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Comparison of Effect of Ischemic Postconditioning on Cardiovascular Mortality in Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention With Versus Without Thrombectomy

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In patients with ST-segment elevation myocardial infarction (STEMI), ischemic postconditioning (iPOST) have shown ambiguous results in minimizing reperfusion injury. Previous findings show beneficial effects of iPOST in patients with STEMI treated without thrombectomy. However, it remains unknown whether the cardioprotective effect of iPOST in these patients persist on long term. In the current study, all patients were identified through the DANAMI-3-iPOST database. Patients were randomized to conventional primary percutaneous coronary intervention (PCI) or iPOST in addition to PCI. Cumulative incidence rates were calculated, and multivariable analyses stratified according to thrombectomy use were performed. The primary end point was a combination of cardiovascular mortality and hospitalization for heart failure. From 2011 to 2014, 1,234 patients with STEMI were included with a median follow-up of 4.8 years. In patients treated without thrombectomy (n = 520), the primary end point occurred in 15% (48/326) in the iPOST group and in 22% (42/194) in the conventional group (unadjusted hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.41 to 0.94, p = 0.023). In adjusted Cox analysis, iPOST remained associated with reduced long-term risk of cardiovascular mortality (HR 0.53, 95% CI 0.29 to 0.97, p = 0.039). In patients treated with thrombectomy (n = 714), there was no significant difference between iPOST (17%, 49/291) and conventional treatment (17%, 72/423) on the primary end point (unadjusted HR 1.01, 95% CI 0.70 to 1.45, p = 0.95). During a follow-up of nearly 5 years, iPOST reduced long-term occurrence of cardiovascular mortality and hospitalization for heart failure in patients with STEMI treated with PCI but without thrombectomy. **(Am J Cardiol 2022;166:18−24)**

Treatments and reperfusion strategies of patients with ST-segment elevation myocardial infarction (STEMI) have improved and become more preventive of adverse complications after STEMI, yet additional myocardial injury may occur immediately after restoration of coronary blood flow and may account for up to 50% of the damage to myocardium, a phenomenon called reperfusion injury.[1−6] Thus, ischemic postconditioning (iPOST) by repetitive brief interruptions of blood flow before establishment of final reperfusion, has demonstrated ambiguous results in minimizing reperfusion injury.[7−13] Our group previously published the Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction (DANAMI-3-iPOST) trial assessing the effect of iPOST during primary percutaneous coronary intervention (PCI) versus conventional PCI alone on the primary composite

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outcome of all-cause mortality and hospitalization for heart failure in patients with STEMI.[14] Although iPOST failed to reduce the primary end point,[11] a post hoc analysis showed that iPOST reduced short-term risk of all-cause mortality and hospitalization for heart failure in patients who were not treated with thrombectomy.[15] Therefore, we performed an analysis of the long-term prognostic impact of iPOST in patients with STEMI treated with and without thrombectomy.

The DANAMI-3 trial was an open-label, randomized controlled trial evaluating 3 different revascularization strategies in patients with STEMI: iPOST (DANAMI-3-iPOST),[11] deferred stenting (DANAMI-3-DEFER),[16] and complete revascularization (DANAMI-3-PRIMULTI).[17] Details of the study design, patient selection, and exclusion criteria have been described previously.[11,14,15] This long-term study of the DANAMI-3-iPOST trial included 1,234 consecutive patients with STEMI ≥18 years. Patients were admitted to 1 of the 4 primary PCI centers in Denmark between March 2011 to February 2014 with ≤12 hours of symptom onset with thrombolysis in myocardial infarction flow 0/1 in culprit vessel on the initial angiogram. STEMI was defined as acute chest pain with <12 hours of duration and ST-segment elevation ≥0.1 mV in ≥2 contiguous leads or documented newly developed left bundle branch block on electrocardiogram.

