Association Between Hypertension, Platelet Reactivity, and the Risk of Adverse Events After Percutaneous Coronary Intervention (From the ADAPT-DES Study)

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Hypertension is associated with vascular and endothelial dysfunction that may result in a greater propensity for reactive platelets to cause thrombosis. We sought to assess whether the risk of major adverse cardiac events (MACE) after percutaneous coronary intervention (PCI) in patients with on-clopidogrel residual high platelet reactivity (HPR) varies in patients with versus without hypertension. Assessment of dual antiplatelet therapy with drug eluting stents (ADAPT-DES) was a prospective, multicenter registry of patients successfully treated with coronary drug-eluting stents (DES). HPR was defined as P2Y12 reaction units (PRU) >208, as assessed by the VerifyNow point-of-care assay. Multivariable Cox proportional hazards regression was used to assess whether the adjusted association between HPR and 2-year risk of MACE (cardiac death, myocardial infarction [MI], or stent thrombosis) was different in patients with versus without hypertension. A total of 6833 of 8582 patients (79.6%) had a history of hypertension. Patients with compared with those without hypertension were older, more likely to have other cardiovascular risk factors, and had higher PRU (190.1 ± 97.3 vs 179.5 ± 94.3; p <0.0001). Patients with hypertension had significantly higher 2-year rates of MACE (7.0% vs 4.4%, p <0.001), all-cause death (4.2% vs 2.5%, p = 0.001), and MI (5.2% vs 3.2%, p <0.001), and had nominally higher rates of stent thrombosis (1.0% vs 0.5%, p = 0.059). A significant interaction was present between hypertension and HPR regarding 2-year MACE risk (adjusted hazard ratio for HPR vs no HPR 1.38, 95% confidence interval 1.14 to 1.68 for patients with hypertension vs 0.81, 95% confidence interval 0.50 to 1.33 for patients without hypertension, p = 0.046). In conclusion, following successful PCI with DES, 2-year MACE rates are increased in patients with both hypertension and residual HPR on clopidogrel. HPR had a greater effect on the risk of adverse events among patients with versus without hypertension. **(Am J Cardiol 2019;124:1380−1388)**

High platelet reactivity (HPR) among patients who have undergone percutaneous coronary intervention (PCI) and are being treated with dual antiplatelet therapy is independently associated with an increased risk of thrombotic events.[1,2] Coronary thrombosis requires platelet activation and adhesion to the coronary lumen,[3] and is influenced by blood rheology as well as circulating prothrombotic and antithrombotic molecules. Under normal conditions the

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endothelial cells that line the arterial lumen suppress platelet adhesion and activation, thereby reducing the risk of thrombosis.[4,5] Arterial hypertension is associated with endothelial dysfunction and impaired interactions between platelets and the endothelial lining of the arterial lumen.[6–8] Hypertension is also associated with altered blood rheology and a relative excess of circulating hemostatic versus fibrinolytic factors.[9] We therefore hypothesized that the association between HPR and thrombotic events is particularly strong among patients with hypertension. Herein we report the association between hypertension, platelet reactivity, and thrombotic events among the 8582 patients in the assessment of dual antiplatelet therapy with drug eluting stents (ADAPT-DES) study.

Methods

The design, protocol, and primary results of the ADAPT-DES study have been previously described in detail.[2] In brief, ADAPT-DES was a prospective, large-scale, international, multicenter study designed to determine the association between residual platelet reactivity and stent thrombosis (ST) following drug-eluting stent implantation in an all-comers patient population. Patients were excluded if a major adverse event occurred during PCI or before platelet function testing, and planned bypass surgery after PCI. All patients received aspirin and clopidogrel before PCI. Platelet function tests were performed after successful PCI with the VerifyNow aspirin, P2Y12, and IIb/IIIa assays (Accumetrics, San Diego, California). VerifyNow P2Y12 testing was performed ≥6 hours after a 600 mg clopidogrel loading dose, ≥12 hours after a 300 mg loading dose, or ≥5 days after a 75 mg loading dose. After PCI, aspirin was recommended indefinitely in all patients, and clopidogrel was recommended for at least 1 year. Clinical follow-up was completed at 30 days, 1 year, and 2 years. ST, myocardial infarction (MI), and death were adjudicated by a central events committee using original source documentation. The rate of lost-to-follow, withdrawal of consent or refusal of contact was 2.3% at 2 years. The study was approved by the institutional review board at each participating center, and all eligible patients signed written informed consent. The data, analytic methods, and study materials are proprietary to the sponsor and will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The principal objective of this ADAPT-DES substudy was to examine the relationship between hypertension, platelet reactivity, and major adverse cardiac events (MACE); and to assess whether the MACE risk associated with high residual platelet reactivity (HPR) is higher among patients with versus without hypertension.

