Optimal Timing for Coronary Intervention in Patients With Transient ST-Elevation Myocardial Infarction

Simcha R Meisel, MSc, MD*, Michael Kleiner-Shochat, MD, PhD, Rami Abu Fanne, MD, PhD, Ofer Kobo, MD, Naama Amsalem, BA, Aaron Frimerman, MD, Yaniv Levi, MD, David S Blondheim, MD, Jameel Mohsen, MD, Asaf Danon, MD, Avraham Shotan, MD, and Ariel Roguin, MD, PhD

STEMI patients admitted urgently to the hospital but experience early complete resolution of both ischemic symptoms and ST-elevations on the electrocardiogram are diagnosed as transient STEMI (TSTEMI). Current evidence indicates that primary intervention is plausible but in certain circumstances intervention can be delayed. We sought to examine whether there is a time limit to such a delay that may affect long-term outcome. Study population included prospectively admitted TSTEMI patients whose demographics, pertinent medical history, and clinical and angiographic features were recorded. Study patients were divided by the median time interval from admission to intervention and their characteristics and long-term survival were compared. Study population comprised 260 consecutive patients (age: 57±10 years, men: 84%) diagnosed as TSTEMI who were included from January 2000 to June 2019, which represent 6% of all STEMI patients. Coronary angiography was performed in 254 patients. The median time interval from admission to angiography was 17 hours (IQR: 7.2 to 38.7 hours). Early (<17 hours from admission) and late (>17 hours from admission) study groups were comparable. One patient died during admission and 41 throughout the long follow-up period of 8.5 ± 5.2 years (median: 8.2 years, IQR: 3.4 to 13.1). Mortality of early-treated TSTEMI patients (11.2%) was significantly lower than of the late-treated patients (21.6%, p <0.04). The Kaplan-Meier curve demonstrated a clear tendency toward improved survival in early-treated TSTEMI patients (p <0.09). In conclusion, the present data suggest that TSTEMI patients should be treated, if not by primary coronary intervention, then at least within 17 hours from admission to achieve better long-term outcome. **(Am J Cardiol 2019;124:1821−1826)**

The electrocardiogram of patients who present with ST-elevations myocardial infarction (STEMI) may occasionally normalize spontaneously or following initial medical treatment before reperfusion therapy. When accompanied by full symptomatic resolution, this clinical entity is termed transient STEMI (TSTEMI), usually characterized by minor myocardial damage and limited coronary disease and portends a benign prognosis.[1,2] TSTEMI seems to result from spontaneous reperfusion of the infarct-related coronary artery with effective restoration of blood flow to ischemic myocardium. TSTEMI represents a distinctive entity among the acute coronary syndromes,[3] but currently there are no clear evidence-based recommendations regarding timing of therapy in these patients. Recently, Lemkes et al have shown that the infarct size in TSTEMI is small and not influenced by timing of invasive therapy.[4] However, there still remains the question whether there is a time limit to the delay, after which coronary intervention should be performed to achieve optimal immediate results and best long-term outcome. The present analysis was performed in an attempt to address this clinical query.

Methods

TSTEMI was defined as a syndrome comprising acute ischemic symptoms with at least one electrocardiogram demonstrating ST-elevations, with both fully resolving before revascularization either spontaneously or shortly following initial medical therapy. STEMI was defined by ST-elevations observed on the electrocardiogram in at least 2 contiguous leads measured at the J point with amplitude of more than ≥0.25 mV in men below the age of 40 years, ≥0.2 mV in men over the age of 40 years, or ≥0.15 mV in women in leads V_2-V_3 or ≥0.1 mV in the other leads (in the absence of left ventricular hypertrophy or bundle branch block). The transient nature of the ST-segment elevations was defined when complete resolution of ST-segment elevations has occurred within 30 minutes with or without medical therapy. The time interval of 30 minutes for ECG normalization was frequently determined by the temporal difference between consecutive ECG recordings as practiced and not by symptom resolution which frequently would have yielded even earlier resolution. In addition, the electrocardiographic criterion for TSTEMI according to the present protocol required >90% resolution of ST-elevations, with the vast majority of patients demonstrating complete normalization of the ECG. Patients with spontaneous reperfusion defined as resolution of symptoms and ST-elevations on the electrocardiogram

Heart Institute, Hillel Yaffe Medical Center, Hadera, Israel. Manuscript received July 24, 2019; revised manuscript received and accepted September 6, 2019.

See page 1826 for disclosure information.

*Corresponding author: Tel: (972) 4-7744419; fax: (972) 4-7744422.
E-mail address: meisel@hymc.gov.il (S.R. Meisel).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.09.005

but with evolution of inverted T-waves in involved leads were not included.

