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Clinical Research

Association of Pulse Pressure With Clinical Outcomes in Patients Under Different Antiplatelet Strategies After Percutaneous Coronary Intervention: Analysis of GLOBAL LEADERS

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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 months of ticagrelor after 1

RÉSUMÉ

Contexte : Nous avons évalué l'association entre la pression différentielle (PD), différents schémas antiplaquettaires et les résultats cliniques et les résultats relatifs à l'innocuité dans une population de patients de tous types ayant subi une intervention coronarienne percutanée (ICP).

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 owing to an increase in systolic BP (SBP) and decrease in diastolic BP (DBP), is considered to be a marker of underlying vascular disease and reflects a reduction in arterial compliance.[2] Specifically, in patients with coronary artery disease (CAD), aortic PP predicts major adverse cardiovascular

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month of dual-antiplatelet therapy (DAPT) versus standard DAPT for 12 months followed by aspirin monotherapy in subjects who underwent PCI and were divided into 2 groups according to the median PP (60 mm Hg). The primary end point (all-cause death or new Q-wave myocardial infarction) and the composite end points: patient-oriented composite end points (POCE), Bleeding Academic Research Consortium (BARC) 3 or 5, and net adverse clinical events (NACE) were evaluated.

Results: At 2 years, subjects in the high-PP group (n = 7971) had similar rates of the primary end point (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% vs 13.7%; $P = 0.037$) compared with the low-PP group (n = 7965). Among patients with PP < 60 mm Hg, the primary end point (3.4% vs 4.4%, adjusted hazard ratio [aHR] 0.77, 95% confidence interval [CI] 0.61-0.96), POCE (11.8% vs 13.5%, aHR 0.86, 95% CI 0.76-0.98), NACE (12.8% vs 14.7%, aHR 0.85, 95% CI 0.76-0.96), and BARC 3 or 5 (1.4% vs 2.1%, aHR 0.69, 95% CI 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 with standard DAPT.

Méthodologie : Dans cette analyse des données de l'étude GLOBAL LEADERS (n = 15 936), nous avons comparé le traitement expérimental de 23 mois par le ticagrélor après 1 mois de bithérapie antiplaquettaire (BTAP) et la BTAP standard de 12 mois suivie de l'administration d'acide acétylsalicylique en monothérapie chez des sujets ayant subi une ICP, qui avaient été divisés en deux groupes en fonction de la PD médiane (60 mmHg). Le critère d'évaluation principal (décès toutes causes ou nouvel infarctus du myocarde avec onde Q) et les critères d'évaluation secondaires composites (critères d'évaluation composites axés sur le patient [POCE, *patient-oriented composite endpoints*], classification 3 ou 5 du BARC [*Bleeding Academic Research Consortium*] et événements indésirables cliniques nets [NACE, *net adverse clinical events*]) ont été évalués.

Résultats : À 2 ans, les sujets présentant une PD élevée (n = 7 971) affichaient des taux similaires à l'égard du critère d'évaluation principal (4,3 % vs 3,9 %; $p = 0,058$), des POCE (14,9 % vs 12,7 %; $p = 0,051$) et de la classification 3 ou 5 du BARC (2,5 % vs 1,7 %; $p = 0,355$), ainsi que des taux plus élevés de NACE (16,4 % vs 13,7 %; $p = 0,037$) comparativement aux sujets présentant une PD faible (n = 7965). Chez les patients ayant une PD < 60 mm Hg, les taux du critère d'évaluation principal (3,4 % vs 4,4 %; rapport des risques instantanés corrigé [RRIc] : 0,77; intervalle de confiance [IC] à 95 % : 0,61 − 0,96), des POCE (11,8 % vs 13,5 %; RRIc : 0,86; IC à 95 % : 0,76 − 0,98), du critère NACE (12,8 % vs 14,7 %; RRIc : 0,85; IC à 95 % : 0,76 − 0,96) et de la classification 3 ou 5 du BARC (1,4 % vs 2,1 %; RRIc : 0,69; IC à 95 % : 0,49 − 0,97) étaient moins élevés dans le groupe traité par le ticagrélor en monothérapie que dans le groupe sous BTAP. Seule l'interaction avec la classification 3 ou 5 du BARC était significative ($p = 0,008$).