Endpoint definitions used in the ADAPT-DES study have been previously described.[2,10] Patients were asked at baseline whether they had been diagnosed with hypertension which was treated with medications. MACE was defined as the composite of definite or probable ST, MI, or cardiac death. HPR was defined as P2Y12 reaction units (PRU) >208, as assessed by the VerifyNow point-of-care assay. Anemia was defined as baseline serum hemoglobin <12.0 mg/dL for women and <13.0 mg/dL for men. Chronic kidney disease was defined as an estimated baseline creatinine clearance <60 mL/min.

Descriptive statistics are presented as mean ± standard deviation or median (interquartile range) and were compared with the Student *t* test or the Mann-Whitney *U* test; categorical variables are reported as percentages and were compared between groups with the Chi-square test. The adjusted association between HPR and hypertension and antihypertensive medications was assessed by multivariable linear regression. Event rates during follow-up were estimated by the Kaplan-Meier method. Unadjusted and adjusted hazard ratios for 2-year outcomes were estimated using Cox proportional hazards models. The following covariable set was included in the multivariable model: age, sex, current smoker, diabetes mellitus, renal insufficiency, hyperlipidemia, previous coronary artery bypass grafting, previous percutaneous coronary intervention, anemia, acute coronary syndrome versus stable coronary artery disease as clinical presentation, second-generation versus first generation drug-eluting stents, target vessel location in the left anterior descending coronary artery, multivessel disease, coronary calcification, peripheral arterial disease, aspirin reaction units, and total stent length. Whether having versus not having hypertension moderated the effects of platelet reactivity or acute coronary syndromes (ACS) on MACE risk was assessed by including interaction terms between hypertension and the covariable of interest in the multivariable model. All tests were 2-sided, and p-values <0.05 were considered significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Among 8582 patients included in ADAPT-DES, 6833 (79.6%) had a history of hypertension, whereas 1749 patients (20.4%) did not. Compared with patients not having hypertension, patients with hypertension were more likely to have other cardiovascular risk factors (Table 1) and more extensive coronary artery disease (Table 2). Subjects with hypertension were more likely to use antiplatelet, statin, and antihypertensive drugs at baseline, but these differences were attenuated at discharge (Supplemental Table 1).

Patients with hypertension had, on average, higher PRU than patients without hypertension (190.1 ± 97.3 vs 179.5 ± 94.3; p <0.0001), but this difference was attenuated after multivariable adjustment (adjusted difference 0.97, 95% confidence interval −4.37 to 6.30, p = 0.72). The frequency of HPR, defined as PRU >208, was higher in the hypertension group (43.8% vs 38.6%; p <0.0001; Table 1).

Patients with hypertension had a significantly higher unadjusted risk of MACE as well as other adverse clinical outcomes at 2 years compared with those without hypertension (Figure 1, Supplemental Figure 1). There was a significant statistical interaction between having versus not having hypertension and HPR in the regards to 2-year MACE risk; with patients with both hypertension and HPR having disproportionally high risk (Figure 2; Table 3). This interaction was also present if PRU was modeled as a continuous variable rather than as HPR versus no HPR