All data on included patients were retrieved from the DANAMI-3-iPOST database. It holds information on clinical, angiographic, and procedural characteristics including prescriptions and co-morbidities before STEMI admission. The database was linked through a unique civil registration number to Danish nationwide administrative registries. The personalized and permanent civil registration number assigned to all Danish residents allow unambiguous and individual linkage between all nationwide registries.[18] Vital status was retrieved from the Civil Registration Registry.[18] Based on death certificates according to the International Classification of Diseases, Eighth and Tenth Revisions (ICD-8 and ICD-10), the cause of death was retrieved from the National Causes of Death Registry which holds information on time of death and both the primary and contributing causes of death.[19] Information on hospitalization for heart failure after STEMI admission was collected from the National Patient Registry according to ICD-10 Code I42, I50, I110, I130, I132, or J819, or ICD-8 Code 425, 428, 4,270, 4,271.[20]

All patients were randomly allocated to either conventional PCI or iPOST in connection with PCI.[11] Thrombectomy was performed at the discretion of the invasive cardiologist. The primary end point of this study was a combination of cardiovascular mortality and hospitalization for heart failure. Secondary outcomes were the individual components of the primary outcome and all-cause mortality. Owing to a long follow-up, we included cardiovascular mortality as a component of the primary outcome because noncardiac mortality such as malignancies or lung diseases are responsible for the majority of deaths on long-term following STEMI.[21] Cardiovascular mortality was defined as a secondary end point in the original DANAMI-3-iPOST trial.[11] In the initial follow-up, identification of outcomes was done by using national registries and checked by an event committee.[11,15] Following the initial follow-up, the identification was done by national registries and ICD-8 and ICD-10 codes for heart failure and cardiovascular mortality (Supplementary Table 1). The follow-up period ran until the occurrence of the outcome of interest, noncardiovascular mortality, date of emigration, or study end (December 31, 2017).

Continuous variables were tested for normality, presented as mean (SD) or median and interquartile range, and compared using *t* test or Mann-Whitney's *U* tests, as appropriate. Categoric variables presented as frequencies and percentages were compared using the chi-square test or Fisher's exact test. Cumulative incidence was calculated taking the competing risk of death from other causes into account. Gray's test was used to compare groups. Both unadjusted and adjusted hazard ratio (HR) and 95% confidence interval (CI) were calculated by Cox proportional hazard analysis, and a test for interaction between iPOST and thrombectomy in the total DANAMI-3-iPOST cohort on the primary and secondary end points was performed. Multivariate Cox models were adjusted for age, gender, and use of glycoprotein IIb/IIIa inhibitor. Interaction between iPOST and age, gender, and use of glycoprotein IIb/IIIa inhibitor was tested on the primary end point. In patients with multivessel disease, interaction between iPOST and treatment with either complete or culprit-only revascularization was tested on the primary outcome, as these patients could secondarily be randomized in DANAMI-3-PRIMULTI. Furthermore, the assumptions for proportional hazard and linearity for numeric values were tested and found valid. Finally, additional analyses investigating event rates and interaction between iPOST and the primary end point were performed for certain subgroups. A 2-sided p value ≤0.050 was considered statistically significant in all analyses. Analyses were performed using SAS (version 9.4, SAS Institute Inc, Cary, North Carolina) and R Core Team (2020).[22] All participants in the DANAMI-3-iPOST trial (ClinicalTrials.gov Identifier NCT01435408) provided oral and written informed consent before initiation of any trial-related treatment. The trial was performed in accordance with the Declaration of Helsinki, and a local ethics committee and an institutional review board approved the study protocol before initiation of the trial. This present study was approved by the Danish Data Protection Agency (2007−58−0015/GEH−2014−014 and I−suite number: 02732). In Denmark, register-based studies in anonymous setup do not require ethical approval.

The study population has been described previously.[15] Among 1,234 DANAMI-3-iPOST included patients with STEMI, 714 underwent thrombectomy (57.9%) and 520 did not (42.1%). Baseline characteristics are presented in Table 1. The median follow-up time was 4.8 (interquartile range 4.2 to 5.50) years.