Conclusions : Après une ICP courante, les sujets présentant une PD élevée ont affiché des taux de NACE plus élevés à 2 ans. Chez les patients présentant une PD faible, le traitement par le ticagrélor en monothérapie a été associé à un risque inférieur d'hémorragie comparativement à la BTAP standard.

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 demonstrated that the combination of high SBP and low DBP—a wide PP—before PCI is associated with myocardial infarction and stroke at 1 year after the procedure.[6] Although previous studies have reported PP predicting poor clinical outcomes after PCI, they were mainly conducted in registries with outdated PCI approaches (balloon angioplasty and bare metal stent implantation) in selected PCI population. Thus, data on PP association with outcomes in clinical trials including a large all-comers population with CAD who have undergone contemporary PCI are lacking.

Recently, the GLOBAL LEADERS trial showed that 23-month ticagrelor monotherapy following 1-month dual-antiplatelet therapy (DAPT) was not superior to standard DAPT in preventing the primary end point—all-cause mortality or new Q-wave myocardial infarction (MI)—among all-comer patients 2 years after PCI.[7] Rates of the secondary composite end points major bleeding (type 3 or 5 according to Bleeding Academic Research Consortium [BARC]),[7] patient-oriented composite end points (POCE), and net adverse clinical events (NACE), which combines POCE and bleeding events,[8] were also similar between the 2 antiplatelet strategies. Nonetheless, ticagrelor monotherapy was shown to be effective and safe.[7]

In the present analysis of the GLOBAL LEADERS trial, which enrolled a large "real-life" population, we sought to evaluate (1) the association of PP with clinical outcomes after contemporary PCI, and (2) the impact of different antiplatelet strategies on the 2-year clinical and safety outcomes in all-comer patients who underwent PCI stratified by low and high PP.

Methods

The trial

This study is a subanalysis of the GLOBAL LEADERS trial (ClinicalTrials.gov registration number NCT01813435) which is described in detail elsewhere.[7,9] In brief, the trial was a randomized, open-label, multicenter superiority study designed to compare 2 antiplatelet therapy strategies in all-comer 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, and the reference therapy was standard DAPT with aspirin (75-100 mg) daily

Table 1. Baseline clinical characteristics according to pulse pressure (PP) group, n (%)

Characteristic	PP < 60 mm Hg (n = 7965)	PP ≥ 60 mm Hg (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
β-Blockers	6351 (80.3)	6202 (78.4)	0.004
Statins	7426 (93.8)	7244 (91.5)	< 0.001

ACE, angiotensin-converting enzyme; BMI, body mass index; 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; STEMI, ST-segment-elevation myocardial infarction.

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. Every participant provided written informed consent at enrollment. An independent data and safety monitoring committee oversaw the safety of all patients.

Study population

The main study enrolled 15,991 patients from July 2013 to November 2015 in an "all-comers" design, ie, no restriction regarding clinical presentation, complexity of the lesions, or number of stents used. Because 23 patients withdrew consent and requested data deletion from the database and 32 subjects had systolic and diastolic BP levels equal to zero (treated as mistakes in completion of the electronic case report form and then excluded), a total of 15,936 subjects remained for this 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 from a single seated BP measurement. Patients were then divided into 2 groups according to the median PP of 60 mm Hg into the low (PP < 60 mm Hg) and high (PP ≥ 60 mm Hg) groups.

Study end points

In this subanalysis of the GLOBAL LEADERS trial we evaluated the association of PP and different antiplatelet strategies with the primary end point—a composite of investigator-reported all-cause mortality or nonfatal new Q-wave MI identified by an independent electrocardiography (ECG) core laboratory[7]—at 2 years in all-comer subjects who underwent PCI and were stratified by low or high baseline PP. Secondarily, we assessed the interaction of these antiplatelet therapies on the key secondary safety end point site-reported bleeding assessed according to the BARC criteria (grade 3 or 5, as detailed in Supplemental Table S1),[10] the POCE, and NACE at 2 years in the PP groups. POCE was defined according to the recent Academic Research Consortium 2 consensus as all-cause mortality, any stroke (ischemic and hemorrhagic), any MI (including periprocedural or spontaneous with ST-segment-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 nontarget vessels).[11] NACE was defined as the combination of clinically relevant ischemic events (POCE) and safety-related bleeding events (BARC 3 or 5). The composite end points were analyzed according to time−to−first event analysis.