Table 1
Baseline clinical characteristics

Variable	Hypertension		p Value
	Yes (n = 6833)	No (n = 1749)	
Age (years)	64.6 ± 10.6 (6833)	59.7 ± 11.1 (1749)	<0.0001
Women	26.9% (1835/6833)	22.3% (390/1749)	0.0001
Body mass index (kg/m^2)	29.8 ± 5.8 (6833)	28.2 ± 5.3 (1749)	<0.0001
Diabetes mellitus	36.6% (2499/6833)	16.2% (284/1749)	<0.0001
Insulin-treated	13.3% (912/6833)	4.9% (86/1749)	<0.0001
Prior peripheral arterial disease	11.5% (784/6833)	5.3% (92/1749)	<0.0001
Prior heart failure	9.1% (620/6833)	4.5% (79/1749)	<0.0001
Previous myocardial infarction	28.2% (1927/6833)	13.6% (237/1749)	<0.0001
Previous coronary artery bypass grafting	19.3% (1318/6833)	8.6% (150/1749)	<0.0001
Previous percutaneous coronary intervention	48.2% (3296/6833)	21.8% (382/1749)	<0.0001
Hyperlipidemia	81.8% (5592/6833)	45.1% (788/1749)	<0.0001
Current smoker	19.9% (1358/6833)	33.3% (582/1749)	<0.0001
Prior renal insufficiency	9.0% (612/6833)	2.7% (48/1749)	<0.0001
Prior dialysis	1.8% (124/6833)	0.8% (14/1749)	0.003
Clinical presentation			
Stable coronary artery disease	52.3% (3574/6833)	32.9% (575/1749)	<0.0001
Acute coronary syndromes	47.7% (3259/6833)	67.1% (1174/1749)	<0.0001
Unstable angina pectoris	28.6% (1955/6833)	23.7% (415/1749)	<0.0001
Non-STEMI	13.1% (892/6833)	20.4% (357/1749)	<0.0001
STEMI	6.0% (412/6833)	23.0% (402/1749)	<0.0001
Number of coronary arteries narrowed			
1	35.5% (2423/6833)	49.2% (860/1749)	<0.0001
2	33.5% (2291/6833)	31.1% (544/1749)	0.054
3	31.0% (2119/6833)	19.7% (345/1749)	<0.0001
Left main >50% stenosis	3.3% (226/6833)	1.8% (31/1749)	0.0008
Ejection fraction (%)	55.1 ± 12.5 (5190)	54.3 ± 12.0 (1491)	0.044
Hemoglobin (g/dL)	13.9 ± 1.5 (6813)	14.4 ± 1.5 (1735)	<0.0001
Creatinine clearance (mL/min)*	92.5 ± 38.2 (6806)	100.4 ± 33.4 (1737)	<0.0001
White blood cells (10^9/L)	7.8 ± 3.2 (6793)	8.5 ± 3.1 (1724)	<0.0001
Platelet count (10^9/L)	225.2 ± 62.6 (6806)	232.9 ± 64.6 (1729)	<0.0001
Platelet reactivity			
P2Y12 reaction units (PRU)	190.1 ± 97.3 (6726)	179.5 ± 94.3 (1722)	<0.0001
High on-clopidogrel platelet reactivity (PRU >208)	43.8% (2945/6726)	38.6% (664/1722)	<0.0001
Aspirin reaction units (ARU)	419.8 ± 55.8 (6793)	416.9 ± 53.3 (1733)	0.04
High ARU (ARU ≥550)	5.8% (396/6793)	4.7% (82/1733)	0.08
Dual resistance (ARU ≥550 and PRU >208)	2.7% (179/6694)	2.0% (34/1707)	0.11

Values are % (n/N) or mean ± standard deviation. STEMI = non−ST-segment elevation myocardial infarction.
* Calculated by the Cockcroft-Gault formula.

($p_{interaction} = 0.026$). Patients with hypertension and HPR also had the highest risk of MI (Figure 3A and Table 3). No statistical interaction was present between having versus not having hypertension and HPR in regard to 2-year risk of clinically relevant bleeding (Table 3; Figure 3C).

The adjusted association between the use of antihypertensive medications at baseline and HPR is presented in the Supplemental Table 2. Among patients with hypertension there was no statistical interaction in regard to 2-year MACE risk between HPR and the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers ($p_{interaction} = 0.99$), β blockers ($p_{interaction} = 0.36$), calcium channel blockers ($p_{interaction} = 0.53$), or diuretics ($p_{interaction} = 0.61$).

There was also a significant interaction between having versus not having hypertension and clinical presentation with ACS versus stable coronary artery disease in regard to 2-year MACE risk, with patients with hypertension and ACS having disproportionally high risk (Figure 4). Patients with hypertension and ACS also had disproportionally high rates of MI and ST (Supplemental Figure 2A and 2B), whereas there was no apparent interaction between clinical presentation and having versus not having hypertension in regard to bleeding risk (adjusted $p_{interaction} = 0.82$; Supplemental Figure 2C). The full multivariable model for the adjusted risk of MACE is presented in Supplemental Table 3).

Discussion

The main finding of this study is that the hypertension moderates the 2-year risk of thrombotic events associated with PRU; with a disproportionally pronounced association between PRU and MACE among patients with versus without hypertension.