In patients treated without thrombectomy, the primary end point occurred in 48 patients (15%) in the iPOST group and in 42 patients (22%) in the conventional group (p = 0.044). Patients treated with iPOST also had a significantly lower event rate of cardiovascular mortality (6% vs 12%, p = 0.014) than the conventional group. There was no significant difference in event rates between groups for patients treated with thrombectomy (Table 2). The

Table 1
Baseline characteristics, PCI procedural data, and medical therapy at discharge in patients who were treated with and without thrombectomy stratified by treatment

	No thrombectomy			Thrombectomy		
	Conventional (n = 194)	iPOST (n = 326)	p Value	Conventional (n = 423)	iPOST (n = 291)	p Value
Demographics						
Age, years	64 ± 12	63 ± 11	0.28	60 ± 12	62 ± 11	0.10
Male	145 (75%)	75 (77%)	0.59	341 (81%)	238 (82%)	0.70
Comorbid and clinical conditions						
Hypertension	77 (40%)	137 (42%)	0.58	132 (32%)	104 (36%)	0.22
Hyperlipidemia	58 (30%)	93 (29%)	0.77	123 (30%)	80 (28%)	0.61
Diabetes mellitus	18 (9%)	30 (9%)	>0.99	32 (8%)	25 (9%)	0.67
Active or previous smoker	145 (75%)	246 (76%)	0.75	332 (79%)	218 (76%)	0.27
Family history of CAD	82 (44%)	136 (44%)	>0.99	175 (44%)	119 (42%)	0.75
Previous myocardial infarction	11 (6%)	17 (5%)	0.84	25 (6%)	13 (5%)	0.50
Previous PCI or CABG	15 (8%)	16 (5%)	0.25	24 (6%)	16 (6%)	>0.99
Symptoms onset to PCI, hours	2.8 (2.0-4.9)	3.0 (2.2-4.9)	0.29	3.0 (2.2-4.8)	2.8 (2.1-4.4)	0.24
Killip class II-IV at any time	14 (7%)	13 (4%)	0.15	35 (8%)	20 (7%)	0.57
LVEF at discharge, %	50 [40; 55]	45 [40; 50]	0.06	50 [40; 55]	45 [40; 55]	0.24
Peak CKMB,* μg/L	156 [73; 258]	187 [92; 317]	0.07	217 [114; 320]	237 [118; 337]	0.38
Intervention						
Culprit vessel						
Right coronary artery	92 (47%)	136 (42%)	0.38	194 (46%)	137 (47%)	0.48
Left main artery	0 (0%)	0 (0%)		0 (0%)	1 (0%)	
Left anterior descending artery	69 (36%)	135 (41%)		176 (42%)	123 (43%)	
Circumflex artery	33 (17%)	55 (17%)		53 (13%)	29 (10%)	
Pre-PCI operator-reported TIMI flow 0-1	194 (100%)	326 (100%)	>0.99	423 (100%)	291 (100%)	0.47
Post-PCI operator-reported TIMI flow 3	181 (93%)	312 (96%)	0.20	400 (95%)	276 (95%)	0.63
Multivessel disease	87 (45%)	149 (46%)	0.86	161 (38%)	100 (36%)	0.34
Procedure-related medicine						
Use of glycoprotein IIb/IIIa inhibitor	13 (7%)	40 (12%)	0.051	55 (13%)	49 (17%)	0.16
Use of bivalirudin	156 (80%)	265 (81%)	0.82	347 (82%)	240 (83%)	0.92
Medical therapy at discharge						
Antiplatelet therapy						
Aspirin	188 (97%)	321 (99%)	0.19	413 (98%)	284 (98%)	>0.99
Clopidogrel	30 (16%)	35 (11%)	0.13	69 (17%)	57 (20%)	0.27
Prasugrel or ticagrelor	161 (84%)	290 (89%)		347 (83%)	228 (80%)	
Statin	185 (96%)	316 (97%)	0.45	417 (99%)	281 (97%)	0.06
β-blocker	161 (83%)	285 (87%)	0.19	383 (91%)	264 (91%)	>0.99
ACE inhibitor or angiotensin II receptor blocker	93 (48%)	161 (50%)	0.79	193 (46%)	162 (56%)	0.010
Calcium channel blocker	26 (13%)	35 (11%)	0.40	20 (5%)	20 (7%)	0.25