Statistical analyses

Continuous variables are expressed as mean ± SD and were compared by means of independent *t* test. Categoric variables are presented as n (%) and were compared with the use of Fisher exact test if dichotomous or chi-square test if > 2

Table 2. Clinical and safety outcomes at 2 years according to pulse pressure (PP) groups

Outcomes at 2 years	PP < 60 mm Hg (n = 7965)	PP ≥ 60 mm Hg (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 are presented as number of events with Kaplan-Meier estimates in parentheses.

BARC, Bleeding Academic Research Consortium; Death/Q-wave MI, composite of all-cause mortality or nonfatal new Q-wave myocardial infarction; NACE: net adverse clinical events; POCE, patient-oriented composite end points.

*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.

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 group were assessed with the use of univariate and multivariate Cox proportional hazards models. The covariates in the multivariate model were included based on clinical relevance as well as factors associated with PP in previous studies, such as age, diabetes, sex, hypertension, peripheral vascular disease, renal failure, history of MI, history of CABG, and presentation of ACS. Hazard ratio (HR) and 95% confidence intervals (CIs) 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 with the use of spline function in the Cox regression analysis. All of the analyses were performed according to the intention-to-treat principle of all randomized patients as time to first event. A 2-sided alpha of 5% was considered to be statistically significant. The analyses were performed in R version 3.4.2.

Results

Baseline clinical characteristics

Out of 15,936 subjects who remained in this subanalysis of the GLOBAL LEADERS trial, 7,965 had a low PP (< 60 mm Hg) and 7,971 had a high PP (≥ 60 mm Hg). 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 low-PP counterparts. In addition, the high-PP group had a higher proportion of patients with peripheral vascular disease, renal failure, previous CABG, and stable CAD compared with patients in the low-PP group. On the other hand, compared with the high-PP group, patients in the low-PP group were more commonly smokers and more likely to present with an NSTEMI or STEMI (Table 1).

Association of pulse pressure levels with clinical outcomes

As presented in Table 2 in the univariate model, at 2 years, rates of primary end point—the composite of all-cause mortality or nonfatal new Q-wave MI—were similar between the PP groups, whereas POCE, NACE, and BARC 3 or 5 occurred more frequently in the group with PP ≥ 60 mm Hg. Multivariate analyses revealed that patients in the high-PP group had significantly higher rates of NACE, although POCE and the primary end point were higher without reaching statistical significance, compared with the patients in the low-PP group. In the multivariate model, rates of BARC 3 or 5 bleeding were similar between the PP groups (Table 2). Spline representation of the HRs 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 high PP for the studied outcomes. On the other hand, subjects with aow PP treated with ticagrelor had a lower risk of the clinical and safety outcomes assessed in this subanalysis—the primary end point, POCE, NACE, and BARC 3 or 5—compared with standard DAPT (Fig. 2). Interaction testing revealed differences in the treatment effect of antiplatelet strategies between PP groups regarding the secondary safety outcome only—BARC 3 or 5 bleeding events—$P = 0.008$ (Fig. 2). Time—to—first event curves for the secondary end points and interaction with the antiplatelet strategies are shown in Figure 3.

Discussion

The main findings of this subanalysis of the GLOBAL LEADERS trial are that (1) at 2 years' follow-up, regardless of confounders, patients with high PP have higher rates of NACE compared with 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 or 5 bleeding compared with standard DAPT in subjects with low PP, but not in 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 SBP but also to a decrease in DBP. Because both components of BP tend to diverge after the age of 55 years,[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 independently from these risk factors it has been