Drawn from more than 8500 patients undergoing PCI with DES, the present report represents the largest prospective study to date on the association between

Table 2
Procedural characteristics

Variable	Hypertension		p Value
	Yes (n = 6833)	No (n = 1749)	
Vascular access site			
Femoral	95.0% (6490/6833)	97.1% (1699/1749)	0.0001
Radial	4.8% (327/6833)	2.7% (48/1749)	0.0002
Brachial	0.2% (16/6833)	0.1% (2/1749)	0.56
Total lesion length (mm)	27.3 ± 20.4 (6833)	26.1 ± 18.6 (1749)	0.02
Thrombus	1.2% (83/6833)	3.7% (65/1749)	<0.0001
Calcium	33.3% (2273/6833)	21.2% (371/1749)	<0.0001
Ostial	13.4% (919/6833)	11.9% (209/1749)	0.10
Chronic total occlusion	4.8% (331/6833)	4.2% (74/1749)	0.28
Lesion within a graft	5.7% (390/6833)	2.2% (39/1749)	<0.0001
Number of vessels treated	1.2 ± 0.4 (6833)	1.2 ± 0.4 (1749)	0.0009
Target coronary vessel			
Left anterior descending	45.0% (3074/6833)	50.0% (875/1749)	0.0002
Right	37.2% (2544/6833)	36.7% (642/1749)	0.69
Left circumflex	32.1% (2195/6833)	26.2% (459/1749)	<0.0001
Left main	4.2% (284/6833)	2.0% (35/1749)	<0.0001
Bypass graft	5.7% (390/6833)	2.2% (39/1749)	<0.0001
Number of narrowings treated per patient	1.52 ± 0.80 (6833)	1.48 ± 0.74 (1749)	0.04
Number of stents implanted per patient	1.73 ± 1.04 (6833)	1.67 ± 0.92 (1749)	0.01
Total stent length (mm)	32.7 ± 22.8 (6833)	31.5 ± 20.6 (1749)	0.02
Intravascular ultrasound used	38.5% (2628/6833)	41.9% (733/1749)	0.008
For incomplete expansion	10.4% (272/2628)	7.8% (57/733)	0.04
For incomplete stent apposition	5.1% (134/2628)	4.2% (31/733)	0.34
Larger diameter stent or balloon	27.6% (726/2628)	29.3% (215/733)	0.36
Drug-eluting stent type			
First-generation	26.7% (1821/6833)	27.1% (474/1749)	0.70
Second-generation	63.4% (4331/6833)	63.5% (1111/1749)	0.91
Both	10.0% (681/6833)	9.4% (164/1749)	0.46

Values are % (n/N) or mean ± standard deviation (n).

hypertension, platelet reactivity, and thrombotic events. To our knowledge this is the first study to report a greater effect of high residual platelet reactivity on MACE risk among patients with versus without hypertension, a finding that has a pathophysiological substrate and could have clinically meaningful implications. Our findings are consistent with a previous META-analysis showing that the association between PRU and the risk of adverse ischemic outcomes was stronger among patients with versus without hypertension and other cardiovascular risk factors.[11]

Hypertension is association with endothelial inflammation and dysfunction.[6–8] Given the central role of endothelial cells in suppressing platelet adhesion and maintaining normal platelet function, dysfunctional coronary endothelium would be expected to promote platelet adhesion and activation.[4,5] Hypertension is also associated with prothrombotic changes in blood rheology and hemostatic and fibrinolytic factors.[9] Thus hypertension constitutes a physiological state in which the propensity for reactive platelets to cause a thrombotic event may be particularly high. Further support for this hypothesis comes from the observation that the adjusted risk of MACE associated with presenting with ACS rather than stable coronary artery disease, that is, having a more prothrombotic clinical phenotype,[12–14] was similarly greater among patients with versus without hypertension. An interaction between hypertension and clinical presentation in regard to the risk of adverse events is consistent with the findings in a recent report from the nationwide Swedish Angiography and Angioplasty Registry (SCAAR), which showed that hypertension moderated the association between clinical presentation and prognosis, with a disproportionally high risk of dying associated with ACS versus stable coronary artery disease among patients with versus without hypertension.[15]

From the perspective of the practicing clinician our results imply that adequate platelet inhibition is particularly important for patients with hypertension. Our findings support further analyses into whether a differential effect of ticagrelor or prasugrel versus clopidogrel among patients with versus without hypertension existed in the Study of Platelet inhibition and Outcomes (PLATO)[16] and the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON-TIMI) trials.[17]

In addition to lowering blood pressure, antihypertensive drugs such as angiotensin-converting enzyme inhibitors

