The impact of pre-procedure heart rate on adverse clinical outcomes in patients undergoing percutaneous coronary intervention: Results from a 2-year follow-up of the GLOBAL LEADERS trial

Rutao Wang[a,b,c], Kuniaki Takahashi[d], Ply Chichareon[d,e], Chao Gao[a,b,c], Norihiro Kogame[d], Rodrigo Modolo[d,f], Mariusz Tomaniak[g,h], Hideyuki Kawashima[c,d], Masafumi Ono[c,d], Hironori Hara[c,d], Volker Schächinger[i], Gincho Tonev[j], Imre Ungi[k], Roberto Botelho[l], Eric Eeckhout[m], Christian Hamm[n], Peter Jüni[o], Pascal Vranckx[p], Stephan Windecker[q], Scot Garg[r], Robert Jan Van Geuns[b], Yoshinobu Onuma[c,g], Patrick W. Serruys[c,s,*]

[a] Department of Cardiology, Xijing Hospital, Fourth Military Medical University, Xi'an, China
[b] Department of Cardiology, Radboudumc, Nijmegen, the Netherlands
[c] Department of Cardiology, National University of Ireland, Galway (NUIG), Galway, Ireland
[d] Amsterdam UMC, University of Amsterdam, Heart Center, Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands
[e] Cardiology Unit, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand
[f] Department of Internal Medicine, Cardiology Division, University of Campinas (UNICAMP), Campinas, Brazil
[g] Department of Cardiology, Erasmus Medical University Center, Thorax Centre, Rotterdam, the Netherlands
[h] First Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
[i] Klinikum Fulda, Medizinische Klinik I, Fulda, Germany
[j] Multi-profile Hospital for Active Treatment, St George's University, Plovdiv, Bulgaria
[k] Division of Invasive Cardiology, Second Department of Internal Medicine and Cardiology Center, University of Szeged, Szeged, Hungary
[l] CT / Instituto Do Coracao Do Triangulo Mineiro, Uberlandia, Brazil
[m] Department of Cardiology, Lausanne University Hospital, Switzerland
[n] Kerckhoff Heart Center, Campus University of Giessen, Bad Nauheim, Germany
[o] Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Canada
[p] Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium
[q] Department of Cardiology, Bern University Hospital, Bern, Switzerland
[r] East Lancashire Hospitals NHS Trust, Blackburn, Lancashire, United Kingdom
[s] National Heart and Lung Institute, Imperial College London, London, UK

HIGHLIGHTS

- Elevated pre-procedure heart rate was an independent predictor of all-cause mortality at 2 years following percutaneous coronary intervention (PCI).
- Elevated pre-procedure heart rate did not impact the bleeding events at 2 years following PCI.
- Ticagrelor monotherapy *versus* standard dual antiplatelet therapy did not improve the bad ischemic prognosis of high pre-procedure heart rate.

ARTICLE INFO

ABSTRACT

Background and aims: The prognostic impact of pre-procedure heart rate (PHR) following percutaneous coronary intervention (PCI) has not yet been fully investigated. This *post-hoc* analysis sought to assess the impact of PHR on medium-term outcomes among patients having PCI, who were enrolled in the "all-comers" GLOBAL LEADERS trial.

Methods and results: The primary endpoint (composite of all-cause death or new Q-wave myocardial infarction [MI]) and key secondary safety endpoint (bleeding according to Bleeding Academic Research Consortium [BARC] type 3 or 5) were assessed at 2 years. PHR was available in 15,855 patients, and when evaluated as a continuous variable (5 bpm increase) and following adjustment using multivariate Cox regression, it

* Corresponding authors. University Road, Galway, H91 TK33, Ireland.
  E-mail address: patrick.w.j.c.serruys@gmail.com (P.W. Serruys).

significantly correlated with the primary endpoint (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.03–1.09, $p < 0.001$). Using dichotomous cut-off criteria, a PHR > 67 bpm was associated with increased all-cause mortality (HR 1.38, 95%CI 1.13–1.69, $p = 0.002$) and more frequent new Q-wave MI (HR 1.41, 95%CI 1.02–1.93, $p = 0.037$). No significant association was found between PHR and BARC 3 or 5 bleeding (HR 1.04, 95% CI 0.99–1.09, $p = 0.099$). There was no interaction with the primary (p-inter = 0.236) or secondary endpoint (p-inter = 0.154) when high and low PHR was analyzed according to different antiplatelet strategies.
Conclusions: Elevated PHR was an independent predictor of all-cause mortality at 2 years following PCI in the "all-comer" GLOBAL LEADERS trial. The prognostic value of increased PHR on outcomes was not affected by the different antiplatelet strategies in this trial.

