2 categories. 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 within the low PP group were more commonly smokers, and more likely to present with a NSTEMI or STEMI (Table 1).

Association of pulse pressure levels with 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 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 of different continuous PP levels 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 (**Figure 2**). 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 (**Figure 2**). Time to first event curves for the secondary endpoints and interaction with the antiplatelet strategies are shown in **Figure 3**.

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 higher rates of NACE compared to those with low PP; and (2) a significant interaction was observed between the antiplatelet strategies and PP groups at 2 years for safety: ticagrelor monotherapy reduced BARC 3-5 bleeding compared to standard DAPT in subjects with low PP, but not 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 (12), PP has emerged as an important risk factor for predicting cardiovascular events (1,13). 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 (14). On the other hand, rises in PP, which reflect a reduction in arterial compliance, have been identified as a simple marker of underlying vascular disease (2). This raises the hypothesis that PP may participate as either a direct risk factor for cardiovascular events or a marker of poor outcome.

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 (5). 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). Of course, these studies linking restenosis to PP have been made in a time where the rate of restenosis was higher than with contemporary PCI. 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 (6). 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. It is worth mentioning, however, that other potential contributors may be associated with the results we noted; PP could be either participating as a simple marker of advanced vascular disease, or as another underlying mechanism related with our findings.

Another finding 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 apparently 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). Beyond its potency in inhibiting platelet aggregation, ticagrelor seems to have additional vascular protective properties. In light of these data, our study suggested that subjects who underwent PCI and had a not yet high PP (<60mmHg) – 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 is due to 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 (35-37). Nevertheless, recent guidelines for the management of arterial hypertension (38), based mainly on a Cochrane systematic review (39), 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 (38). 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 (40) and associate with coronary atherosclerosis (41) 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 (42) – 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 (7). Nonetheless, a meta-analysis has supported that central PP does not offer a significant increase in predictive ability for clinical events over peripheral PP (43).

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. The results should be interpreted as hypothesis-generating, therefore prospective confirmation of our results is needed.

Funding sources

GLOBAL LEADERS was sponsored by the European Clinical Research Institute, which received funding from Biosensors International, AstraZeneca, and the Medicines Company.

Author disclosures

Rodrigo Modolo: received research grants from Biosensors and SMT, outside the submitted work**. Ply Chichareon:** reports research grant from Biosensors outside the submitted work.**Christian Hamm:** reports advisory Board and speaker fees from AstraZeneca. **Peter Juni:** reports grants from Canadian Institutes of Health Research (CIHR), during the conduct of the study; grants from Astra Zeneca, grants from Biotronik, grants from Biosensors International, grants from Eli Lilly, grants from The Medicines Company, outside the submitted work; and Peter Jüni serves as unpaid member of the steering group of trials funded by Astra Zeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company. **Pascal Vranckx:** reports personal fees from Astra Zeneca, personal fees from The Medicines Company, during the conduct of the study; personal fees from Daiichi Sankyo, personal fees from Bayer Health Care, personal fees from CLS Bhering, personal fees from Terumo, outside the submitted work. **Marco Valgimigli:** reports grants and personal fees from Abbott, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from Astrazeneca, personal fees from Idorsia, personal fees from Coreflow, personal fees from Vifor, personal fees from Bristol Myers Squib SA, personal fees from iVascular, outside the submitted. **Yoshinobu Onuma:** reports being Advisory board member of Abbot Vascular. **Philipe Gabriel Steg:** reports grants and personal fees from Bayer/Janssen, grants and personal fees from Merck, grants and personal fees from Sanofi, grants and personal fees from Amarin, personal fees from Amgen, personal fees from Bristol Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Pfizer, personal fees from Novartis, personal fees from Regeneron, personal fees from Lilly, personal fees from AstraZeneca, grants and personal fees from Servier, outside the submitted work. **Patrick W. Serruys:** reports personal fees from Abbott Laboratories, personal fees from AstraZeneca, personal fees from Biotrinik, personal fees from Cardialysis, personal fees from GLG Research, personal fees from Medtronic, personal fees from Sino Medical Sciences Technology, personal fees from Société Europa Digital Publishing, personal fees from Stentys France, personal fees from Svelte Medical Systems, personal fees from Philips/Volcano, personal fees from St. Jude Medical, personal fees from Qualimed, personal fees from Xeltis, outside the submitted work.
The other authors have no disclosures.