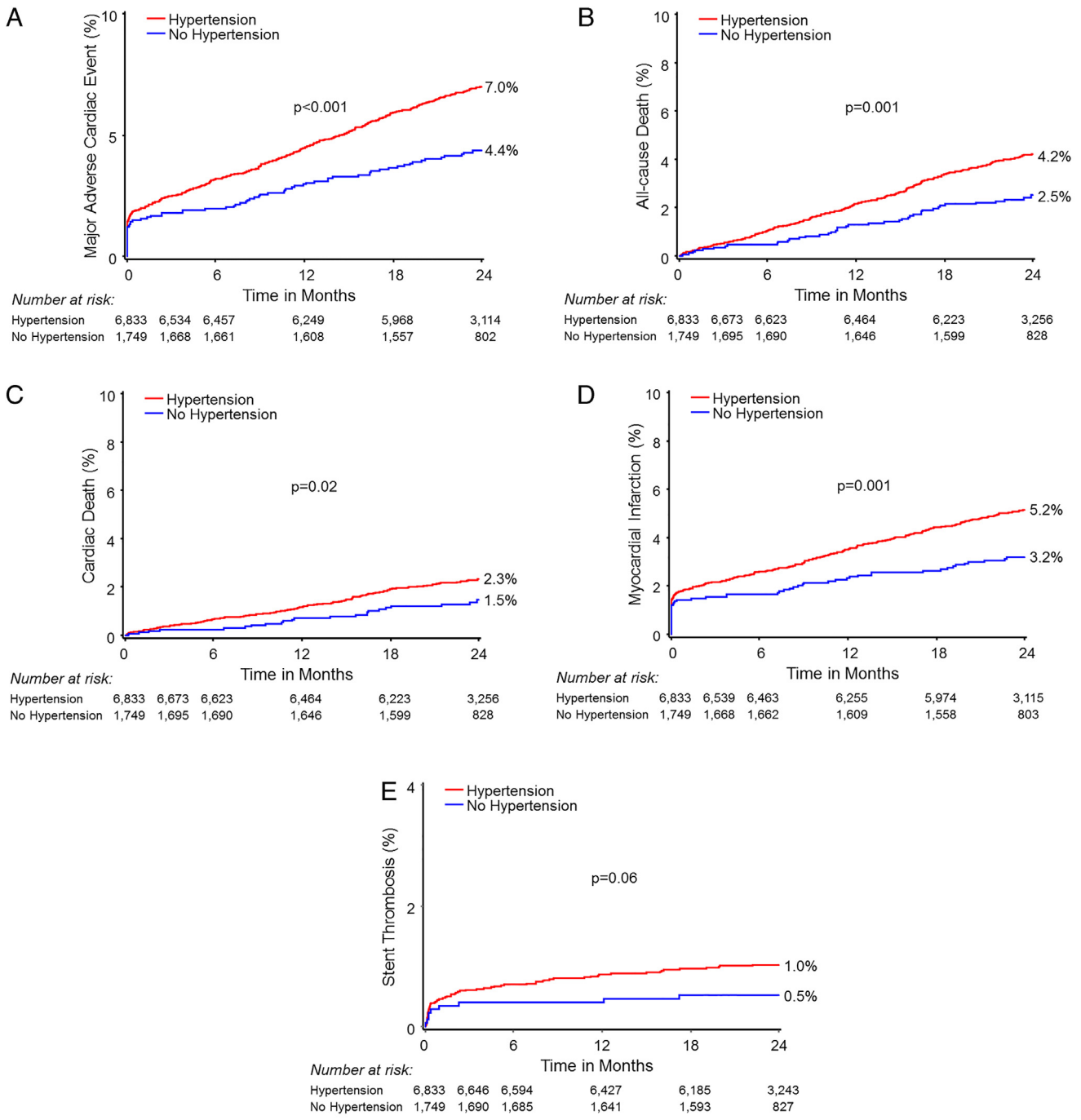

Figure 1. Kaplan-Meier failure rates for patients with versus without hypertension *(A)* Major adverse cardiac event; *(B)* all-cause death; *(C)* cardiac death; *(D)* myocardial infarction; *(E)* stent thrombosis.

and angiotensin II receptor blockers have been shown to attenuate intravascular inflammation and endothelial dysfunction.[18–20] Furthermore, several of the antihypertensive drug classes have been suggested to inhibit platelet activity and thrombosis.[21–24] We therefore hypothesized that the disproportionally large effect associated with residual platelet reactivity that was observed among patients with hypertension would be attenuated among patients who were using these drugs. However, we could not detect any differential effect of PRU among patients with hypertension according to whether or not they were treated with these drugs, and neither of these drug classes was independently associated with PRU.

