ORIGINAL ARTICLE

Arterial excess-reservoir pressure integral as a predictor of cardiovascular complications in patients with acute coronary syndrome

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KEY WORDS

acute coronary syndrome, cardiovascular events, ejection fraction, reservoir–excess pressure

ABSTRACT

INTRODUCTION The excess pressure–time integral (excess PTI) and reservoir pressure–time integral (reservoir PTI) are new measures derived from blood pressure (BP) waveform decomposition. These markers predict cardiovascular (CV) complications and are associated with target organ damage in patients on antihypertensive treatment or those with chronic and acute heart failure.

OBJECTIVES We investigated whether reservoir PTI or excess PTI predict future CV events (death, stroke, myocardial infarction [MI]) in patients with acute coronary syndrome (ACS) and reduced ejection fraction (EF).

PATIENTS AND METHODS BP waveforms were obtained by radial tonometry in 251 patients with ACS (median age, 64 years) and reduced EF (median, 40%). Left ventricular EF was assessed by transthoracic echocardiography. Reservoir PTI and excess PTI were derived by decomposition of the BP waveform.

RESULTS A total of 78 CV events occurred during the follow-up (median, 1245 days). A Kaplan–Meier analysis showed that the highest tertile of excess PTI was a significant predictor of adverse outcome. A multivariate Cox regression analysis demonstrated that excess PTI was a predictor of CV events after adjustment for EF, age, history of stroke, MI, and coronary artery bypass grafting (hazard ratio, 1.9; 95% confidence interval, 1.1–3.3; $P = 0.02$).

CONCLUSIONS In conclusion, excess PTI, a new measure derived from reservoir–pressure analysis, predicts outcome in survivors of ACS with reduced EF.

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INTRODUCTION Prognostic evaluation of patients who survive myocardial infarction (MI) includes clinical risk scores and evaluation of the degree of cardiac dysfunction, most often by assessing left ventricular (LV) ejection fraction (EF) and, more recently, global LV longitudinal strain. Individual risk evaluation using these methods is still far from perfect; therefore, new risk markers are constantly being evaluated. Recently, there has been an increasing interest in assessing the predictive role of measures extracted from the blood pressure (BP) waveform.

Heterogeneous interactions between the heart and arterial system are reflected in the BP waveform. Intensive research in the area of arterial waveform analysis has led to the development of several indices with potential predictive value regarding adverse cardiovascular (CV) clinical outcomes in populations at risk.[1-3] In short, 2 models of the circulation served as the basis for explaining the BP waveform, namely, the Windkessel model and the model of wave transmission, both of which have been the subject of intense debate and criticism. More recently, an alternative approach combining the elements of wave analysis and the Windkessel model has been developed: the reservoir–excess pressure model.[4-7] Reservoir pressure is related to arterial compliance,

whereas excess pressure is the difference between the total pressure and reservoir pressure waveform and represents the extra work performed by the LV. Recent clinical trials have demonstrated that reservoir-wave analysis allows for the extraction of indices that are useful for the prediction of CV events. For example, in the conduit artery, a functional evaluation substudy of the Anglo-Scandinavian Cardiac Outcome Trial revealed that the excess pressure–time integral (excess PTI) was a significant and independent predictor of CV events and target organ damage after adjustment for several well-established risk factors.[8] Moreover, in another trial, excess PTI predicted long-term all-cause mortality in patients with stable heart failure.[9] It has also been established that reservoir-wave analysis improves the prediction of clinical outcomes in elderly patients with hypertension.[10]

To the best of our knowledge, no studies have examined the prognostic importance of the measures associated with reservoir–excess pressure analysis in addition to existing echocardiographic indices in patients with acute coronary syndrome (ACS). We hypothesized that excess PTI and/or the reservoir pressure–time integral (reservoir PTI) would be independently related to CV outcomes in survivors of ACS when EF is included in the model. Accordingly, we explored the individual prognostic importance of excess PTI and reservoir PTI together with established clinical and echocardiographic predictors of adverse events (death, stroke, MI), after an ACS episode.

PATIENTS AND METHODS The present substudy included participants of a larger study funded by the National Science Centre in Poland (DEC-2011/03/B/NZ7/06 241) who had EF values lower than normal.