Some of the table content has previously been published.[15]

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKMB = creatine kinase myocardial band; Ipost = ischemic postconditioning; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

* Peak CKMB has 42% and 36% missing values for patients without and with thrombectomy, respectively.

cumulative incidences of the primary end point and individual components hereof are presented in Figure 1. In patients treated without thrombectomy, iPOST was associated with a reduced long-term risk of both the primary end point (HR 0.62, 95% CI 0.41 to 0.94, p = 0.023) and cardiovascular mortality (HR 0.46, 95% CI 0.25 to 0.83, p = 0.010) (Table 2). In multivariate Cox analysis, iPOST remained associated with reduced long-term risk of cardiovascular mortality (HR 0.53, 95% CI 0.29 to 0.97, p = 0.039) (Table 2). In patients treated with thrombectomy, there was no significant association between any outcome and iPOST, whether analyzed unadjusted or adjusted (Table 2). In addition, there was no interaction between complete revascularization, age, gender, and iPOST on the primary end point. In patients treated without thrombectomy, there was a significant interaction between iPOST and use of glycoprotein IIb/IIIa inhibitor (p = 0.025) on the primary end point. Subgroup analyses are presented in Table 3.

In the full DANAMI-3-iPOST cohort, there was a significant interaction between thrombectomy and iPOST on cardiovascular mortality (p = 0.025), but no interaction between thrombectomy and iPOST on the primary end point (p = 0.07) or hospitalization for heart failure (p = 0.58). The primary end point occurred in 97 patients (16%) treated with iPOST and in 114 patients (19%) treated with conventional PCI. There was no significant association between iPOST and any included end points (Supplementary Table 2).

The main finding of this 5-year follow-up study of the DANAMI-3-iPOST trial including patients with STEMI

Table 2
Event rates and association between iPOST and outcomes in patients with STEMI stratified by treatment with thrombectomy

No thrombectomy (n = 520)	iPOST (n = 326)	Conventional (n = 194)	p Value	Unadjusted analysis			Adjusted analysis*		
				HR	95% CI	p Value	HR	95% CI	p Value
Primary end point†	48 (15%)	42 (22%)	0.044	0.62	[0.41; 0.94]	0.023	0.69	[0.46; 1.05]	0.08
Cardiovascular mortality	20 (6%)	24 (12%)	0.014	0.46	[0.25; 0.83]	0.010	0.53	[0.29; 0.97]	0.039
Heart failure	33 (10%)	25 (13%)	0.33	0.71	[0.42; 1.20]	0.20	0.78	[0.46; 1.32]	0.35
All-cause mortality	45 (14%)	37 (19%)	0.11	0.64	[0.41; 0.99]	0.045	0.73	[0.47; 1.13]	0.16
Thrombectomy (n = 714)									
	iPOST (n = 291)	Conventional (n = 423)	p Value	Unadjusted analysis			Adjusted analysis*		
				HR	95% CI	p Value	HR	95% CI	p Value
Primary end point†	49 (17%)	72 (17%)	0.95	1.01	[0.70; 1.45]	0.95	0.97	[0.67; 1.40]	0.87
Cardiovascular mortality	25 (9%)	33 (8%)	0.70	1.12	[0.67; 1.88]	0.67	1.10	[0.65; 1.85]	0.72
Heart failure	26 (9%)	46 (11%)	0.40	0.84	[0.52; 1.36]	0.48	0.80	[0.49; 1.30]	0.36
All-cause mortality	34 (12%)	52 (12%)	0.81	0.96	[0.63; 1.48]	0.86	0.94	[0.61; 1.46]	0.79

CI = confidence interval; HR = hazard ratio; iPOST = ischemic postconditioning; STEMI = ST-segment elevation myocardial infarction.
* Adjusted for continuous age, gender, and use of glycoprotein IIb/IIIa inhibitor.
† The primary end point was a combination of cardiovascular mortality and hospitalization for heart failure.

presenting with myocardial infarction flow 0/1 treated with primary PCI was that iPOST reduced cardiovascular mortality and hospitalization for heart failure in patients treated without thrombectomy. This reduction was driven mainly by reduced cardiovascular mortality, and iPOST remained associated with this outcome after adjusting for potential confounders. Conversely, we found no benefit of iPOST on clinical outcomes in patients treated with thrombectomy.