References

1. Benetos A, Zureik M, Morcet J et al. A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with a higher cardiovascular mortality in men. J Am Coll Cardiol 2000;35:673-80.
2. Safar ME. Systolic blood pressure, pulse pressure and arterial stiffness as cardiovascular risk factors. Curr Opin Nephrol Hypertens 2001;10:257-61.
3. Chirinos JA, Zambrano JP, Chakko S et al. Relation between ascending aortic pressures and outcomes in patients with angiographically demonstrated coronary artery disease. Am J Cardiol 2005;96:645-8.
4. Selvaraj S, Steg PG, Elbez Y et al. Pulse Pressure and Risk for Cardiovascular Events in Patients With Atherothrombosis: From the REACH Registry. J Am Coll Cardiol 2016;67:392-403.
5. Domanski MJ, Sutton-Tyrrell K, Mitchell GF et al. Determinants and prognostic information provided by pulse pressure in patients with coronary artery disease undergoing revascularization. The Balloon Angioplasty Revascularization Investigation (BARI). Am J Cardiol 2001;87:675-9.
6. Warren J, Nanayakkara S, Andrianopoulos N et al. Impact of Pre-Procedural Blood Pressure on Long-Term Outcomes Following Percutaneous Coronary Intervention. J Am Coll Cardiol 2019;73:2846-2855.
7. Vranckx P, Valgimigli M, Juni P et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940-949.
8. Serruys PW, Tomaniak M, Chichareon P et al. Patient-oriented composite endpoints and net adverse clinical events with ticagrelor monotherapy following percutaneous coronary intervention: Insights from the randomized GLOBAL LEADERS trial. EuroIntervention 2019.
9. Vranckx P, Valgimigli M, Windecker S et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention 2016;12:1239-1245.
10. Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
11. Garcia-Garcia HM, McFadden EP, Farb A et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Circulation 2018;137:2635-2650.
12. Franklin SS, Gustin Wt, Wong ND et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96:308-15.
13. Blacher J, Staessen JA, Girerd X et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med 2000;160:1085-9.
14. Domanski M, Norman J, Wolz M, Mitchell G, Pfeffer M. Cardiovascular risk assessment using pulse pressure in the first national health and nutrition examination survey (NHANES I). Hypertension 2001;38:793-7.
15. Jankowski P, Kawecka-Jaszcz K, Czarnecka D. Ascending aortic blood pressure waveform is related to coronary atherosclerosis in hypertensive as well as in normotensive subjects. Blood Press 2007;16:246-53.

16. Nakayama Y, Tsumura K, Yamashita N, Yoshimaru K, Hayashi T. Pulsatility of ascending aortic pressure waveform is a powerful predictor of restenosis after percutaneous transluminal coronary angioplasty. Circulation 2000;101:470-2.
17. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001;38:932-7.
18. Weber T, Auer J, O'Rourke MF et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation 2004;109:184-9.
19. Weber T, Auer J, O'Rourke M F et al. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. Eur Heart J 2005;26:2657-63.
20. Safar ME, Blacher J, Jankowski P. Arterial stiffness, pulse pressure, and cardiovascular disease-is it possible to break the vicious circle? Atherosclerosis 2011;218:263-71.
21. Jankowski P, Bilo G, Kawecka-Jaszcz K. The pulsatile component of blood pressure: its role in the pathogenesis of atherosclerosis. Blood Press 2007;16:238-45.
22. Van Herck JL, De Meyer GR, Martinet W et al. Impaired fibrillin-1 function promotes features of plaque instability in apolipoprotein E-deficient mice. Circulation 2009;120:2478-87.
23. Lee RT, Schoen FJ, Loree HM, Lark MW, Libby P. Circumferential stress and matrix metalloproteinase 1 in human coronary atherosclerosis. Implications for plaque rupture. Arterioscler Thromb Vasc Biol 1996;16:1070-3.
24. Shiratsuch H, Basson MD. Differential regulation of monocyte/macrophage cytokine production by pressure. Am J Surg 2005;190:757-62.
25. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. Circulation 1999;100:354-60.
26. Leung MC, Meredith IT, Cameron JD. Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. Am J Physiol Heart Circ Physiol 2006;290:H624-30.
27. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
28. Campo G, Vieceli Dalla Sega F, Pavasini R et al. Biological effects of ticagrelor over clopidogrel in patients with stable coronary artery disease and chronic obstructive pulmonary disease. Thromb Haemost 2017;117:1208-1216.
29. Alemayehu M, Kim RB, Lavi R et al. Effect of Ticagrelor Versus Clopidogrel on Vascular Reactivity. J Am Coll Cardiol 2017;69:2246-2248.
30. Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. J Cardiovasc Pharmacol Ther 2014;19:209-19.
31. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. J Am Coll Cardiol 2014;63:2503-2509.
32. Hasko G, Pacher P. Regulation of macrophage function by adenosine. Arterioscler Thromb Vasc Biol 2012;32:865-9.
33. Jeong HS, Hong SJ, Cho SA et al. Comparison of Ticagrelor Versus Prasugrel for Inflammation, Vascular Function, and Circulating Endothelial Progenitor Cells in Diabetic Patients With Non-ST-Segment Elevation Acute Coronary Syndrome Requiring Coronary Stenting: A Prospective, Randomized, Crossover Trial. JACC Cardiovasc Interv 2017;10:1646-1658.