Participants analyzed in the present substudy were enrolled consecutively after a diagnosis of ACS within 12 hours of symptom onset with 50% coronary artery narrowing exceeding 50%.[11] All time frames for invasive treatment were within limits approved in current guidelines. The mean door-to-baloon time for ST-segment elevation myocardial infarction (STEMI) was 50 minutes.

The criteria for exclusion from the study were as follows: cardiogenic shock (defined as hypotension: systolic BP <90 mm Hg for 30 minutes, despite fluid challenge, and need for supportive measures to maintain systolic BP of 90 mm Hg with evidence of end-organ hypoperfusion), advanced and refractory chronic heart failure (defined as stage D according to the American College of Cardiology / American Heart Association: marked symptoms of dyspnea, fatigue, or symptoms relating to end-organ hypoperfusion at rest or with minimal exertion despite optimal medical therapy before admission with current ACS diagnosis), atrial fibrillation or flutter (during current hospitalization), known neoplasm or chronic condition with life expectancy of less than 1 year, and chronic renal disease on dialysis program. Briefly, all laboratory assessments (including hemodynamic parameters and echocardiography) were performed 48 to 72 hours after hospital admission (47% on the second and 53% on the third day). All patients had an EF of less than 50%. The primary study endpoint was a composite of all-cause mortality, stroke, and MI. Patients were followed for a maximum of 1704 days (starting October 2012; median follow-up, 1245 days). Finally, 251 patients were included in the study, of whom 78 had a CV event (death in 47 patients, MI in 21, and stroke in 10).

The thrombolysis in myocardial infarction (TIMI) risk score for STEMI was calculated with MDCalc (www.mdcalc.com) and represents a composite of age, presence of diabetes, hypertension or angina, systolic BP <100 mm Hg, heart rate >100 bpm, Killip class II–IV, weight <67 kg, anterior ST-segment elevation or left bundle brunch block, and time to treatment >4 hours. The TIMI risk score for non–ST-segment elevation myocardial infarction (NSTEMI) was also calculated with MdCalc and represents a composite of age >65 years, ≥3 risk factors for coronary artery disease (CAD) (hypertension, hypercholesterolemia, diabetes, family history of CAD, or current smoking), known CAD (stenosis ≥50%), acetylsalicylic acid use in the past 7 days, severe angina (≥2 episodes in 24 hours), ST-segment changes on electrocardiogram ≥0.5mm, and positive cardiac marker.

Written informed consent was obtained from all patients prior to their inclusion in the study. The study was approved by the Poznan University Ethics Committee, and the protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Echocardiography All patients underwent complete 2-dimensional and Doppler echocardiographic examination using a commercially available ultrasound system (MyLab Class C, Esaote, Italy) equipped with a 3.0-MHz transducer. LV mass (LVM) was calculated using the American Society of Echocardiography formula modified by Devereux et al,[12] based on the average of 3 measurements of the LV diameter and wall thickness. LV volume and EF were estimated using the Simpson's modified biplane method based on 3 measurements.[13] LVM measurements were corrected for the body surface area to yield the LVM index.

Pulsed-wave Doppler-derived transmitral inflow velocities were obtained with the transducer in the apical 4-chamber view and the sampling volume at the tips of the mitral valve leaflet. Early diastolic wave (E) and atrial wave (A) velocities, as well as E-wave deceleration time (DT), were measured, and the E/A ratio was calculated. Longitudinal velocities were recorded by Doppler tissue imaging, with the sample volume placed at the junction between the septal and lateral LV wall and the mitral annulus in the 4-chamber view, and peak early myocardial wave (e') velocities were measured. The ratio of mitral E peak