Previous studies have found various effects of iPOST, even though several studies have suggested a cardioprotective effect of iPOST in patients with STEMI.[8,11–13] Yet, the existing ambiguous results could be explained by the interaction between different interventions mimicking the effect of other interventions.[23] In previous studies failing to confirm beneficial cardioprotective effects of iPOST, thrombectomy was used in 35% to 58% of the included patients.[11–13] The lack of iPOST effect in patients treated

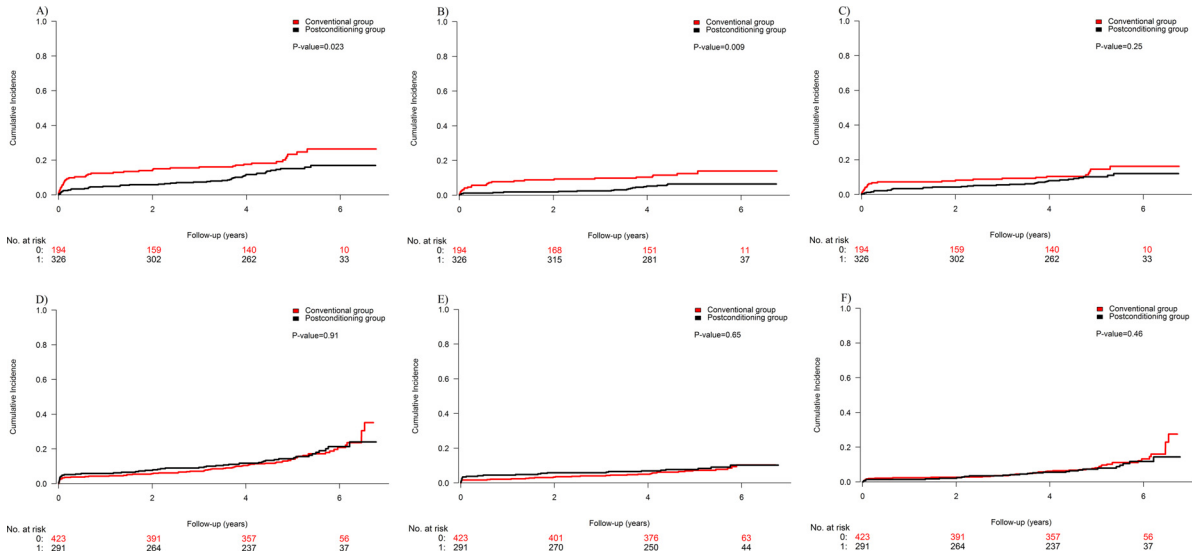

Figure 1. Cumulative incidence of the primary end point and individual components hereof stratified by randomized treatment in DANAMI-3-iPOST patients without (*A, B, C*) and with (*D, E, F*) previous thrombectomy. The Graphs A and D present the cumulative incidence of the primary end point in patients treated without thrombectomy (*A*) and with thrombectomy (*D*) during follow-up. The Graphs B and E present the cumulative incidence of cardiovascular mortality in patients treated without thrombectomy (*B*) and with thrombectomy (*E*). The Graphs C and F present the cumulative incidence of hospitalization for heart failure in patients treated without thrombectomy (*C*) and with thrombectomy (*F*). The cumulative incidence was calculated taking the competing risk of death from other causes into account. Gray's test was used to compare groups. The primary end point was a combination of cardiovascular mortality and hospitalization for heart failure. The *y* axes present the cumulative incidence of the end points, respectively, and the *x* axes present follow-up time in years. The red graphs present patients treated with conventional PCI, and the black graphs present patients treated with iPOST during primary PCI. Numbers at risk for each treatment group is given below the graphs. No. = number.