TSTEMI patients were treated by immediate anticoagulant therapy with heparin or low molecular weight heparin, intense antiplatelet therapy including aspirin with clopidogrel, prasugrel, or ticagrelor whereas occasionally, depending on the clinical presentation, an intravenous IIb/IIIa glycoprotein inhibitor was also added, and sometimes intravenous nitrates. A few TSTEMI patients were immediately referred for primary percutaneous coronary intervention (PCI), mostly because of vague symptoms and availability of the cath lab, despite resolution of their ST-elevations. Otherwise, as occurred with the vast majority of patients, coronary angiography and revascularization were performed on an early invasive approach basis.[1] In-hospital survival data were obtained from hospital records and long-term out-of-hospital mortality data were retrieved from the Israeli Ministry of the Interior.

We assumed for years that complete clinical and electrocardiographic resolution indicate that myocardial ischemia has absolved, rendering immediate intervention less urgent. This was, in fact, the basis of the local protocol of early invasive approach taking into consideration the benefit of delay in the hope of achieving pharmacologically-facilitated dissolution of lesion-associated thrombus. With this objective in mind, the present study population of TSTEMI patients was divided according to the median time from admission to intervention segregating study patients to early and late subgroups compared with regard to demographics, lab tests, clinical characteristics, medical history, and long-term outcome.

TSTEMI patients were recorded prospectively in a local registry since January 2000 when the treatment protocol was implemented. Patients were consecutively included up to June 2019 when their vital status was assessed. Demographics, concomitant medical conditions, risk factors, laboratory results, and echocardiographic data were collected from the hospital file. Angiographic findings and details of the intervention were obtained from the procedural report. The local institutional review board approved this registry-based retrospective analysis of prospectively collected data. Informed consent was waived due to the retrospective and diagnostic nature of the study. The study required no external funding.

Continuous variables were expressed as mean ± standard deviation (SD) and median and interquartile range when appropriate. Categorical variables were expressed as frequency and percent. The difference between early-treated and later-treated TSTEMI study groups (as determined by timing of coronary intervention relative to the median interval) and categorical variables was examined using the Chi-square test (or Fisher's exact test). The *t* test or the Mann-Whitney *U* tests were used for continuous variables. Kaplan-Meier survival curves were constructed and compared by the Log-rank test. Statistical analysis and data management were performed using SPSS version 25 software. Statistical significance was considered when $p < 0.05$.

Results

Since January 2000, 4,574 STEMI patients were admitted to the intensive cardiac care unit of our medical center. Of these, 260 patients, who comprise the study population, were diagnosed as TSTEMI (6%, Figure 1). Their median age was 57 ± 10 years, mostly were men (84%), with their demographic features, pertinent medical history, and clinical characteristics shown in Table 1. As expected, myocardial damage in this patient population was minor as evidenced by low levels of maximal creatinine kinase and troponin. Left ventricular systolic function was not significantly reduced [LVEF: 60 ± 9% median: 65% (IQR: 52 to 65%)] and regional wall motion abnormalities index also low, 1.25 ± 0.3 (median: 1.2, IQR: 1 to 1.3).

Six patients did not undergo coronary angiography. Two patients refused the procedure and in 4 other patients it was decided to treat conservatively. Hence, 254 patients were available for analysis. The distribution of the admission-to-intervention time intervals showed that patients were indeed treated according to the early invasive approach (Figure 2), and the median time that elapsed from admission to intervention was 17 hours (IQR: 7.2 to 38.7 hours). Dividing study population according to this value yielded 2 study groups that were fully comparable in their demographics, concomitant medical conditions, blood tests, extent of the coronary disease, the infarct-related artery or the territory of STEMI (Table 1).

The present analysis was characterized by a long follow-up for most patients (8.5 ± 5.2 years, median: 8.2 years, IQR: 3.4 to 13.1). During the index hospitalization only one patient died. Forty-one patients died during the follow-up period with an overall mortality of 16.4%. The mortality rate during the follow-up period among the early-treated TSTEMI patients (<17 hours) was 11.2% compared with 21.6% in the late-treated patient subgroup (>17 hours, $p < 0.04$). The Kaplan-Meier survival curve showed separation of curves for study groups after 8 years of follow-up with a tendency toward statistical significance (Figure 3, $p = 0.09$). Perhaps the extended follow-up period of study patients, allowed to observe the long-term impact of small myocardial damage, probably undetectable in the immediate setting.