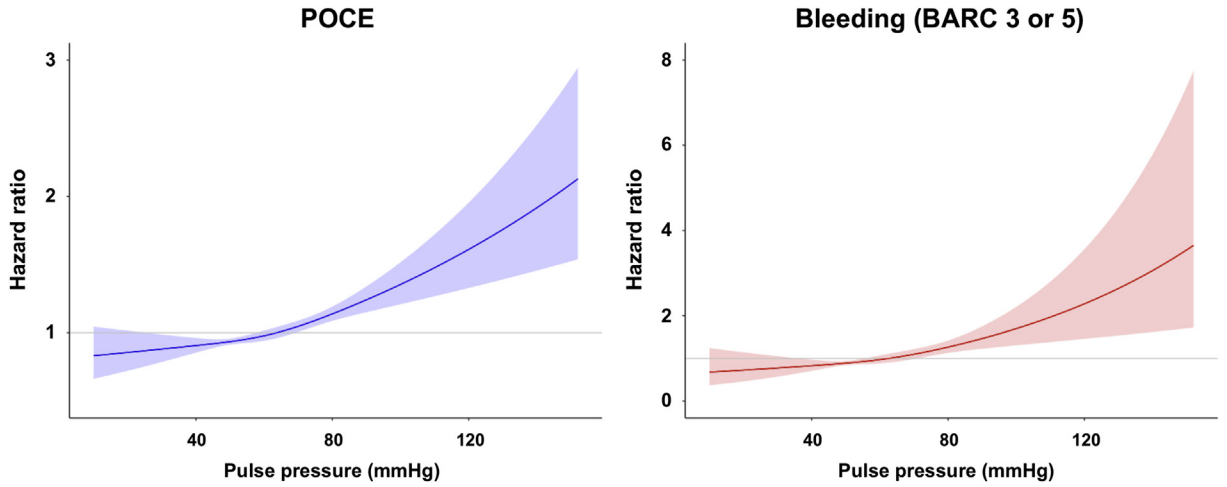

Figure 1. Spline representation of the unadjusted hazard ratios for patient-oriented composite end points (POCE) and major bleeding (Bleeding Academic Research Consortium 3 or 5) at 2 years according to pulse pressure values.

shown to be a strong predictor of death from cardiovascular disease, with an increased risk of 10% in individuals 46-77 years old per 10 mm Hg 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 with the extent of coronary atherosclerosis regardless of the presence of hypertension,[15] and was 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 after PCI, mean BP-normalized PP was a powerful predictor of restenosis 3 months after the procedure (odds ratio 33.5, 95% CI 2.04-550.6, 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 1.01-1.15, per 10 mm Hg increment in PP) in coronary patients followed for 5 years after revascularization.[5] Furthermore, increased noninvasive heart rate—corrected aortic amplification index, which assesses arterial stiffness,[17,18] predicted the occurrence of the combination of death, MI, and clinical restenosis in CAD patients within 2 years after PCI.[19] Of course, these studies linking restenosis to PP were done in a time when the rate of restenosis was higher than currently. Most recently, a