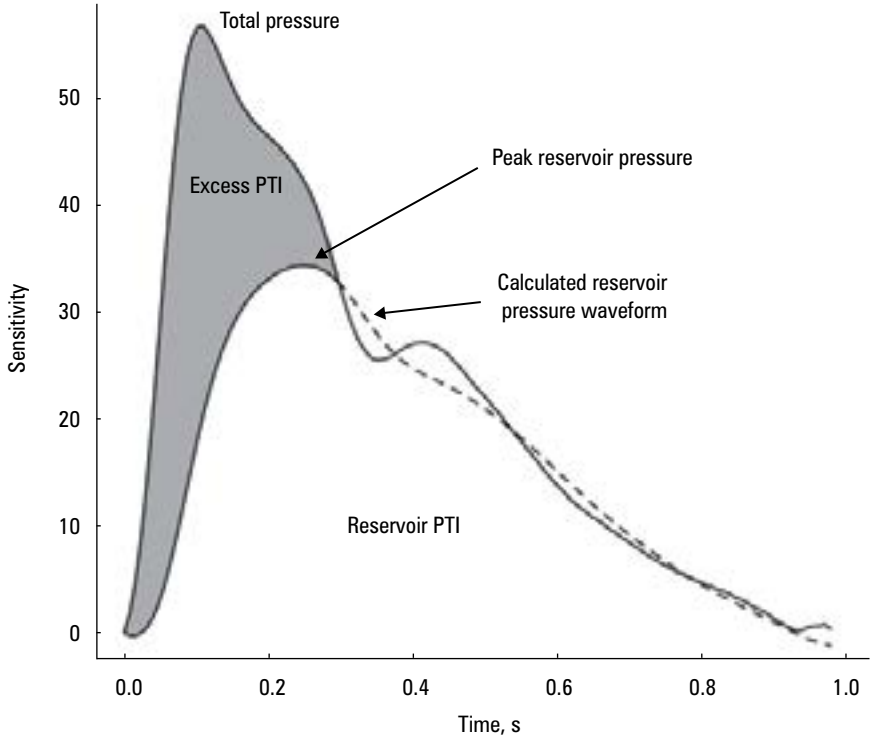

FIGURE 1 Example of reservoir–excess decomposition of the radial pressure waveform. Abbreviations: excess PTI, excess pressure––time integral; reservoir PTI, reservoir pressure––time integral

velocity and averaged e' velocity (E/e') was calculated. All measurements were performed offline and according to the recommendations of the European Association of Echocardiography and the American Society of Echocardiography.[13] Studies were performed by one experienced echocardiographer (AS).

Noninvasive assessment of the pressure waveform Radial pressure waveforms were recorded noninvasively using a Piezoelectric tonometer (Colin BPM 7000, Komaki, Japan). The analog signal recorded was sent in real time to a SphygmoCor Mx Aortic BP Monitoring System (AtCor Medical, Sydney, Australia) for online reconstruction (using a validated transfer function) of a pressure waveform characteristic of an ascending aorta. Pulse-wave analysis was used to assess peripheral and central hemodynamics. Indices of central pressure were obtained using commercial software (AtCor Medical). In the case of radial access during angiography, the study was performed on the contralateral arm. Studies were performed by one experienced researcher (TK). The measurements were repeated until accepted by software quality control.

Reservoir–excess pressure model The reservoir–excess pressure is an approximate global model that summarizes the properties and connectivities of individual arteries (an example of the decomposition of the BP waveform is shown in FIGURE 1). The model assumes that the experimentally measured pressure is actually the sum of the reservoir pressure and excess pressure. The reservoir pressure corresponds to the effect of compliant arteries storing and releasing blood, whereas the excess pressure is proportional to flow. The waveforms measured were obtained using applanation tonometry (SphygmoCor), which generated the radial and corresponding central aortic waveforms as text files. These files were analyzed numerically using an in-house Python program that was written according to published references.[5,7] The area under the excess pressure or reservoir pressure curves (pressure–time integral) is presented in units of mm Hg·ms.

Statistical analysis Continuous data were presented as the median with interquartile range, whereas categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the Mann–Whitney test or the Fisher exact test (for categorical variables). The Kaplan–Meier survival analysis was also performed. The significance of differences between subgroups was assessed using the log-rank test. Cox proportional hazard regression models (univariate and multivariate) were used to determine significant predictors of the composite endpoint (death, stroke, MI). For patients with more than one CV event, the time to the primary endpoint was determined as the time to the first event. Univariate Cox proportional hazard regression models were used to estimate associations between EF, age, sex, previous MI, history of coronary artery bypass grafting (CABG), history of stroke, hypertension, diabetes, current percutaneous coronary intervention (PCI), excess PTI, reservoir PTI, and the risk of the composite primary outcome of all-cause mortality, stroke, and recurrent MI. The covariates used for adjustment were selected on the basis of a significant effect of the variable on the studied

TABLE 1 Clinical characteristics of the study group (n = 251)