34. Bonello L, Frere C, Cointe S et al. Ticagrelor increases endothelial progenitor cell level compared to clopidogrel in acute coronary syndromes: A prospective randomized study. Int J Cardiol 2015;187:502-7.
35. Kai H, Kohro T, Fukuda K, Yamazaki T, Nagai R. Impact of systolic blood pressure on hemorrhagic stroke in patients with coronary artery disease during anti-platelet therapy: The Japanese Coronary Artery Disease (JCAD) study. Int J Cardiol 2016;224:112-113.
36. Arima H, Anderson C, Omae T et al. Effects of blood pressure lowering on intracranial and extracranial bleeding in patients on antithrombotic therapy: the PROGRESS trial. Stroke 2012;43:1675-7.
37. Toyoda K, Yasaka M, Uchiyama S et al. Blood pressure levels and bleeding events during antithrombotic therapy: the Bleeding with Antithrombotic Therapy (BAT) Study. Stroke 2010;41:1440-4.
38. Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-3104.
39. Lip GY, Felmeden DC, Dwivedi G. Antiplatelet agents and anticoagulants for hypertension. Cochrane Database Syst Rev 2011:CD003186.
40. Roman MJ, Devereux RB, Kizer JR et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension 2007;50:197-203.
41. Jankowski P, Kawecka-Jaszcz K, Czarnecka D et al. Ascending aortic, but not brachial blood pressure-derived indices are related to coronary atherosclerosis. Atherosclerosis 2004;176:151-5.
42. Steppan J, Barodka V, Berkowitz DE, Nyhan D. Vascular stiffness and increased pulse pressure in the aging cardiovascular system. Cardiol Res Pract 2011;2011:263585.
43. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 2010;31:1865-71.

515 **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)	0.919
Renal failure	895 (11.3)	1272 (16.0)	<0.001
Previous stroke	197 (2.5)	224 (2.8)	0.199
Previous MI	1937 (24.4)	1764 (22.2)	0.001
Previous PCI	2565 (32.2)	2640 (33.2)	0.218
Previous CABG	405 (5.1)	533 (6.7)	<0.001
Clinical presentation			<0.001
Stable CAD	3866 (48.5)	4592 (57.6)	
Unstable angina	1026 (12.9)	994 (12.5)	
NSTEMI	1818 (22.8)	1549 (19.4)	
STEMI	1255 (15.8)	836 (10.5)	
Medication use at discharge			

ACE inhibitors	4838 (61.2)	4721 (59.7)	0.054
Angiotensin-II receptor blockers	1156 (14.6)	1494 (18.9)	<0.001
Beta-blockers	6351 (80.3)	6202 (78.4)	0.004
Statins	7426 (93.8)	7244 (91.5)	<0.001

Data shown are n (%), unless otherwise indicated. PP: pulse pressure; 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; ACE: Angiotensin-converting enzyme.