1. Introduction

Previous studies have demonstrated that resting heart rate is a risk factor for mortality in patients with coronary artery disease (CAD) [1–3], heart failure [4,5] and even in the general population [6,7]. Given the association between heart rate and subsequent higher rates of adverse outcomes, the need to identify the relationship between heart rate and CAD patients in the modern era of primary percutaneous coronary intervention (PCI), is of interest. The few studies that have examined the association of heart rate and clinical outcomes following PCI have mainly focused on patients with acute coronary syndrome (ACS) [8,9]. The prognostic impact of heart rate on outcomes in a wide spectrum of CAD patients who underwent PCI has not yet been fully investigated. In addition, whilst O'Brien et al. identified that pre-procedure heart rate (PHR) is an independent predictor of adverse outcomes in a registry of patients undergoing PCI, this was only for short-term (30-day) outcomes [10]. Consequently, whether an elevated PHR is related to an increased risk of adverse outcomes after PCI in a wide spectrum of CAD patients (including patients with stable CAD or ACS) during medium-term follow-up remains unknown. Therefore, in this study, we aimed to evaluate the impact of PHR on 2-year clinical outcomes following PCI in the prospective, contemporary "all-comer" GLOBAL LEADERS trial.

2. Patients and methods

The design of the GLOBAL LEADERS trial has been reported previously elsewhere [11]. Briefly, patients were randomized before PCI to the experimental strategy of 23-month ticagrelor monotherapy (after 1-month of ticagrelor and aspirin), *versus* the reference strategy of 12-month dual antiplatelet treatment (aspirin and either ticagrelor for ACS or clopidogrel for stable CAD) followed by 12 months of aspirin monotherapy. The trial was conducted at 130 hospitals in 18 countries with a total of 15,991 patients in an "all-comer" design [12]. Of those, 15,855 participants were included in the present analysis (23 withdrew consent and requested the deletion of their data from the database; 85 did not undergo PCI and were treated with medical therapy alone or urgent coronary artery bypass grafting [CABG]; 28 were excluded due to missing data on heart rate; Supplementary Fig. S1).

The primary endpoint was composite endpoint of all-cause death or new Q-wave myocardial infarction (MI) at 2 years. Deaths from any cause were ascertained without adjudication. Q-wave MI was defined in compliance with the Minnesota classification (new major Q wave abnormalities) or by the appearance of a new left bundle branch block in conjunction with symptoms, abnormal cardiac biomarkers, or loss of myocardial viability. Electrocardiogram (ECG) was examined at discharge, 3-month and 2-year follow up and when ischemic events were suspected or if repeat revascularization was performed. All ECGs were adjudicated at the core laboratory with the Minnesota classification (Cardialysis, Rotterdam, Netherlands) by analysts and physicians who were blinded to the treatment allocation [13,14]. The key secondary safety endpoint was site-reported bleeding assessed according to the BARC criteria (type 3 or 5) [15]. Time to first event was used for the analysis. PHR was obtained in the 24 h prior to PCI. All patients data were prospectively collected in the trial. The trial was approved by the institutional review board or ethics committee at each center and followed the ethical principles of the Declaration of Helsinki. All the patients signed written informed consent prior to participation in the trial.

Continuous data are presented as mean ± standard deviation or medians and 25th and 75th percentiles as appropriate. Categorical data are expressed as frequencies and percentages. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared with the χ^2 test. The relationship between PHR, as either a continuous or categorical variable, and adverse outcomes was evaluated by multivariable Cox proportional hazards regression models. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcomes were entered into the multivariate Cox proportional hazards regression model. Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final model. Three models were fitted for the current analysis: model 1 was adjusted for age and gender; model 2 for conventional risk factors including hypertension, systolic and diastolic blood pressure, diabetes, hypercholesterolemia, impaired renal function, body-mass index (BMI), chronic obstructive pulmonary diseases (COPD), peripheral vascular disease (PVD), left ventricular ejection fraction (LVEF); and model 3 was corrected for age, gender, conventional risk factors and previous medical history including previous stroke, MI, CABG and major bleeding, which were all associated with the primary endpoint with a p value < 0.1 in the univariate analysis. Elevated PHR was analyzed as a continuous variable in primary analyses, and then as a categorical variable using the cut-off value of 67 bpm, which was derived from the maximally selected rank statistics analysis (Supplementary Fig. S2). We performed an adjusted cubic spline model to show the relationship between PHR, as a continuous covariate, and adverse outcomes using 60 bpm as the reference. Events rates were plotted in Kaplan-Meier curves for all-cause death, and BARC 3 or 5 bleeding according to heart rate tertiles (< 64 bpm, 64–73 bpm, > 73 bpm), and the log-rank test was used for comparisons among groups. In addition, interaction testing on outcomes between PHR and antiplatelet strategy was assessed in the Cox regression model using PHR as a dichotomous variable. All tests were 2-sided, and a p value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA).

3. Results

A total of 15,855 patients with available PHR were analyzed. The median age was 65 [57–72] years, and 76.7% were men. The distribution of PHR in the overall study population is shown in Supplementary Fig. S3; the median PHR was 69 [60–76] bpm. Baseline characteristics according to the cut-off PHR of 67 bpm are reported in Table 1. Compared to patients with a PHR ≤ 67 bpm, patients with PHR > 67 bpm were more likely to be female, younger, current smokers, with higher BMI, and higher rates of diabetes, hypertension, COPD, ACS, previous stroke, MI, PCI or CABG and a lower LVEF. They were less likely to have hypercholesterolemia. No significant differences were found between the two groups (high PHR *vs* low PHR) in rates of PVD, impaired renal function and previous major bleeding.