Discussion

About 6% to 15% of patients admitted urgently to the hospital with typical symptoms and electrocardiographic criteria of STEMI experience complete early resolution of the ST-elevations on the electrocardiogram and subsidence of the ischemic symptoms, hence the descriptive term TSTEMI.[1,2,4] The clinical and electrocardiographic resolution occur either spontaneously or after initial medical therapy but before revascularization. TSTEMI patients are often admitted to the intensive cardiac care unit without delay but present a therapeutic dilemma. The clinician must decide whether to apply the therapeutic protocol recommended for STEMI commensurate to the electrocardiographic presentation or the approach suitable for NSTEMI as appropriate after ST resolution. The present analysis showed that the invasive procedure, usually a coronary intervention, should be performed at least within 17 hours from admission. The long-term mortality of TSTEMI patients treated within 17 hours from admission was significantly lower than that of those treated later than 17 hours ($p < 0.04$). The Kaplan-Meier curve

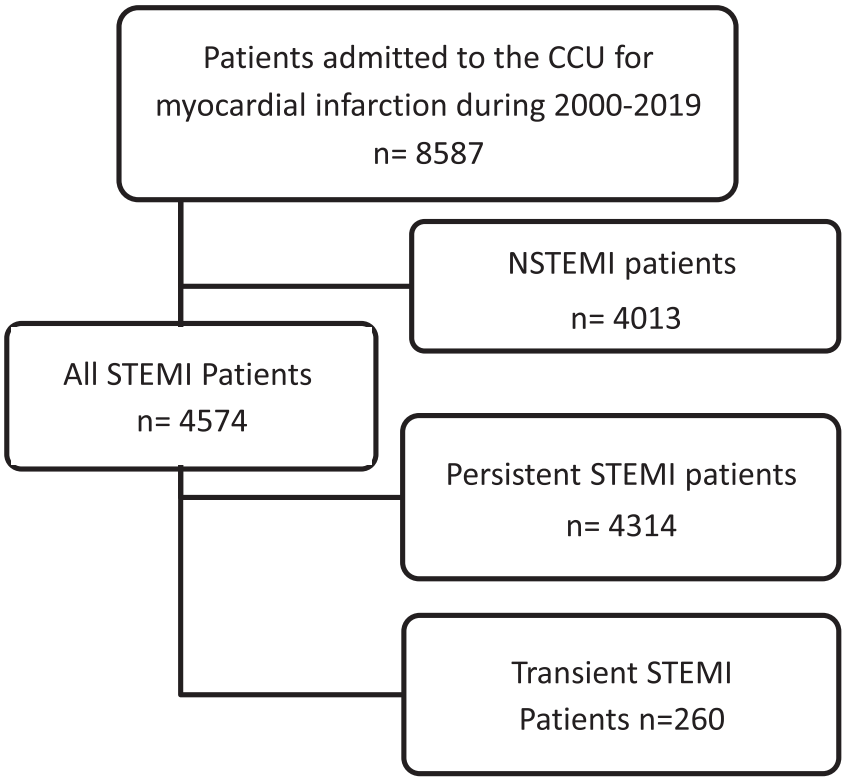

Figure 1. Study patient flow chart. STEMI = ST-elevation myocardial infarction; NSTEMI = Non-STEMI.

also demonstrated a clear tendency toward improved survival in TSTEMI treated early (Figure 3, p <0.09).

The unique TSTEMI condition has not been formally classified or discriminated from either the STEMI or NSTEMI syndromes and is commonly included in the NSTEMI guidelines without direct reference for a specific therapeutic approach.[5,6] In most cases the pathophysiological basis underlying TSTEMI seems to be the restoration of effective flow in the culprit artery resulting in pronounced or complete relief of ischemia and ST-segment resolution. The latter mirrors the overall impact of myocardial reperfusion versus infarct-related artery epicardial patency alone, and aligns best with clinical outcomes in STEMI patients. In fact, it signals both epicardial vessel recanalization as well as microvascular flow at the cellular level.[7,8] Partial resolution of a plaque-associated thrombus appears to be the preponderant mechanism underlying the TSTEMI syndrome, though recruitment of robust collaterals may serve as another mechanism of ischemia relief in TSTEMI patients as rarely observed in the present study. An additional conceivable mechanism of TSTEMI may be spasm of a coronary artery. Cyclic variation in the tone of vascular smooth muscle cells in an angiographically-normal but endothelium-dysfunctional coronary artery may induce transient occlusion and transient ST-elevations. However, plaque rupture with platelet activation and thrombin generation likewise increase the propensity for coronary vasoconstriction. Indeed, angiography demonstrated normal or near-normal coronary arteries in 42 patients (16.6%) included in the present study, similar to previous reports.[4,8] Furthermore, smoking known to precipitate coronary spasm was observed in many TSTEMI patients in the current and previous studies[8,9] suggesting that coronary spasm might play an important role in this population.