Variable		Value
Sex, male/female		178 (71) / 73 (29)
History of MI		77 (31)
History of PCI		53 (21)
History of CABG		11 (4)
Hypertension		205 (82)
Diabetes		97 (39)
Current smoking		97 (39)
STEMI		120 (48)
NSTEMI/UA		131 (52)
Current PCI		184 (73)
Medications	Aspirin	246 (98)
	Clopidogrel	246 (98)
	ACEI or ARB	230/8 (95)
	β-blocker	234 (93)
	Statin	241 (96)
	Diuretic	105 (42)
	Aldosterone antagonist	132 (53)
	Long-acting nitrate	46 (18)
Age, y		64 (58–72)
BMI, kg/m^2		27.5 (24.1–30.8)
SBP, mm Hg		113 (102–125)
DBP, mm Hg		68 (61–75)
HR, bpm		70 (63–79)
Hs-TnT, ng/l		685 (175–2091)
QRS duration, ms		102 (94–114)
Reservoir PTI, mm Hg·ms		9306 (7554–10 065)
Excess PTI, mm Hg·ms		3805 (3136–4125)
EF, %		40 (38–46)
TIMI risk score STEMI		4 (2–5)
TIMI risk score NSTEMI		5 (4–6)

Dichotomized variables are presented as number (%) of patients and continuous variables are presented as median (interquartile range).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; hs-TnT, high-sensitivity troponin T; MI, myocardial infarction; NSTEMI/UA, non–ST-segment myocardial infarction/unstable angina; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; others, see FIGURE 1

outcome in the unadjusted model. All tests were 2-sided, and a *P* value of less than 0.05 was considered significant. All analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, New York, United States).

RESULTS The baseline characteristics of the study group are presented in TABLE 1. The median age of the patients was 64 years, and the median EF was 40%. A large proportion of patients suffered from hypertension (82%), diabetes (39%), or previous MI (31%) and had a history of coronary revascularization (21%). Ninety percent of patients reported that hypertension was treated before the ACS episode. At discharge patients had been treated according to clinical guidelines with antiplatelet drugs (98%), β-blockers (93%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (95%), and statins (96%).

Follow-up The study cohort included 251 patients who were followed for a median of 1245 days (interquartile range, 1009–1502 days). During the follow-up, 78 events were recorded (47 deaths, 21 MIs, 10 strokes): in the first tertile of excess PTI (19 deaths, 2 strokes, 4 MIs), in the second tertile of excess PTI (7 deaths, 4 strokes, 10 MIs), and in the third tertile of excess PTI (21 deaths, 4 strokes, 7 MIs).

Patients who experienced CV events (TABLE 2) were older (*P* = 0.001) and more often suffered from diabetes (*P* = 0.01) or had a history of previous MI (*P* = 0.002). They also had lower EF (*P* = 0.004), higher LVM (*P* = 0.01), higher LV diastolic and systolic volumes (*P* = 0.01 and *P* = 0.004, respectively), higher E/e' values (*P* = 0.0001), and higher peripheral and central systolic BP (*P* = 0.02 and *P* = 0.002, respectively). Moreover, reservoir–excess pressure measures were higher in patients with CV sequelae (reservoir PTI, *P* = 0.01; excess PTI, *P* = 0.001).

Clinical and reservoir–excess pressure predictors of cardiovascular complications during follow-up The primary composite endpoint comprised death, stroke, and MI. During the follow-up, 30% of patients experienced one of the events constituting the composite primary endpoint. Peripheral and central systolic and diastolic BP as well as mean BP did not predict the incidence of the primary endpoint in the unadjusted univariate model (highest vs lowest tertile; data not shown). Moreover, neither the medications (TABLE 1) nor cholesterol concentrations predicted future complications (data not shown). Similarly, the type of MI (STEMI vs NSTEMI), as well as current PCI, did not contribute significantly to the multivariate model (data not shown). A similar analysis (TABLE 3) using parameters derived from reservoir–excess pressure decomposition revealed that excess PTI, but not reservoir PTI, was associated with an increased risk of an adverse outcome: hazard ratio (HR) 2.2; 95% confidence interval (CI), 1.3–3.8; *P* = 0.003 vs HR, 1.5; 95% CI, 0.9–2.6; *P* = 0.12, respectively. Excess PTI is derived from BP decomposition. Therefore, this measure is highly correlated with systolic BP (*r* = 0.74) and a number of other BP parameters. To avoid multicollinearity, these variables were not used together in the regression model.

The Kaplan–Meier curves for the composite endpoint events according to the excess PTI tertiles are shown in FIGURE 2 (*P* = 0.004 by log-rank test).