The clinical outcomes are presented in Table 2. At 2-year follow-up, the primary endpoint (consisting of all-cause death or new Q-wave MI)

Table 1
Baseline characteristics of patients.

	≤67 bpm (N = 7363)	> 67 bpm (N = 8492)	p-value
Age, years	65 [58–73]	64 [57–72]	< 0.001
BMI	27.4 [24.9–30.2]	27.8 [25.2–31.1]	< 0.001
Male	79.2 (5829/7363)	74.6 (6336/8492)	< 0.001
Female	20.8 (1534/7363)	25.4 (2156/8492)	< 0.001
DM	21.5 (1585/7359)	28.6 (2427/8485)	< 0.001
Insulin-dependent DM	6.2 (457/7346)	9.0 (759/8462)	< 0.001
Hypertension	72.4 (5313/7335)	74.7 (6327/8466)	0.001
Systolic blood pressure	135 [120–150]	137 [122–150]	< 0.001
Diastolic blood pressure	75 [68–81]	80 [70–87]	< 0.001
Hypercholesterolaemia	70.9 (5096/7189)	68.6 (5599/8164)	0.002
Current smoker	24.3 (1790/7363)	27.8 (2358/8492)	< 0.001
PVD	6.4 (464/7288)	6.3 (530/8422)	0.850
COPD	4.5 (328/7331)	5.7 (484/8453)	< 0.001
Previous major bleeding	0.6 (45/7355)	0.6 (53/8479)	0.916
Impaired renal function[a]	13.2 (965/7319)	14.1 (1192/8452)	0.094
Previous stroke	2.1 (155/7352)	3.1 (263/8480)	< 0.001
Previous MI	25.1 (1841/7342)	21.8 (1845/8469)	< 0.001
Previous PCI	36.0 (2646/7357)	29.9 (2538/8484)	< 0.001
Previous CABG	6.9 (507/7358)	5.1 (430/8484)	< 0.001
Stable CAD	56.7 (4178/7363)	49.8 (4228/8492)	< 0.001
ACS	43.3 (3185/7363)	50.2 (4264/8492)	< 0.001
Unstable angina	12.9 (950/7363)	12.5 (1058/8492)	
Non-STEMI	20.5 (1508/7363)	21.8 (1849/8492)	
STEMI	9.9 (727/7363)	16.0 (1357/8492)	
LVEF	55 [50–62]	55 [50–60]	< 0.001

Data are % (n/N), unless otherwise specified.
BMI: body-mass index, DM: diabetes mellitus, PVD: peripheral vascular disease, COPD: chronic obstructive pulmonary disease, myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CAD: coronary artery disease, ACS: acute coronary syndrome, STEMI: ST elevation myocardial infarction, LVEF: left ventricular ejection fraction.

[a] Defined as an estimated glomerular filtration rate of creatinine clearance of < 60 mL/min per 1.73 m^2 based on the Modification of Diet in Renal Disease formula.

occurred in 648 (4.09%) patients in the overall population, 244 (3.31%) patients in the group with PHR ≤ 67 bpm, and 404 (4.76%) patients in the group with PHR > 67 bpm (adjusted HR for PHR > 67 bpm *vs* PHR ≤ 67 bpm: 1.38, 95% CI [1.17–1.64]). The secondary endpoint (BARC 3 or 5 bleeding) was observed in 331 (2.09%) patients in the overall population, 147 (2.00%) patients in the group with PHR ≤ 67 bpm and 184 (2.17%) patients in the group with PHR > 67 bpm (adjusted HR for PHR > 67 bpm *vs* PHR ≤ 67 bpm: 1.06, 95% CI [0.84–1.34]).

Kaplan-Meier curves for all-cause mortality and BARC 3 or 5 bleeding up to 2 years according to heart rate tertiles are shown in Fig. 1. Patients in the group with a PHR > 73 bpm had significant higher rates for all-cause mortality (3.70% *vs* 2.47%, *p* = 0.0005) compared with the lowest tertile with a PHR < 64 bpm. On the contrary, bleeding event rates among groups were comparable. A multivariable analysis was conducted to evaluate the impact of PHR on clinical outcomes. Three models were fitted for analysis as described earlier. The association between clinical outcomes and increased PHR using the 3 multivariable Cox proportional hazards models is shown in Table 3. In model 3, when using PHR as a continuous variable, each 5 bpm increase in PHR resulted in a significant 6% increased risk of the primary endpoint, which was mainly driven by the increased risk of the all-cause mortality (HR 1.07, 95% CI 1.03–1.11, *p* < 0.001). Increased PHR represented a higher cardiovascular death (HR 1.10, 95% CI 1.04–1.15, *p* < 0.001). As a continuous covariate, increases in PHR did not have any significant relationship with new Q-wave MI or the secondary endpoints. The adjusted cubic spline model was performed to investigate the relationship between continuous PHR and outcomes. Fig. 2 shows that increases in PHR were associated with a higher risk of all-cause mortality in a J shaped distribution.

Table 2
Two-year outcomes in the overall population and 2 groups divided by 67 bpm.