Ascertainment of the presence of hypertension as well as the VerifyNow PRU assay was done at a single point in time. It is possible that hypertension status and/or PRU

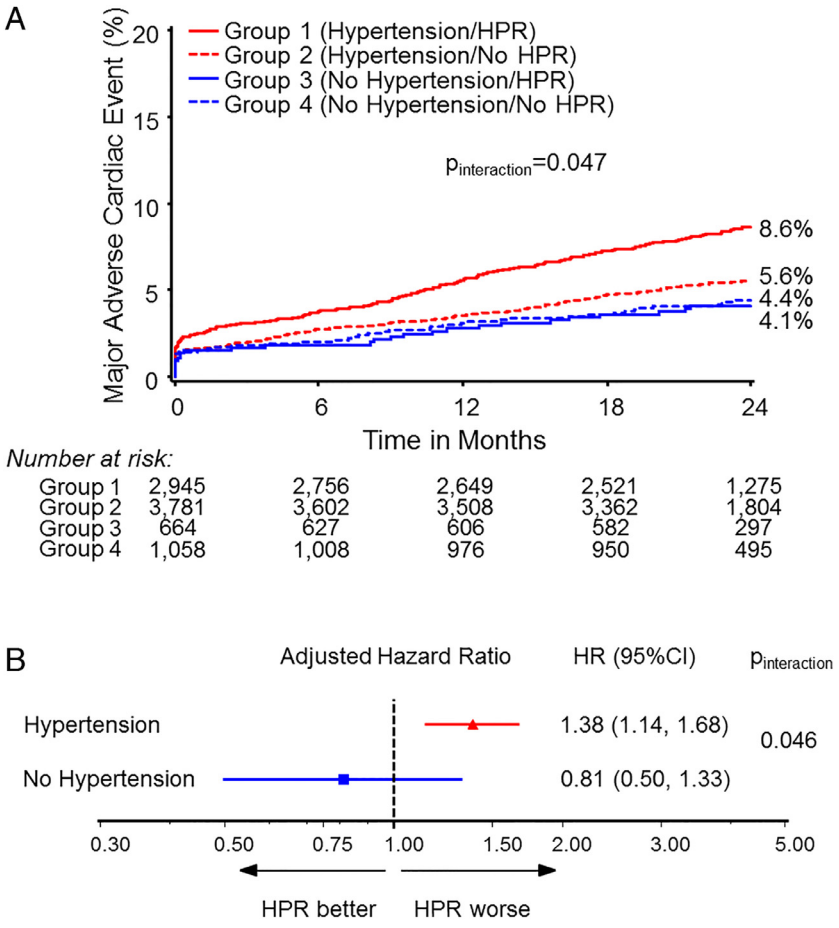

Figure 2. Unadjusted and adjusted association between hypertension, platelet reactivity, and major adverse cardiac events *(A)* Kaplan-Meier failure rates for patients with versus without hypertension according to whether or not they had high residual on-clopidogrel platelet reactivity (HPR), defined as >208 P2Y12 reaction units (PRU). Also presented is the unadjusted p-value for interaction between HPR and hypertension. *(B)* Adjusted hazard ratio (HR) associated with having versus not having HPR for patients with versus without hypertension, as assessed using multivariable Cox proportional hazards regression including an interaction term between hypertension and platelet reaction units. The multivariable model also included age, sex, current smoker, diabetes mellitus, history of renal insufficiency, hyperlipidemia, previous coronary artery bypass grafting, previous percutaneous coronary intervention, anemia, acute coronary syndrome versus stable coronary artery disease as clinical presentation, second-generation drug-eluting stents, target vessel location of left anterior descending artery, multivessel disease, coronary calcification, peripheral arterial disease, aspirin reaction units, and total stent length. CI = confidence interval.

Table 3
Adjusted association between having versus not having hypertension and the risk of adverse events at 2-year follow-up according to whether or not high platelet reactivity was present

Variable	Adjusted hazard ratio (95% confidence interval)		$p_{interaction}$
	PRU <208	PRU >208	
Major adverse cardiac event*	0.97 (0.69 to 1.36)	1.65 (1.08 to 2.53)	0.046
Myocardial infarction or stent thrombosis	0.87 (0.60 to 1.27)	1.78 (1.09 to 2.93)	0.02
Myocardial infarction	0.87 (0.60 to 1.28)	1.74 (1.04 to 2.89)	0.029
Stent thrombosis	1.12 (0.47 to 2.65)	1.65 (0.68 to 3.99)	0.52
Cardiac death	1.29 (0.65 to 2.57)	1.17 (0.61 to 2.25)	0.84
Death	1.20 (0.74 to 1.97	1.21 (0.74 to 1.98)	0.99
Ischemia-driven target vessel revascularization	1.13 (0.85 to 1.46)	1.24 (0.89 to 1.72)	0.61
Clinically relevant bleeding	1.11 (0.85 to 1.47)	1.24 (0.87 to 1.79)	0.62