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. 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.

Figure legends

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

Figure 2: Forest-plot representation of ischemic and safety outcomes at 2 years according to antiplatelets therapies in pulse pressure groups.

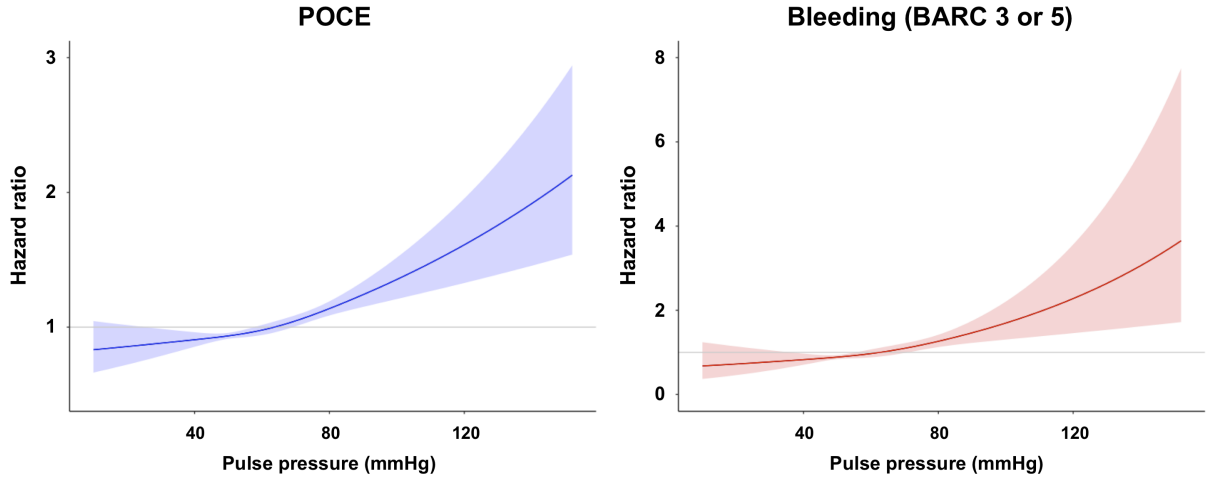
Data shown are number of events (Kaplan-Meier estimates).

* 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. 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

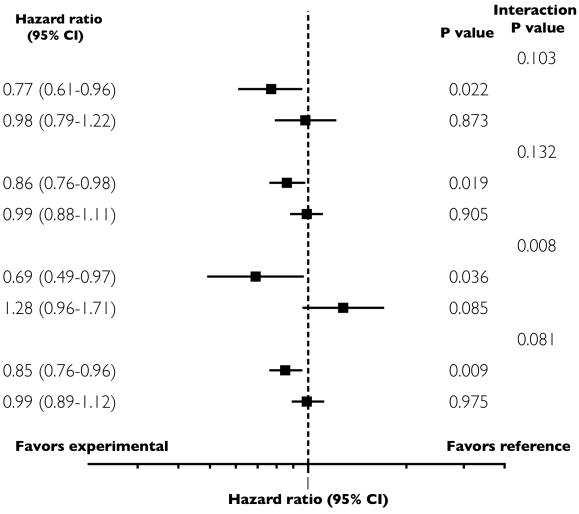
Figure 3A: Interaction of the two antiplatelet therapies on the clinical endpoint POCE in the pulse pressure groups.