Outcomes	≤67 bpm % (n/N)	> 67 bpm % (n/N)	Total events % (n/N)	Unadjusted HR > 67 bpm *vs* ≤ 67 bpm	Adjusted HR > 67 bpm *vs* ≤ 67 bpm
All-cause mortality or new Q-wave MI	3.31 (244/7363)	4.76 (404/8492)	4.09 (648/15855)	1.45 (1.24–1.70)	1.38 (1.17–1.64)
All-cause mortality	2.38 (175/7363)	3.50 (297/8492)	2.98 (472/15855)	1.48 (1.23–1.79)	1.38 (1.13–1.69)
Cardiovascular death	0.96% (71/7363)	1.84% (156/8492)	1.43% (227/15855)	1.92 (1.45–2.54)	1.64 (1.21–2.21)
New Q-wave MI	0.98 (72/7363)	1.34 (114/8492)	1.17 (186/15855)	1.39 (1.03–1.86)	1.41 (1.02–1.93)
BARC 3 or 5 bleeding	2.00 (147/7363)	2.17 (184/8492)	2.09 (331/15855)	1.10 (0.88–1.36)	1.06 (0.84–1.34)
BARC 5 bleeding	0.27 (20/7363)	0.31 (26/8492)	0.29 (46/15855)	1.14 (0.63–2.03)	1.03 (0.55–1.93)
BARC 3 bleeding	1.83 (135/7363)	2.04 (173/8492)	1.94 (308/15855)	1.12 (0.90–1.41)	1.09 (0.85–1.38)

Adjusted for age, gender, hypertension, systolic and diastolic blood pressure, diabetes, hypercholesterolemia, impaired renal function, BMI, COPD, PVD, LVEF and previous stroke, MI, CABG or major bleeding.
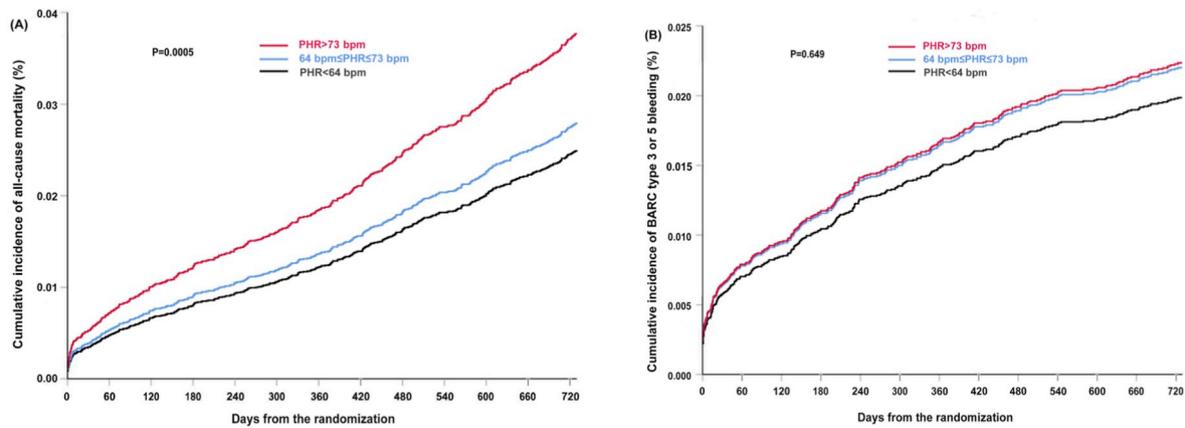MI: myocardial infarction.

Fig. 1. Kaplan–Meier time-to-event plots for clinical outcome at 2-year follow-up for PHR in tertiles.
(A) All-cause mortality, (B) BARC 3 or 5 bleeding. PHR: pre-procedure heart rate.

Table 3
Clinical outcomes and heart rate as continuous and binary variable.