* Composite of cardiac death, myocardial infarction, and stent thrombosis. The multivariable model also included age, sex, current smoker, diabetes mellitus, hyperlipidemia, history of renal insufficiency, previous coronary artery bypass grafting, previous PCI, anemia, acute coronary syndrome versus stable coronary artery disease as clinical presentation, second-generation drug-eluting stent, target vessel location of left anterior descending artery, multi-vessel disease, aspirin reaction units, and total stent length.

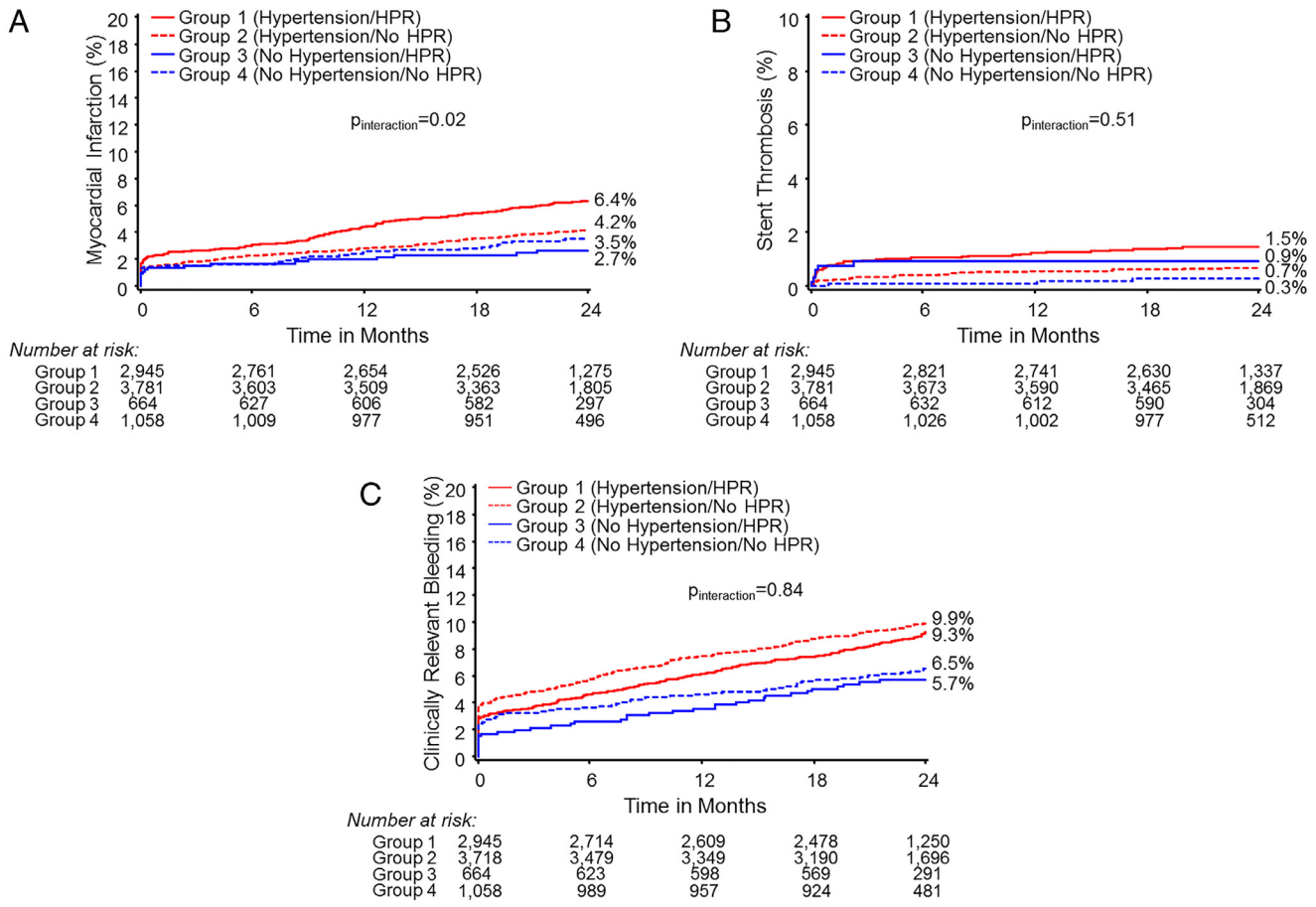

Figure 3. Kaplan-Meier failure rates for patients with versus without hypertension according to whether or not they have high residual platelet reactivity (HPR) *(A)* Myocardial infarction; *(B)* stent thrombosis; *(C)* clinically relevant bleeding.