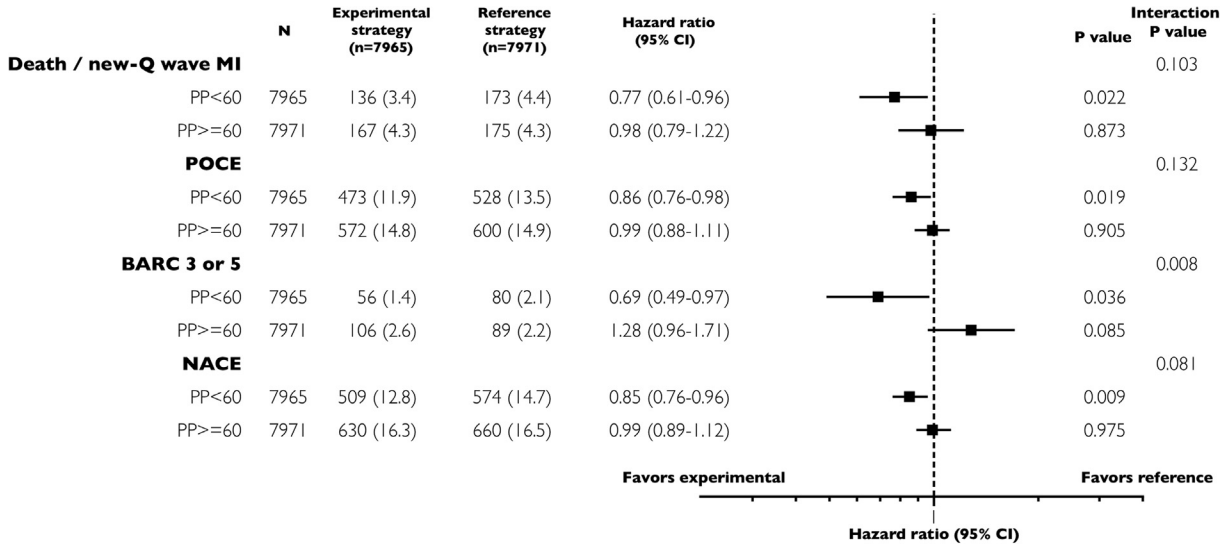

Figure 2. Forest-plot representation of ischemic and safety outcomes at 2 years according to antiplatelet therapies in different pulse pressure (PP) groups. Data shown are number of events with Kaplan-Meier estimates in parentheses. Hazard ratios adjusted for age, diabetes, sex, hypertension, peripheral vascular disease, renal failure, history of myocardial infarction, history of coronary artery bypass grafting and presentation of acute coronary syndrome. BARC, Bleeding Academic Research Consortium; Death/Q-wave MI, composite of all-cause mortality or nonfatal new Q-wave myocardial infarction; NACE: net adverse clinical events; POCE, patient-oriented composite end points.