Outcomes	Model 1		Model 2		Model 3	
	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
All-cause mortality or new Q-wave MI						
PHR > 67 bpm *vs* PHR ≤ 67 bpm	1.52 (1.29–1.78)	< 0.001	1.33 (1.13–1.58)	0.001	1.38 (1.17–1.64)	< 0.001
PHR higher by 5 bpm	1.08 (1.05–1.11)	< 0.001	1.05 (1.02–1.08)	0.003	1.06 (1.03–1.09)	< 0.001
All-cause mortality						
PHR > 67 bpm *vs* PHR ≤ 67 bpm	1.56 (1.30–1.89)	< 0.001	1.34 (1.10–1.63)	0.004	1.38 (1.13–1.69)	0.002
PHR higher by 5 bpm	1.10 (1.06–1.14)	< 0.001	1.06 (1.02–1.10)	0.002	1.07 (1.03–1.11)	< 0.001
Cardiovascular death						
PHR > 67 bpm *vs* PHR ≤ 67 bpm	2.00 (1.51–2.64)	< 0.001	1.64 (1.21–2.21)	0.001	1.64 (1.21–2.21)	0.001
PHR higher by 5 bpm	1.14 (1.09–1.19)	< 0.001	1.09 (1.04–1.15)	< 0.001	1.10 (1.04–1.15)	< 0.001
New Q-wave MI						
PHR > 67 bpm *vs* PHR ≤ 67 bpm	1.42 (1.05–1.90)	0.021	1.34 (0.98–1.83)	0.068	1.41 (1.02–1.93)	0.037
PHR higher by 5 bpm	1.03 (0.98–1.09)	0.247	1.03 (0.97–1.09)	0.387	1.04 (0.98–1.10)	0.252
BARC 3 or 5 bleeding						
PHR > 67 bpm *vs* PHR ≤ 67 bpm	1.13 (0.91–1.40)	0.277	1.04 (0.83–1.31)	0.741	1.06 (0.84–1.34)	0.611
PHR higher by 5 bpm	1.05 (1.01–1.10)	0.018	1.03 (0.99–1.08)	0.156	1.04 (0.99–1.09)	0.099
BARC 5 bleeding						
PHR > 67 bpm *vs* PHR ≤ 67 bpm	1.16 (0.64–2.08)	0.627	0.97 (0.52–1.80)	0.917	1.03 (0.55–1.93)	0.924
PHR higher by 5 bpm	1.05 (0.94–1.18)	0.349	1.01 (0.89–1.14)	0.925	1.02 (0.90–1.16)	0.717
BARC 3 bleeding						
PHR > 67 bpm *vs* PHR ≤ 67 bpm	1.15 (0.92–1.44)	0.218	1.06 (0.84–1.35)	0.623	1.09 (0.85–1.38)	0.505
PHR higher by 5 bpm	1.05 (1.01–1.10)	0.018	1.03 (0.99–1.08)	0.148	1.04 (0.99–1.09)	0.094

Model 1 was adjusted for age and gender.
Model 2 was adjusted for hypertension, systolic and diastolic blood pressure, diabetes, hypercholesterolemia, impaired renal function, BMI, COPD, PVD and LVEF.
Model 3 was adjusted for age, gender, hypertension, systolic and diastolic blood pressure, diabetes, hypercholesterolemia, impaired renal function, BMI, COPD, PVD, LVEF and previous stroke, MI, CABG or major bleeding.
MI: myocardial infarction, PHR: pre-procedure heart rate.

When PHR was analyzed as a dichotomous variable, the hazard ratios for patients with PHR > 67 bpm *vs.* PHR ≤ 67 group were 1.38 (95% CI 1.17–1.64, *p* < 0.001) for the primary endpoint, 1.38 (95% CI 1.13–1.69, *p* = 0.002) for all-cause mortality, 1.64 (95% CI 1.21–2.21, *p* = 0.001) for cardiovascular death and 1.41 (95% CI 1.02–1.93, *p* = 0.037) for new Q-wave MI. On the contrary, no significant difference was observed in BARC 3 or 5 bleeding events rates between the two groups. The interaction term between antiplatelet strategy and PHR was negative for the primary and secondary endpoint (*p*-inter = 0.236, *p*-inter = 0.154, respectively, Supplementary Table S1). Furthermore, the clinical presentation of ACS or stable CAD did not interact with the prognostic role of PHR on the primary (*p*-inter = 0.528) or secondary endpoint (*p*-inter = 0.164). Similarly, the presence or absence of diabetes or impaired renal function did not change the impact of PHR on the primary (*p*-inter = 0.129 and *p*-inter = 0.942 for diabetes and impaired renal function, respectively) or secondary endpoint (*p*-inter = 0.823 and *p*-inter = 0.773 for diabetes and impaired renal function, respectively) either.

4. Discussion

In a large size contemporary "all-comer" population with both stable CAD and ACS following PCI in GLOBAL LEADERS trial, we found: 1) elevated PHR is an independent predictor of all-cause mortality and cardiovascular death; 2) each increase of 5 bpm in PHR is associated with a significant 7% increased risk of for all-cause mortality; 3) PHR > 67 bpm was an independent predictor of all-cause mortality, cardiovascular death and new Q-wave MI; 4) no significant relationship exists between PHR and bleeding events; and 5) the prognostic value of increased PHR on outcomes was not affected by the two antiplatelet strategies.

Previous studies have demonstrated that heart rate was an independent predictor of adverse outcomes in various populations, including patients with hypertension, CAD, left ventricular dysfunction and even in general populations [1–7,16,17]. However, there are very few prospective studies that have evaluated the relationship between heart rate and adverse outcomes in the full spectrum of CAD patients
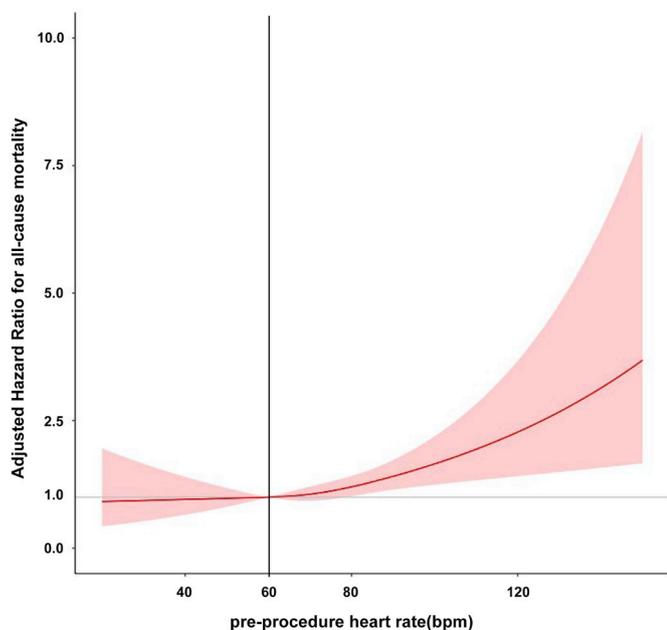
Fig. 2. Association of PHR and all-cause mortality in an adjusted cubic spline model.