Predictors of cardiovascular events after adjustment for known risk factors All measures derived from the reservoir–excess pressure analysis were tested in a model adjusted for known risk factors of

TABLE 2 Basic demographic characteristics, excess–reservoir pressure, and echocardiography paramaters in patients with and without cardiovascular complications

Variable	Cardiovascular complications		*P* value
	No (n = 173)	Yes (n = 78)	
Death/MI/Stroke	–	47/21/10	–
Male sex	122 (71)	56 (72)	0.9
Hypertension	137 (79)	68 (87)	0.2
Diabetes	60 (35)	37 (47)	0.01
History of MI	42 (24)	35 (45)	0.002
History of CABG	3 (2)	8 (10)	0.01
Current PCI	129 (75)	55 (71)	0.5
Age, y	63 (57–71)	68 (60–75)	0.001
Peripheral SBP, mm Hg	112 (102–124)	118 (104–132)	0.02
Peripheral DBP, mm Hg	68 (61–75)	70 (62–76)	0.4
Central SBP, mm Hg	101 (91–111)	107 (94–119)	0.02
Central DBP, mm Hg	69 (62–76)	71 (62–76)	0.5
Reservoir PTI, mm Hg·ms	8579 (6795–10 861)	9126 (7218–11 846)	0.01
Excess PTI, mm Hg·ms	3507 (2884–4211)	4020 (3081–5197)	0.001
LVEDV, ml	93 (73–116)	105 (85–145)	0.01
LVESV, ml	52 (40–71)	65 (48–92)	0.004
SV index, ml/m^2	20 (16–24)	21 (18–27)	0.18
E/A	0.86 (0.68–1.14)	0.88 (0.68–1.39)	0.06
DT, ms	222 (183–270)	233 (183–290)	0.29
E/e'	9.9 (7.9–12.4)	12.4 (9.5–18.6)	0.0001
EF, %	43 (36–48)	41 (32–45)	0.004
LVM index, g/m^2	124 (102–147)	149 (111–173)	0.01

Dichotomized data are presented as the number (%) of patients and continuous variables are presented as the median (interquartile range).

Abbreviations: DT, deceleration time; E/A, ratio of mitral inflow peak early velocity (E) to mitral inflow peak late velocity (A); E/e', ratio of mitral inflow peak early velocity (E) to mitral annular peak early velocity (e'); LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; SV, stroke volume; others, see **FIGURE 1** and **TABLE 1**

TABLE 3 Results of univariate and multivariate Cox proportional hazards regression models for associations between excess–reservoir pressure measures, clinical characteristics, and risk of the primary composite endpoint (all-cause mortality or stroke or myocardial infarction)

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Reservoir PTI (>10 065 vs <7554), mm Hg·ms	1.5 (0.9–2.6)	0.12	–	–
Excess PTI (>4125 vs <3136), mm Hg·ms	2.2 (1.3–3.8)	0.003	1.9 (1.1–3.3)	0.02
History of stroke	2.1 (1.1–3.8)	0.02	2.0 (1.1–3.8)	0.03
History of MI	1.4 (0.8–2.2)	0.22		
History of CABG	2.3 (1.1–5.0)	0.04	2.1 (1.0–4.9)	0.05
Diabetes	1.2 (0.7–1.9)	0.5		
Age	1.0 (1.0–1.05)	0.045	1.02 (1.0–1.04)	0.05
EF (>46% vs <38%)	0.43 (0.22–0.83)	0.01	0.49 (0.24–0.97)	0.04

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; others, see **FIGURE 1** and **TABLE 1**