Table 3
Subgroup analysis of event rates and association between iPOST and primary end point in patients with STEMI stratified by treatment with thrombectomy

		No. of events, n (%)			Interaction between the primary end point* and variable
	n	iPOST	Conventional	p Value	p Value
No thrombectomy					
Symptom onset to PCI					
≤4 h	200	17 (13%)	13 (19%)	0.30	0.63
>4 h	103	18 (25%)	8 (27%)	0.83	
Culprit					
LAD	204	26 (19%)	20 (29%)	0.12	0.93
Non-LAD	316	22 (12%)	22 (18%)	0.13	
DM					
DM	48	6 (20%)	4 (22%)	>0.99	0.65
No DM	472	18 (11%)	35 (14%)	0.31	
Thrombectomy					
Symptom onset to PCI					
≤4 h	310	21 (16%)	26 (14%)	0.61	0.68
>4 h	150	13 (26%)	23 (23%)	0.69	
Culprit					
LAD	299	31 (25%)	37 (21%)	0.40	0.12
Non-LAD	414	18 (11%)	35 (14%)	0.31	
DM					
DM	57	4 (16%)	≤3 (≤10%)	0.69	0.60
No DM	657	45 (17%)	69 (18%)	0.81	

CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; iPOST = ischemic postconditioning; LAD = left anterior descending artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
* The primary end point was a combination of cardiovascular mortality and hospitalization for heart failure.

with thrombectomy remains unclear. One explanation could be that the thrombectomy catheter itself introduces reperfusion and thus injury; therefore, the sweet spot for any positive effect of subsequent iPOST is missed. Hereof, thrombectomy may blur the effect of iPOST because the latter may simply be instituted too late to be effective.[15] Hence, an analysis stratified by use of thrombectomy in DANAMI-3-iPOST showed an association between iPOST and reduced risk of 35-month all-cause mortality and hospitalization for heart failure.[15] However, noncardiac mortality because of malignancies or lung diseases are responsible for the majority of deaths on long-term following STEMI.[21] To reduce the impact of mortality unrelated to ischemic heart disease, our analyses investigated cardiovascular mortality censoring all patients with an event of noncardiovascular mortality. Thus, the cardioprotective effect of iPOST in patients with STEMI who were not treated with thrombectomy persisted in accordance with the findings of Nepper-Christensen et al.[15] So, iPOST might reduce reperfusion injury if an appropriate treatment strategy is chosen in patients with STEMI, in whom thrombectomy is precluded.[8,15,23] Moreover, thrombectomy may itself lead to harmful outcomes and should not be used in routine primary PCI[11,23,24] however, thrombectomy per se did not have any effect on either the outcomes presented here. Yet, in DANAMI-3-iPOST, treatment with thrombectomy was not randomized and was, in addition, unbalanced between treatment groups which could have confounded the results. Our previous findings in patients treated with thrombectomy stratified by randomized treatment did not show any statistical impact on the study outcomes,[15] and the current results persisted in adjusted analyses after including potential confounders. Hence, larger randomized clinical trials are needed to determine the true impact of iPOST in patients with STEMI. We are presently awaiting the results of the well-powered Ischemic Postconditioning in STEMI Patients Treated with Primary PCI (iPOST2) trial (ClinicalTrials.gov Identifier NCT03787745) evaluating the effect of iPOST in patients with STEMI without use of thrombectomy.

This study has some limitations owing to its observational and post hoc nature including residual confounding and only hypothesis-generating findings. Patients were not randomly assigned to thrombectomy and were more frequently used in the conventional group, which could potentially influence the risk-profile between treatment groups. Moreover, it is expected that patients who were treated with thrombectomy had larger thrombus burden which have may conferred a poorer prognosis per se and, thus, any effect of iPOST may have been blunted. The outcomes of this study were validated by a committee in the first part of the follow-up period and conducted according to registries for subsequent follow-up. This could lead to greater uncertainty with regard to clinical end points. However, the diagnosis for heart failure has a positive predictive value of 70% to 80% in Danish registries.[25] Furthermore, causes of death were obtained from death certificates completed by medical doctors and not based on autopsies, which may have affected the study findings.[19]

Our findings suggest that ischemic postconditioning in patients with STEMI treated with primary PCI but without

thrombectomy reduces long-term cardiovascular mortality and hospitalization for heart failure, and the effect is not confined to particular patient subsets. These findings are promising; iPOST is easy to perform, cost virtually nothing, and is well tolerated by the patients, but owing to the post hoc nature of the study, large randomized clinical trials are needed to confirm the promising cardioprotective effect of iPOST in patients with STEMI treated without thrombectomy.