The adjusted cubic spline model shows the relationship between PHR and all-cause mortality, when taking 60 bpm as the reference. Adjusted for age, gender, hypertension, systolic and diastolic blood pressure, diabetes, hypercholesterolemia, impaired renal function, BMI, COPD, PVD, LVEF and previous stroke, MI, CABG or major bleeding.

undergoing PCI [18]. Pre-procedure heart rate has recently been shown by O'Brien et al. [10] to be an independent predictor of adverse 30-day cardiovascular outcomes in 3720 patients after PCI. However, whilst higher PHR was not an independent predictor of 30-day mortality, it was a predictor of 30-day MACE (death, MI and target vessel revascularization [TVR]) when PHR was analyzed in quintiles, suggesting that a sample size of 3720 patients may not be significantly powered for a single event such as all-cause death. Therefore, in the present large size study, we also examined the relationship between PHR and outcome at 30-days, as well as in a prespecified 30 days landmark analysis up to 2-years. No association with 30-day primary or secondary endpoints was seen when using PHR as a dichotomous variable even after adjustment. However, as a continuous variable, each 5 bpm increase in PHR was associated with a significant 14% increased risk of all-cause mortality at 30 days (Supplementary Table S2 and Table S3). This difference may be due to the relatively small number of deaths at 30-day follow-up (only 0.26% [19/7363] deaths in the PHR ≤ 67 bpm group and 0.57% [48/8492] deaths in the PHR > 67 bpm group), suggesting that analysis of PHR as a continuous value would be more powerful than by a categorical approach. Further studies, especially in a high risk population, are still needed to investigate the prognostic role of heart rate on short term outcomes.

More recently, a single-center retrospective cohort study indicated that PHR is an independent predictor of adverse outcomes at 10-year follow-up in 6049 CAD patients who underwent PCI. High PHR was associated with an increased risk of all-cause mortality, but had no relationship with bleeding events [19]. Our analysis confirmed these findings in a multicenter, much larger size CAD population. To our knowledge, this is the first time that the relationship between heart rate and adverse outcomes has been investigated in a larger, multicenter, prospective, contemporary, all-comers PCI trial. Supplementary Table S4 shows the characteristics and results of the present study and previous ones [10,18,19].

Heart rate is an easily measured and readily available clinical sign. However, to date there is no defined threshold heart rate for

consideration of preventive treatment in contemporary CAD patients undergoing PCI. In the current study, our observations suggest a threshold of 67 bpm, as a poor prognosis was observed when PHR was higher than 67 bpm. Most previous studies chose their cut-off values arbitrarily (or according to previous studies); however, we used maximally selected rank statistics analysis to establish a cut-off which would be the most specific and sensitive in assessing the relationship between heart rate and outcomes, although the C statistic and Youden's index were very low (C statistic = 0.56, Youden's index: 0.097). In contrast to other methodological approaches, maximally selected rank statistics to find the optimal cut-off value is statistically suitable for survival analysis [20]. The threshold heart rate in our analysis is slightly lower than in previous studies [3,8,9,19], which may be a consequence of the heterogenous study cohorts enrolled. Further studies are needed to define a critical threshold beyond which therapeutic prospective intervention (e.g. pharmacological therapy) might be recommended to reduce the frequency of adverse outcomes.

Since the higher heart rate predicts worse clinical outcomes, heart rate-lowering medications, particularly beta-blockers, have been associated with the prevention of angina and reduction of myocardial ischemia [3]. Accordingly, the predictive impact of heart rate on adverse outcomes may be influenced by the use of beta-blocker. However, several studies demonstrated the impact of heart rate on outcomes were not affected by beta-blocker use [1,9,18,19], suggesting heart rate predicts the adverse outcomes independently. In our trial, beta-blocker use was not recorded at baseline before PCI, however, after adjustment for the use of beta-blocker, ACE inhibitor, angiotensin receptor blocker, and statin at discharge, heart rate still was an independent risk factor to the primary and secondary endpoint.