adverse CV outcome. The selection of covariates was based on clinical judgment, and in the multivariate model only predictors significantly associated with outcome in the univariate analysis were included. The following parameters were tested: age, sex, previous MI, history of CABG, history of stroke, hypertension, diabetes, current PCI, and EF. Other echocardiographic parameters were not included in the model because they were significantly correlated with EF. In the multivariate model, excess PTI was independently associated with the primary outcome (HR, 1.9; 95% CI, 1.1–3.3; $P = 0.02$). Moreover, increased risk of events was associated with a history of stroke (HR, 2.0; 95% CI, 1.1–3.8; $P = 0.03$); borderline significance was revealed for previous CABG (HR, 2.1; 95% CI, 1.0–4.9; $P = 0.05$) and older age (HR, 1.02; 95% CI, 1.0–1.04; $P = 0.05$), whereas higher EF was protective (HR, 0.49; 95% CI, 0.24–0.97; $P = 0.04$). Reservoir PTI was not an independent predictor of CV events in the adjusted model. After adjusting the model for TIMI risk score for NSTEMI and STEMI, the significant predictors of CV events were excess PTI (HR, 2.0; 95% CI, 1.3–3.2; $P = 0.004$) and history of stroke (HR, 2.2; 95% CI, 1.2–4.2; $P = 0.01$). Higher EF was protective (HR, 0.46; 95% CI, 0.25–0.86; $P = 0.01$). The remaining factors, that is, age (HR, 1.0; 95% CI, 0.9–1.04; $P = 0.07$), CABG (HR, 0.9; 95% CI, 0.48–1.69; $P = 0.7$), TIMI risk score for NSTEMI (HR, 1.1; 95% CI, 0.9–1.2; $P = 0.4$), and TIMI risk score for STEMI (HR, 1.0; CI 0.9–1.2, $P = 0.8$) were not associated with the risk of CV events.

The angiographic characteristics of patients are presented in **TABLE 4**. In the multivariate model, none of the measures were significant and independent predictors of CV events (data not shown).

DISCUSSION

The results of the present study indicate that elevated excess PTI, a new measure derived from pressure-wave analysis, predicts the incidence of CV events in survivors of ACS with reduced EF after adjustment for important clinical characteristics.

Peripheral and central BP is a well-known risk factor for future CV complications.[14-18] It is also generally accepted that after an acute coronary event, strict control of both systolic and diastolic BP is indicated, although evidence-based target values have not been set for either peripheral or central BP. In the present study, despite the fact that peripheral and central BP was within the reference ranges, patients who experienced a future CV event had significantly higher peripheral and central systolic, but not diastolic, BP. However, neither peripheral nor central systolic or diastolic BP was predictive of future CV complications. Newly described measures, such as reservoir PTI and excess PTI, derived from BP wave decomposition have been shown to predict CV events and target organ damage in prospective clinical trials.[8-10] In the CAFE (Conduit Artery Function Evaluation) study,[8] excess PTI was a significant predictor of a CV event in a Cox regression

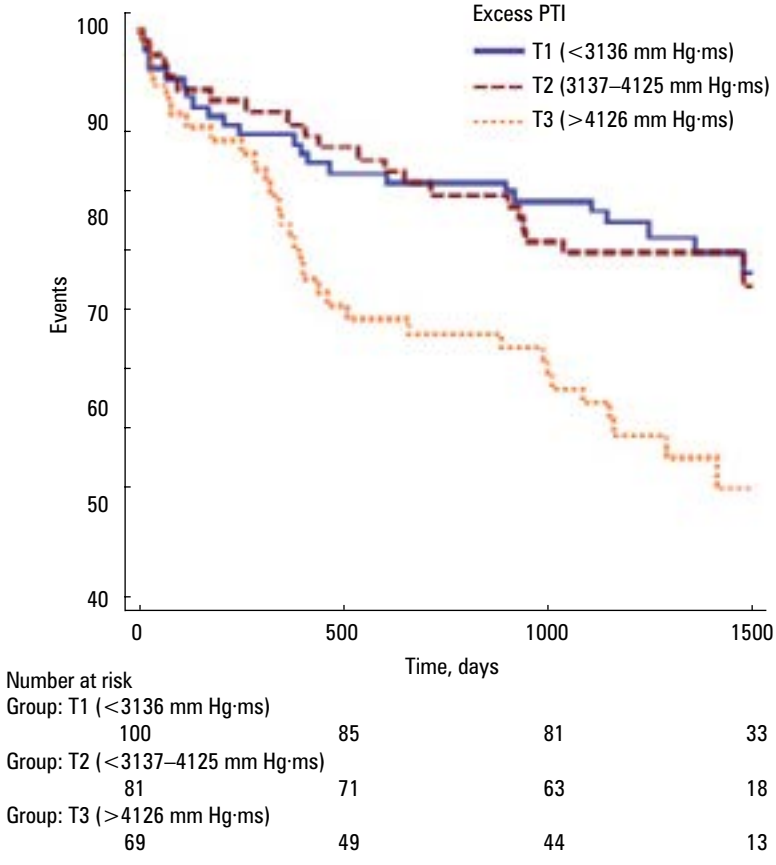

FIGURE 2 Kaplan–Meier estimates of event-free survival according to tertiles of the excess pressure–time integral (excess PTI; $P = 0.004$, log-rank test)