Disclosures

Dr. Mæng has received lecture fees and advisory board fees from Novo Nordisk and a research grant from Bayer. Dr. Torp-Pedersen has received grants for studies from Bayer and Novo Nordisk. Dr. Køber has received speaker's honorarium from Novo Nordisk, AstraZeneca, Boehringer, and Novartis, unrelated to this topic. Dr. Engstrøm has received speakers/advisory board fee from Abbot Vascular, Boston Scientific, Bayer, and Novo Nordisk.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.11.014.

1. Lønborg J, Vejlstrup N, Kelbæk H, Holmvang L, Jørgensen E, Helqvist S, Saunamäki K, Ahtarovski KA, Bøtker HE, Kim WY, Clemmensen P, Engstrøm T. Final infarct size measured by cardiovascular magnetic resonance in patients with ST elevation myocardial infarction predicts long-term clinical outcome: an observational study. *Eur Heart J Cardiovasc Imaging* 2013;14:387–395.
2. Hausenloy DJ, Botker HE, Engstrom T, Erlinge D, Heusch G, Ibanez B, Kloner RA, Ovize M, Yellon DM, Garcia-Dorado D. Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and tribulations. *Eur Heart J* 2017;38:935–941.
3. Heusch G, Gersh BJ. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. *Eur Heart J* 2017;38:774–784.
4. Vogel B, Claessen BE, Arnold SV, Chan D, Cohen DJ, Giannitsis E, Gibson CM, Goto S, Katus HA, Kerneis M, Kimura T, Kunadian V, Pinto DS, Shiomi H, Spertus JA, Steg PG, Mehran R. ST-segment elevation myocardial infarction. *Nat Rev Dis Primers* 2019;5:39.
5. Nepper-Christensen L, Lønborg J, Høfsten DE, Sadjadieh G, Schoos MM, Pedersen F, Jørgensen E, Kelbæk H, Haahr-Pedersen S, Flensted Lassen J, Køber L, Holmvang L, Engstrøm T. Clinical outcome following late reperfusion with percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2021;10:523–531.
6. Desta L, Jernberg T, Löfman I, Hofman-Bang C, Hagerman I, Spaak J, Persson H. Incidence, temporal trends, and prognostic impact of heart failure complicating acute myocardial infarction. The SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): a study of 199,851 patients admitted with index acute myocardial infarctions, 1996 to 2008. *JACC Heart Fail* 2015;3:234–242.
7. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 2003;285:H579–H588.
8. Lønborg J, Kelbaek H, Vejlstrup N, Jørgensen E, Helqvist S, Saunamäki K, Clemmensen P, Holmvang L, Treiman M, Jensen JS, Engstrøm T. Cardioprotective effects of ischemic postconditioning in patients treated with primary percutaneous coronary intervention, evaluated by magnetic resonance. *Circ Cardiovasc Interv* 2010;3:34–41.
9. Thibault H, Piot C, Staat P, Bontemps L, Sportouch C, Rioufol G, Cung TT, Bonnefoy E, Angoulvant D, Aupetit JF, Finet G, André-Fouët X, Macia JC, Raczka F, Rossi R, Itti R, Kirkorian G, Derumeaux G, Ovize M. Long-term benefit of postconditioning. *Circulation* 2008;117:1037–1044.
10. Sun H, Guo T, Liu L, Yu Z, Xu W, Chen W, Shen L, Wang J, Dou X. Ischemic postconditioning inhibits apoptosis after acute myocardial infarction in pigs. *Heart Surg Forum* 2010;13:E305–E310.
11. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Clemmensen P, Holmvang L, Jørgensen E, Pedersen F, Saunamaki K, Ravkilde J, Tilsted HH, Villadsen A, Aarøe J, Jensen SE, Raungaard B, Bøtker HE, Terkelsen CJ, Maeng M, Kaltoft A, Krusell LR, Jensen LO, Veien KT, Kofoed KF, Torp-Pedersen C, Kyhl K, Nepper-Christensen L, Treiman M, Vejlstrup N, Ahtarovski K, Lønborg J, Køber L. Third Danish Study of Optimal Acute Treatment of Patients With ST Elevation Myocardial Infarction −Ischemic Postconditioning (DANAMI-3−iPOST) Investigators. Effect of ischemic postconditioning during primary percutaneous coronary intervention for patients with ST-segment elevation myocardial infarction: a randomized clinical trial. *JAMA Cardiol* 2017;2:490–497.