The mechanisms explaining the deleterious effects of increased heart rate is likely to be multifactorial. An imbalance between oxygen demand and supply could contribute to myocardial ischemia. An elevated heart rate leads to an increase myocardial oxygen consumption and also reduces the diastolic time, resulting in reduced coronary blood flow, and therefore to lower oxygen supply [21]. Increased heart rate impairs endothelial function in animal models and may contribute to reduced shear stress and vascular compliance [22]. Heart rate was also associated with calcification of left-sided heart valves, which has been associated with increased risk of cardiovascular disease mortality [23]. Increased inflammation has been thought to play an important role in the development, progression, and disruption of atherosclerotic plaques [24]. Whelton et al. [25] reported that an increased resting heart rate was associated with a higher level of inflammation, and the effects of this on cardiovascular mortality appear to be strongly amplified by a faster resting heart rate [26]. Plaque disruption is the central pathophysiological mechanism underlying ACS and the progression of coronary atherosclerosis. Heidland et al. reported positive associations between plaque disruption and a mean heart rate > 80 bpm and a negative association with the use of beta -blockers. These findings may help identify patients who are at a high risk of plaque disruption and who may benefit from medical interventions aimed at reducing heart rate [27].

Our analysis has several strengths, which include a large sample size, a wide spectrum of CAD clinical presentation and a relatively long follow-up. There are also some limitations. First, the present study is a *post hoc* analysis, and should be considered hypothesis-generating. Second, in the GLOBAL LEADERS trial there was no detailed information on heart rhythm, therefore, we could not exclude atrial fibrillation (AF) as a cause of high heart rate, however, patients who needed anticoagulation were excluded. More importantly, prior studies reported that the prognostic impact of high heart rate on outcomes was not specifically documented in AF [28,29]. Finally, given the large population and relative large event number, we adjusted the multiple Cox proportional-hazard regression models for all available and clinical relevant confounders, even though, not all confounders may have been identified.

In conclusion, elevated PHR was an independent predictor of all-cause mortality and cardiovascular death at 2 years following PCI in a contemporary "all-comer" trial. The prognostic value of increased PHR on outcomes was not affected by the randomized allocation to the experimental or reference antiplatelet therapy. Further studies are warranted to define a critical threshold heart rate for targeted intervention in contemporary CAD patients following PCI.

Financial support

CRediT authorship contribution statement

Rutao Wang: Writing - original draft, Formal analysis, Data curation. **Kuniaki Takahashi:** Writing - original draft, Formal analysis, Data curation. **Ply Chichareon:** Data curation, Writing - review & editing. **Chao Gao:** Data curation, Writing - review & editing. **Norihiro Kogame:** Data curation, Writing - review & editing. **Rodrigo Modolo:** Data curation, Writing - review & editing. **Mariusz Tomaniak:** Data curation, Writing - review & editing. **Hideyuki Kawashima:** Data curation, Writing - review & editing. **Masafumi Ono:** Data curation, Writing - review & editing. **Hironori Hara:** Data curation, Writing - review & editing. **Volker Schächinger:** Data curation, Writing - review & editing. **Gincho Tonev:** Data curation, Writing - review & editing. **Imre Ungi:** Data curation, Writing - review & editing. **Eric Eeckhout:** Data curation, Writing - review & editing. **Christian Hamm:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Peter Jüni:** Conceptualization, Methodology, Writing - review & editing, Supervision, Formal analysis. **Pascal Vranckx:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Stephan Windecker:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Scot Garg:** Writing - review & editing. **Robert Jan Van Geuns:** Conceptualization, Methodology, Writing - review & editing, Supervision, Data curation, Writing - review & editing. **Yoshinobu Onuma:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Patrick W. Serruys:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of competing interest

Dr. Chichareon reports research grant from Biosensors, outside the submitted work. Dr. Modolo received research grant form Biosensors and SMT. Dr. Eeckhout reports research grant from Biosensors. Dr. Hamm received advisory board fees from AstraZeneca. Dr. Jüni received 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. Dr. Vranckx received personal fees from Astra Zeneca, personal fees from Bayer Health Care, personal fees from Daiichi Sankio, personal fees from Terumo, personal fees from CLS Behring, outside the submitted work. Dr. Windecker reports research and educational grants to the institution from Amgen, Abbott, Biotronik, Boston Scientific, Bayer, BMS, CSL Behring, Edwards Lifesciences, Medtronic, Polares and Sinomed. Dr. van Geuns received speakers fee from Abbott Vascular and Boston Scientific. Dr. Serruys reports personal fees from Biosensors, personal fees from Cardialysis, personal fees from Medtronic, personal fees from Micel Technologies, personal fees from Sinomedical Sciences Technology, personal fees from Philips/Volcano, personal fees from Xeltis, personal fees from HeartFlow, outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2020.04.010.

References

[1] A. Diaz, M.G. Bourassa, M.C. Guertin, et al., Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease, Eur. Heart J. 26 (2005) 967–974.

[2] M.T. Jensen, M. Pereira, C. Araujo, et al., Heart rate at admission is a predictor of in-hospital mortality in patients with acute coronary syndromes: results from 58 European hospitals: the European Hospital Benchmarking by Outcomes in acute coronary syndrome Processes study, Eur. Heart J. Acute Cardiovasc. Care 7 (2018) 149–157.

[3] Kim Fox, Ian Ford, P. Gabriel Steg, et al., Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial, Lancet 372 (2008) 817–821.