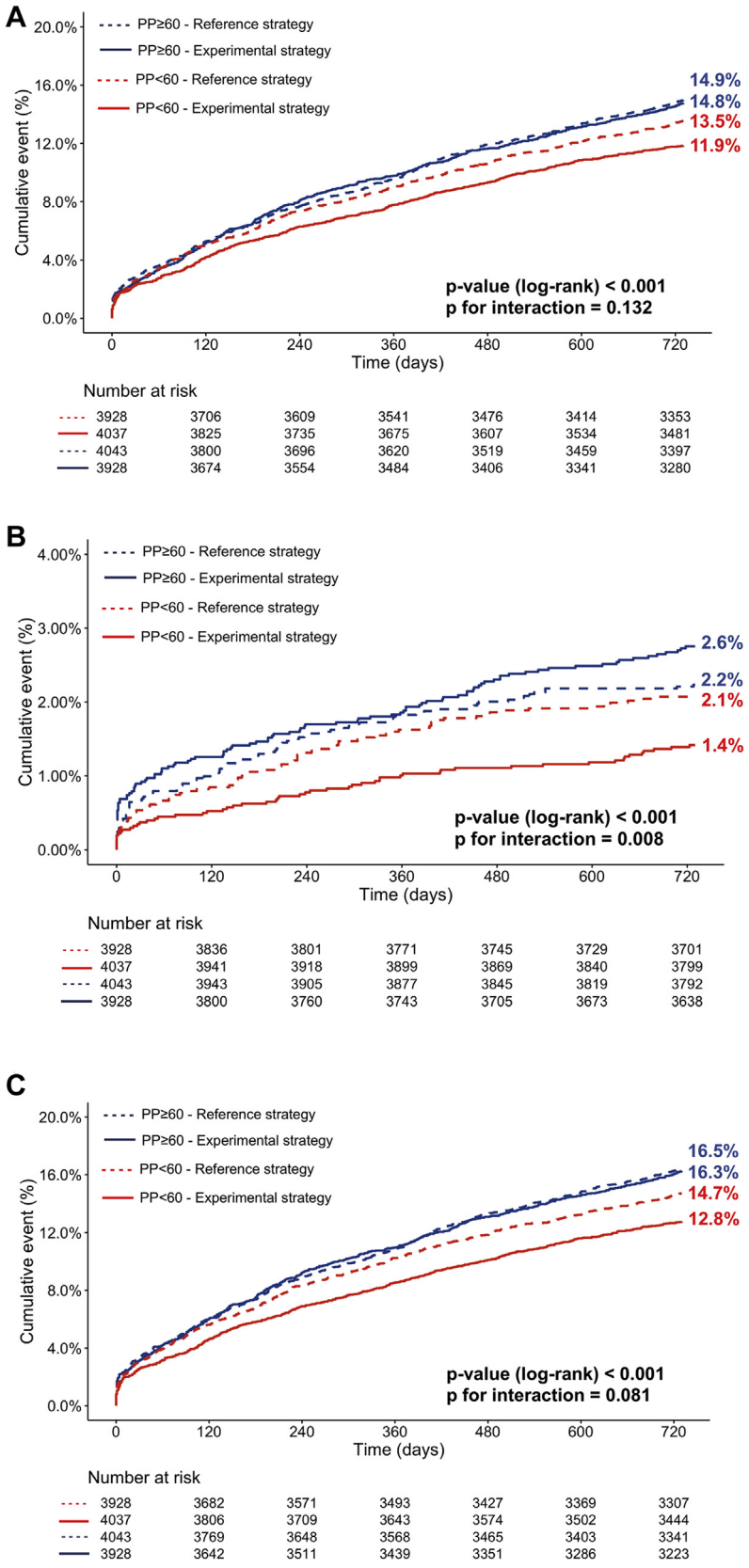

Figure 3. (**A**) Interaction of the 2 antiplatelet therapies on the clinical patient-oriented composite end points in the different pulse pressure (PP) groups. (**B**) Interaction of the 2 antiplatelet therapies on the safety end point Bleeding Academic Research Consortium 3 or 5 in the different PP groups. (**C**) Interaction of the 2 antiplatelet therapies on the combination of clinically relevant ischemic events and safety-related bleeding events in the different PP groups.

large retrospective analysis associated higher preprocedural PP (high SBP combined with low DBP) 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 baseline PP in subjects undergoing PCI. The present study supports the prognostic importance of PP—which reflects 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 signalling pathways ultimately leading to atherosclerotic remodelling, proinflammatory cell migration, and increased oxidative stress.[20] A bidirectional link is also present: Whereas on one hand elevated PP mediates progression of atherosclerosis, on the other hand plaque formation impairs the elastic properties of the arterial wall, elevating PP and 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 SBP and DBP).[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 with those with compliant aortas, those with stiffer aortas had a lower hyperemic coronary blood flow response to adenosine as well as 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 participating as either a simple marker of advanced vascular disease or another underlying mechanism related to our findings.

Another finding of this subanalysis of the GLOBAL LEADERS trial was that prolonged ticagrelor monotherapy was beneficial in reducing the risk of bleeding events compared with conventional DAPT followed by aspirin alone in subjects who had low PP, whereas no different effect was observed between the therapies in those with high PP. Since the relevant **Plat**elet Inhibition and Patient **O**utcomes (PLATO) trial[27] revealed the superiority of ticagrelor over clopidogrel in terms of the primary efficacy end point 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 to be due to increasing adenosine levels[30-32]—have been associated with improvements in endothelial function compared with clopidogrel[28,29] and increases in circulating endothelial progenitor cell levels (EPCs) and decreases in proinflammatory cytokines compared with prasugrel.[33] In fact, studies have suggested that increasing circulating EPCs in ACS subjects is critical to improving 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 (< 60 mm Hg)—reflecting a healthier profile of arterial compliance—were the target group who, possibly owing to ticagrelor-related pleiotropic effects, have a reduced risk of bleeding from ticagrelor compared with DAPT. On the other hand, no effect of ticagrelor on cardiovascular and bleeding events was noticeable in the group with high PP, which is probably 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, antiplatelet therapy in individuals with high BP who presented with either 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 the 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 that our subanalysis was exploratory and not a prespecified analysis of the GLOBAL LEADERS trial, so the results should be considered as hypothesis generating. The trial did not have a clinical adjudication committee for serious adverse events, owing to limited financial resources. Except for the primary end point—all-cause death and new Q-wave MI—which was assessed by an independent ECG core laboratory, the end points were site reported. However, the trial was monitored for consistency and reporting of events, and on-site monitoring visits were regularly performed. We based our analyses on single office BP measurement, but it would be more accurate and precise to use the mean of multiple BP readings or ambulatory monitoring. Central PP has been shown to predict cardiovascular events[40] and to be associated with coronary atherosclerosis[41] more strongly than peripheral PP, but aortic measurements were 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 because the population included in the GLOBAL LEADERS trial had a mean age of 64.5 years.[7] Nonetheless, a meta-analysis has supported that central PP does not offer a significant increase over peripheral PP in predictive ability for clinical events.[43]

Conclusion

Subjects with high PP experienced higher rates of the combination of clinically relevant ischemic events and safety-related bleeding events (NACE) at 2 years after PCI compared with those with low PP. In addition, ticagrelor monotherapy was favourable 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; prospective confirmation of our results is needed.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.10.015.