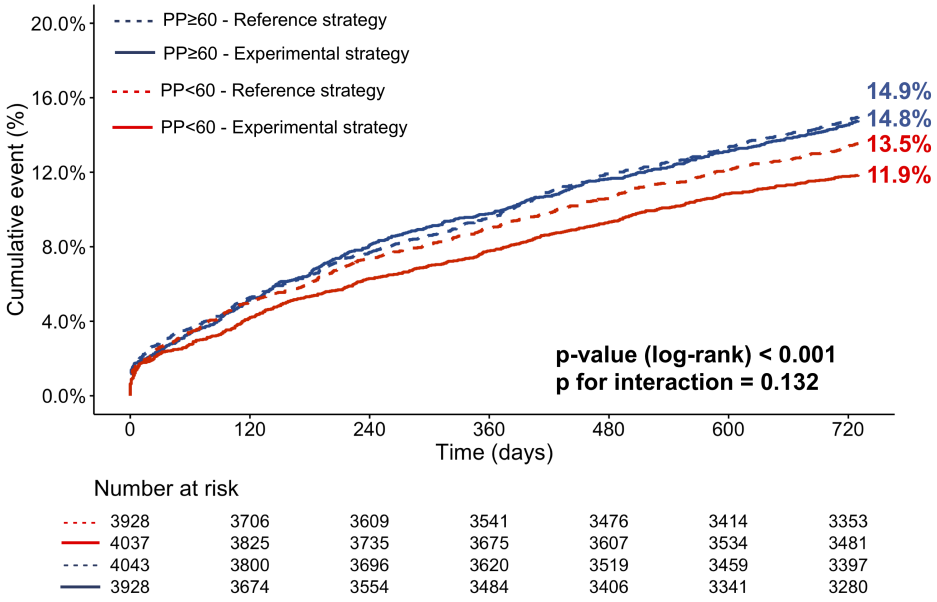
Figure 3B: Interaction of the two antiplatelet therapies on the safety endpoint BARC type 3 or 5 in the pulse pressure groups.

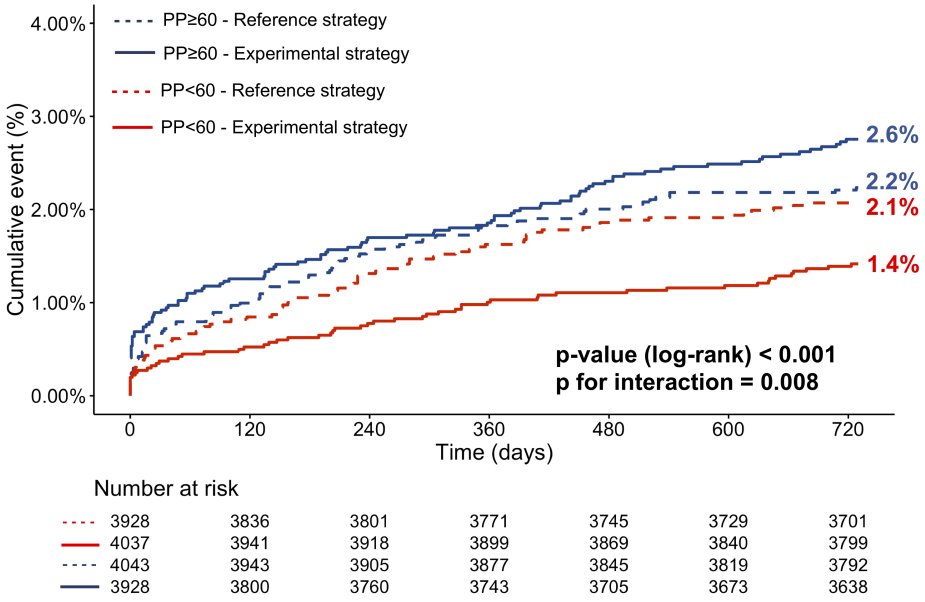
Figure 3C: Interaction of the two antiplatelet therapies on the combination of clinically relevant ischemic events and safety-related bleeding events NACE in the pulse pressure groups.