[4] Michael Böhm, Swedberg Karl, Michel Komajda, et al., Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial, Lancet 376 (2010) 886–894.

[5] D. Castagno, H. Skali, M. Takeuchi, et al., Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: assessment of Reduction in Mortality and morbidity) program, J. Am. Coll. Cardiol. 59 (2012) 1785–1795.

[6] C. Kannel, W.B. Kannel, R.S.J.R. Paff enbarger, L.A. Cupples, Heart rate and cardiovascular mortality the farmingham study, Am. Heart J. 113 (1987) 1489–1494.

[7] A. Vazir, B. Claggett, S. Cheng, et al., Association of resting heart rate and temporal changes in heart rate with outcomes in participants of the atherosclerosis risk in communities study, JAMA Cardiol. 3 (2018) 200–206.

[8] G. Parodi, B. Bellandi, R. Valenti, et al., Heart rate as an independent prognostic risk factor in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention, Atherosclerosis 211 (2010) 255–259.

[9] M.L. Antoni, H. Boden, V. Delgado, et al., Relationship between discharge heart rate and mortality in patients after acute myocardial infarction treated with primary percutaneous coronary intervention, Eur. Heart J. 33 (2012) 96–102.

[10] J. O'Brien, C.M. Reid, N. Andrianopoulos, et al., Heart rate as a predictor of outcome following percutaneous coronary intervention, Am. J. Cardiol. 122 (2018) 1113–1120.

[11] P. Vranckx, M. Valgimigli, S. Windecker, 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 12 (2016) 1239–1245.

[12] Vranckx Pascal, Marco Valgimigli, Jüni Peter, 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 392 (2018) 940–949.

[13] P.W. Serruys, K. Takahashi, P. Chichareon, et al., Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial, Eur. Heart J. 40 (2019) 2595–2604.

[14] P.W. Serruys, M. Tomaniak, P. Chichareon, 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.

[15] R. Mehran, S.V. Rao, D.L. Bhatt, et al., Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium, Circulation 123 (2011) 2736–2747.

[16] P. Palatini, Role of elevated heart rate in the development of cardiovascular disease in hypertension, Hypertension 58 (2011) 745–750.

[17] A. Wang, X. Liu, X. Guo, et al., Resting heart rate and risk of hypertension: results of the Kailuan cohort study, J. Hypertens. 32 (2014) 1600–1605 discussion 1605.

[18] M.T. Jensen, C. Kaiser, K.E. Sandsten, et al., Heart rate at discharge and long-term prognosis following percutaneous coronary intervention in stable and acute coronary syndromes–results from the BASKET PROVE trial, Int. J. Cardiol. 168 (2013) 3802–3806.

[19] Y.Y. Zheng, T.T. Wu, Y. Chen, et al., Resting heart rate and long-term outcomes in patients with percutaneous coronary intervention: results from a 10-year follow-up of the CORFCHD-PCI study, Cardiol. Res. Pract. 2019 (2019) 5432076.

[20] Torsten Hothorn, Berthold Lausen, On the exact distribution of maximally selected rank statistics, Comput. Stat. Data Anal. 43 (2003) 121–137.

[21] C.C. Lang, S. Gupta, P. Kalra, et al., Elevated heart rate and cardiovascular outcomes in patients with coronary artery disease: clinical evidence and pathophysiological mechanisms, Atherosclerosis 212 (2010) 1–8.

[22] F. Custodis, S.H. Schirmer, M. Baumhakel, et al., Vascular pathophysiology in response to increased heart rate, J. Am. Coll. Cardiol. 56 (2010) 1973–1983.

[23] K. Amoakwa, O.E. Fashanu, M. Tibuakuu, et al., Resting heart rate and the incidence and progression of valvular calcium: the Multi-Ethnic Study of Atherosclerosis (MESA), Atherosclerosis 273 (2018) 45–52.

[24] P. Libby, Inflammation in atherosclerosis, Nature 420 (2002) 868–874.

[25] S.P. Whelton, V. Narla, M.J. Blaha, et al., Association between resting heart rate and inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin-6, and fibrinogen) (from the Multi-Ethnic Study of Atherosclerosis), Am. J. Cardiol. 113 (2014) 644–649.

[26] O. Hartaigh B, J.A. Bosch, D. Carroll, et al., Evidence of a synergistic association between heart rate, inflammation, and cardiovascular mortality in patients undergoing coronary angiography, Eur. Heart J. 34 (2013) 932–941.

[27] U.E. Strauer BE Heidland, Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption, Circulation 104 (2001) 1477–1482.

[28] A.L. Bui, M.V. Grau-Sepulveda, A.F. Hernandez, et al., Admission heart rate and in-hospital outcomes in patients hospitalized for heart failure in sinus rhythm and in atrial fibrillation, Am. Heart J. 165 (2013) 567–574 e566.

[29] B.A. Steinberg, S. Kim, L. Thomas, et al., Increased heart rate is associated with higher mortality in patients with atrial fibrillation (AF): results from the outcomes registry for better informed treatment of AF (ORBIT-AF), J. Am. Heart Assoc. 4 (2015) e002031.