12. Freixa X, Bellera N, Ortiz-Pérez JT, Jiménez M, Paré C, Bosch X, De Caralt TM, Betriu A, Masotti M. Ischaemic postconditioning revisited: lack of effects on infarct size following primary percutaneous coronary intervention. *Eur Heart J* 2012;33:103–112.
13. Hahn JY, Song YB, Kim EK, Yu CW, Bae JW, Chung WY, Choi SH, Choi JH, Bae JH, An KJ, Park JS, Oh JH, Kim SW, Hwang JY, Ryu JK, Park HS, Lim DS, Gwon HC. Ischemic postconditioning during primary percutaneous coronary intervention: the effects of postconditioning on myocardial reperfusion in patients with ST-segment elevation myocardial infarction (POST) randomized trial. *Circulation* 2013;128:1889–1896.
14. Høfsten DE, Kelbæk H, Helqvist S, Kløvgaard L, Holmvang L, Clemmensen P, Torp-Pedersen C, Tilsted HH, Bøtker HE, Jensen LO, Køber L, Engstrøm T. DANAMI 3 Investigators. The Third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation myocardial infarction: ischemic postconditioning or deferred stent implantation versus conventional primary angioplasty and complete revascularization versus treatment of culprit lesion only: rationale and design of the DANAMI 3 trial program. *Am Heart J* 2015;169:613–621.
15. Nepper-Christensen L, Høfsten DE, Helqvist S, Lassen JF, Tilsted HH, Holmvang L, Pedersen F, Joshi F, Sørensen R, Bang L, Bøtker HE, Terkelsen CJ, Maeng M, Jensen LO, Aarøe J, Kelbæk H, Køber L, Engstrøm T, Lønborg J. Interaction of ischaemic postconditioning and thrombectomy in patients with ST-elevation myocardial infarction. *Heart* 2020;106:24–32.
16. Kelbæk H, Høfsten DE, Køber L, Helqvist S, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, De Backer O, Bang LE, Kofoed KF, Lønborg J, Ahtarovski K, Vejlstrup N, Bøtker HE, Terkelsen CJ, Christiansen EH, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Jensen LO, Clemmensen P, Grande P, Madsen JK, Torp-Pedersen C, Engstrøm T. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. *Lancet* 2016;387:2199–2206.
17. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L. DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386:665–671.
18. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–549.
19. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health* 2011;39:26–29.
20. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–490.
21. Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, Holmvang L, Clemmensen P, Engstrøm T, Grande P,

Saunamäki K, Jørgensen E. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol* 2014;64:2101–2108.
22. R Core Team, R Foundation for Statistical Computing. R: A language and environment for statistical computing. Available at: https://www.R-project.org/https://www.R-project.org/. Accessed on October 28, 2021.
23. Lønborg JT. Targeting reperfusion injury in the era of primary percutaneous coronary intervention: hope or hype? *Heart* 2015;101:1612–1618.
24. Jolly SS, James S, Džavík V, Cairns JA, Mahmoud KD, Zijlstra F, Yusuf S, Olivecrona GK, Renlund H, Gao P, Lagerqvist B, Alazzoni A, Kedev S, Stankovic G, Meeks B, Frøbert O. Thrombus aspiration in ST-segment-elevation myocardial infarction: an individual patient meta-analysis: thrombectomy trialists collaboration. *Circulation* 2017;135:143–152.
25. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;6:e012832.