TABLE 4 Angiographic characteristics of the study population (n = 251)

Characteristic	Value
Infarct-related artery, n (%)	
None	6 (2)
LM	18 (7)
LAD	93 (37)
Cx	41 (16)
RCA	91 (36)
CABG	2 (1)
Treated vessels, n (%)	
None	67 (27)
LM	2 (1)
LAD	101 (40)
Cx	61 (24)
RCA	89 (35)
CABG	2 (1)
Procedural characteristics	
Radial access, n (%)	84 (33)
DES length / patient, mm, mean (SD)	23 (20)
DES length per ACS culprit lesion, mm, mean (SD)	18 (15)
DES diameter per ACS culprit lesion, mm, mean (SD)	2.6 (1.9)
DES implantation pressure, ATM, mean (SD)	10 (4.3)
Implantation procedure (direct stenting), n (%)	73 (29)
Postdilation pressure, ATM, mean (SD)	9 (3.8)

Abbreviations: ATM, atmosphere; Cx, circumflex artery; DES, drug-eluting stent, LAD, left anterior descending artery; LM, left main artery; RCA, right coronary artery; others, see TABLE 1

analysis after adjustment for age and sex, as well as in another model after adjustment for several conventional clinical risk factors either individually or when summarized by the Framingham risk score. Wang et al[9] assessed long-term all-cause mortality in patients with stable heart failure and showed that excess PTI was the only significant independent predictor of total mortality after adjusting for age and sex. In further analysis, this association was not affected by other confounding factors, such as EF, glomerular filtration rate, N-terminal pro-B-type natriuretic peptide, smoking, hypertension, and diabetes. Interestingly, in a recent study in patients with acute heart failure, Sung et al[19] demonstrated that excess PTI remained significantly and independently associated with postdischarge events, such as death and rehospitalization. In the present study, individuals who experienced a significant CV event (death, stroke, MI) during follow-up were older and were more likely to have comorbidities. Importantly, these patients had lower EF, higher LVM index, and higher excess PTI and reservoir PTI. After adjustment for important prognostic factors, excess PTI remained a significant predictor of future CV events. It should be noted that the reservoir–excess pressure analyses in the above trials were applied to pressure waves obtained at different locations. Specifically, Wang et al[9] analyzed waveforms obtained from the carotid artery, whereas in the CAFE trial and the present study the analyses were performed on radial artery pressure waveforms. Peng et al[20]

showed that arterial reservoir characteristics are modified through the arteries of the upper limb. In general, reservoir pressure remains relatively constant, whereas excess pressure increases stepwise from the aorta to the brachial and arterial arteries. Nevertheless, excess PTI remained significantly associated with adverse outcomes, regardless of the location from which the pressure wave was sampled for further analysis.

It is currently difficult to speculate about the mechanisms underlying the association between excess PTI and future CV complications. Theoretically, excess pressure may be associated with target organ damage, and this has been confirmed by Climie et al.[21] In their study, the authors demonstrated that excess pressure was inversely associated with gray matter volume. Moreover, in another study, higher excess PTI was noted in patients with subclinical white matter lesions compared with controls.[22] Obviously, these observations do not suggest causality between higher excess pressure and the sequelae observed. It cannot be excluded that excess PTI is simply a marker of an adverse outcome in a population at risk.

The immediate implication of the present results is that increased excess PTI should be considered as a useful measure for the estimation of the risk of death, stroke, or MI in survivors of ACS with reduced EF.

The present study has several limitations. First, adverse CV outcomes were pooled due to low rate of individual CV events. Second, the current substudy represents a retrospective post hoc analysis; therefore, the observations need to be confirmed in prospective trials. Third, men constituted the majority of the study population, so the effect of sex on the results could not be unequivocally determined. Fourth, we cannot provide a simple mechanistic explanation for the association between increased excess PTI and CV events. Finally, we were not able to collect reliable data on previous antihypertensive treatment.

In summary, excess PTI, a new measure of reservoir–pressure analysis, predicts outcome in survivors of ACS with reduced EF.

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CONTRIBUTION STATEMENT AW conceived the idea of the study. AW, PG, and ASch contributed to the design of the research. All authors were involved in data collection. AW, PG, JP, and ASch analyzed the data. AW coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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