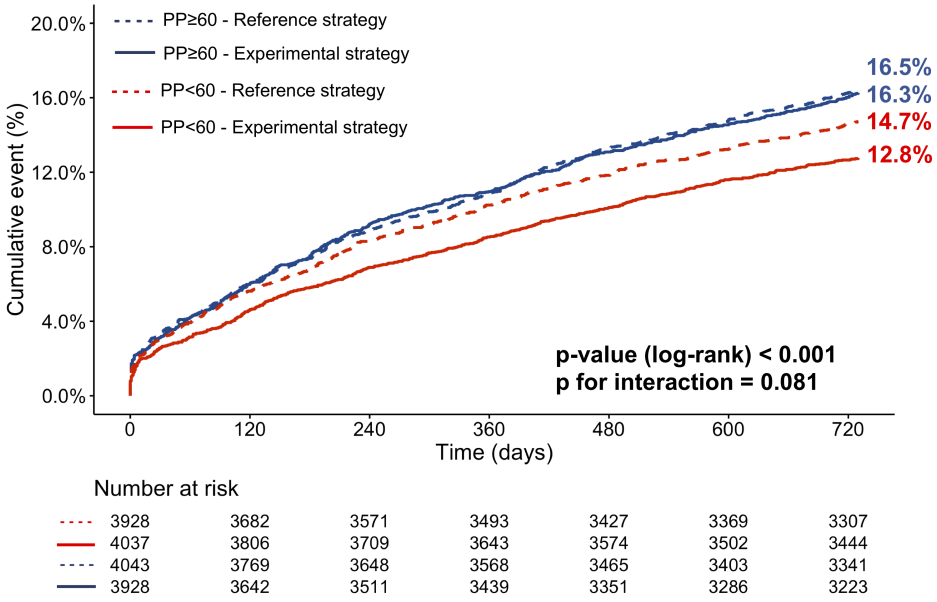

POCE
Hazard ratio
3
2
1
40
80
120
Pulse pressure (mmHg)
Bleeding (BARC 3 or 5)
Hazard ratio
8
6
4
2
0
40
80
120
Pulse pressure (mmHg)

	N	Experimental strategy (n=7965)	Reference strategy (n=7971)	Hazard ratio (95% CI)	P value	Interaction P value
Death / new-Q wave MI						0.103
PP<60	7965	136 (3.4)	173 (4.4)	0.77 (0.61-0.96)	0.022	
PP>=60	7971	167 (4.3)	175 (4.3)	0.98 (0.79-1.22)	0.873	
POCE						0.132
PP<60	7965	473 (11.9)	528 (13.5)	0.86 (0.76-0.98)	0.019	
PP>=60	7971	572 (14.8)	600 (14.9)	0.99 (0.88-1.11)	0.905	
BARC 3 or 5						0.008
PP<60	7965	56 (1.4)	80 (2.1)	0.69 (0.49-0.97)	0.036	
PP>=60	7971	106 (2.6)	89 (2.2)	1.28 (0.96-1.71)	0.085	
NACE						0.081
PP<60	7965	509 (12.8)	574 (14.7)	0.85 (0.76-0.96)	0.009	
PP>=60	7971	630 (16.3)	660 (16.5)	0.99 (0.89-1.12)	0.975	




PP≥60 - Reference strategy
PP≥60 - Experimental strategy
PP<60 - Reference strategy
PP<60 - Experimental strategy
Cumulative event (%)
20.0%
16.0%
12.0%
8.0%
4.0%
0.0%
14.9%
14.8%
13.5%
11.9%
p-value (log-rank) < 0.001
p for interaction = 0.132
0
120
240
360
480
600
720
Time (days)
Number at risk
3928 3706 3609 3541 3476 3414 3353
4037 3825 3735 3675 3607 3534 3481
4043 3800 3696 3620 3519 3459 3397
3928 3674 3554 3484 3406 3341 3280


PP≥60 - Reference strategy
PP≥60 - Experimental strategy
PP<60 - Reference strategy
PP<60 - Experimental strategy
Cumulative event (%)
4.00%
3.00%
2.00%
1.00%
0.00%
2.6%
2.2%
2.1%
1.4%
p-value (log-rank) < 0.001
p for interaction = 0.008
0
120
240
360
480
600
720
Time (days)
Number at risk
3928 3836 3801 3771 3745 3729 3701
4037 3941 3918 3899 3869 3840 3799
4043 3943 3905 3877 3845 3819 3792
3928 3800 3760 3743 3705 3673 3638


PP≥60 - Reference strategy
PP≥60 - Experimental strategy
PP<60 - Reference strategy
PP<60 - Experimental strategy
Cumulative event (%)
20.0%
16.0%
12.0%
8.0%
4.0%
0.0%
16.5%
16.3%
14.7%
12.8%
p-value (log-rank) < 0.001
p for interaction = 0.081
0
120
240
360
480
600
720
Time (days)
Number at risk
3928 3682 3571 3493 3427 3369 3307
4037 3806 3709 3643 3574 3502 3444
4043 3769 3648 3568 3465 3403 3341
3928 3642 3511 3439 3351 3286 3223