changes over time; however, this limitation would be expected to reduce the likelihood of detecting a differential effect of PRU for patients with versus without hypertension (i.e., bias estimates towards "no differential effect"). There was no detailed assessment of the degree of hypertension and we did not directly assess endothelial function; however, the ADAPT-DES cohort represents the largest cohort of prospectively followed subjects for whom data on PRU are available and is therefore the most suitable dataset available for addressing this hypothesis. Lastly, hypertension is associated with other disease states. Despite adjusting for a considerable number of covariates, we cannot rule out that residual confounding remains.

Disclosures

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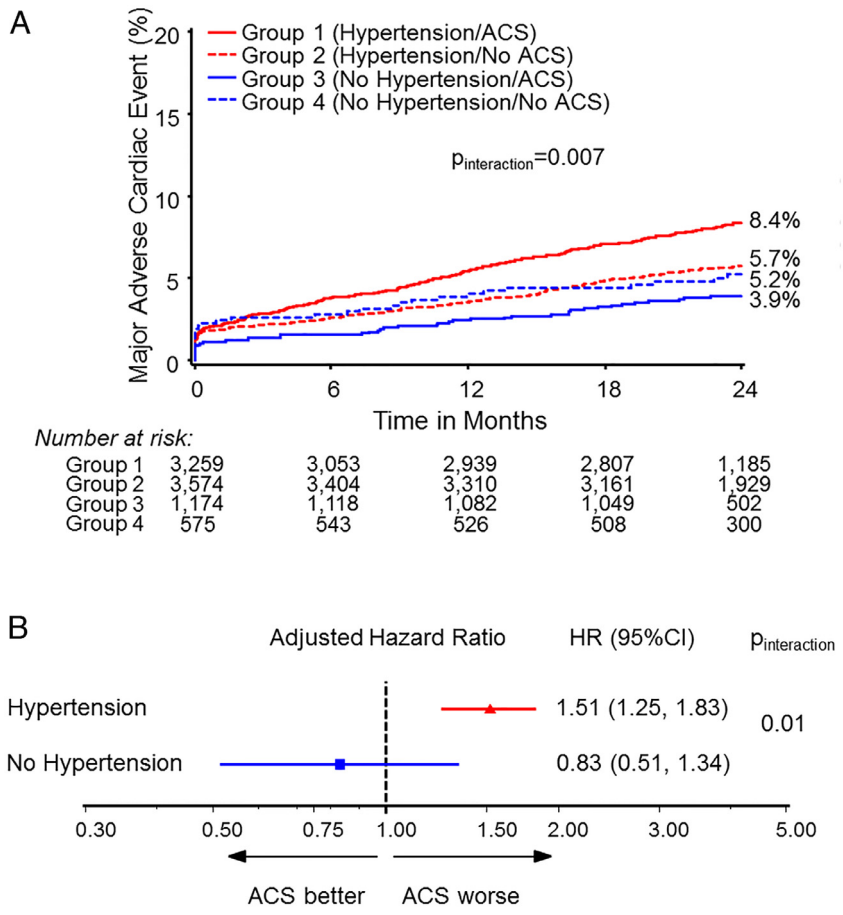

Figure 4. Unadjusted and adjusted association between hypertension, clinical presentation, and major adverse cardiac events *(A)* Kaplan-Meier failure rates for patients presenting with acute coronary syndrome (ACS) versus stable coronary artery disease (CAD) according to whether or not they had hypertension. *(B)* Adjusted hazard ratio (HR) associated with presenting with ACS versus stable CAD for patients with versus without hypertension, as assessed using multivariable Cox proportional hazards regression including an interaction term between hypertension and platelet reaction units. The multivariable model also included age, sex, current smoker, diabetes mellitus, history of renal insufficiency, hyperlipidemia, previous coronary artery bypass grafting, previous percutaneous coronary intervention, anemia, acute coronary syndrome versus stable coronary artery disease as clinical presentation, second-generation drug-eluting stents, target vessel location of left anterior descending artery, multivessel disease, coronary calcification, peripheral arterial disease, aspirin reaction units, and total stent length. CI=confidence interval.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi:10.1016/j.amjcard.2019.07.044.

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