Whatever the mechanism, one treatment option is to perform primary PCI on TSTEMI patients as for ordinary persistent STEMI patients in keeping with initial ST-elevation on the presenting ECG. The proponents of this approach advocate primary PCI in concern of possible re-occlusion of the putative infarct-related coronary artery.[3] Others prefer to defer intervention, to administer immediately intense anti-platelet and anticoagulant therapy, and to perform early coronary angiography, similar to the approach in NSTEMI patients. This policy is based on the sound clinical thought of attempting to achieve dissolution of lesion-associated thrombus in order to avert microvascular obstruction during subsequent angioplasty. Badings et al have claimed, based on their findings, that early treatment did not result in myocardial salvage and that the presence of temporary ST-segment elevation did not require a STEMI-like approach with urgent revascularization.[10]

Similarly, Meneveau et al[11] performed a nonrandomized, matched comparison of immediate versus delayed angioplasty in 78 TSTEMI patients with patent infarct related artery and >70% ST-segment resolution at the time of angiography. They found that administration of dual antiplatelet therapy and GPIIb-IIIa inhibitors and delaying PCI for 24 hours, resulted in a higher procedural success rate and lower peak CK-MB levels without an increased risk of major adverse coronary events or in-hospital bleeding complications. Only recently, a randomized controlled study performed by Lemkes et al has demonstrated, as we have advocated previously, that the infarct size in TSTEMI assessed by biomarker levels and CMR imaging is small

Table 1
The demographics, lab tests, incidence of atherosclerosis risk factors, and concomitant medical conditions in the overall population and in study groups by timing of coronary angiography—earlier or later than 17 hours

Variable	Overall study population	Early PCI group (<17.2 hours, n = 127)	Later PCI group (≥17.2 hours, n = 127)
Age	57 ± 10	56 ± 10	58 ± 10
Man	214 (84%)	102 (80%)	112 (88%)
Religion (Jew)	165 (65%)	81 (64%)	84 (66%)
Hemoglobin (gr/dl)	14 ± 1.5	14 ± 1.5	14 ± 1.5
WBC (10^3 cells/mm^3)	10 ± 3	10 ± 3	9 ± 2
Monocytes (10^3 cells/mm^3)	0.7 ± 0.4	0.8 ± 0.5	0.7 ± 0.2
Platelets (10^3 cells/mm^3)	234 ± 64	238 ± 71	229 ± 56
CPK (Units/liter)	161 (92-306)	167 (109-306)	158 (92-297)
Creatinine (mg/dl)	1 ± 0.3	0.9 ± 0.3	1 ± 0.3
Admission glucose (mg/dl)	148 ± 68	147 ± 58	150 ± 76
Fasting glucose (mg/dl)	112 ± 38	113 ± 37	111 ± 39
Troponin T (ng/ml)	0.2 (0.1-0.8)	0.2 (0.1-0.8)	0.2 (0.1-0.6)
CRP (mg/liter)	3.7 (2-10)	3.9 (2-7)	3.7 (2-10)
Total cholesterol (mg/dl)	183 ± 41	185 ± 43	180 ± 39
Triglycerides (mg/dl)	133 (82-208)	133 (82-208)	133 (94-199)
High-density lipoprotein (mg/dl)	39.2 ± 13.2	39 ± 14	39 ± 13
Low-density lipoprotein (mg/dl)	115 ± 48	116 ± 47	114 ± 49
Heart rate (beats/minute)	76 ± 17	75 ± 18	76 ± 16
Systolic blood pressure (mm Hg)	142 ± 30	144 ± 29	139 ± 31
Diastolic blood pressure (mm Hg)	85 ± 19	85 ± 17	85 ± 20
History of heart failure	5 (2%)	1 (1%)	4 (3%)
S/P myocardial infarction	45 (18%)	25 (20%)	20 (16%)
S/P percutaneous coronary intervention	52 (20%)	25 (20%)	27 (21%)
S/P coronary artery bypass	7 (3%)	3 (2%)	4 (3%)
S/P cerebrovascular accident	13 (5%)	4 (3%)	9 (7%)
Hypertension	123 (48%)	62 (49%)	61 (48%)
Type 2 diabetes mellitus	44 (17%)	20 (16%)	24 (19%)
Insulin-dependent diabetes mellitus	13 (5%)	8 (6%)	5 (4%)
Diabetes mellitus	57 (22%)	29 (23%)	57 (22%)
New onset diabetes mellitus	4 (2%)	3 (3%)	1 (1%)
Current/past smoker	179 (70%)	86 (68%)	93 (73%)
Hyperlipidemia	158 (63%)	74 (58%)	84 (67)
Peripheral vascular disease	6 (2%)	4 (3%)	2 (2%)
Chronic renal failure	12 (5%)	3 (2%)	9 (7%)
Paroxysmal atrial fibrillation	5 (2%)	1 (1%)	4 (3%)
Persistent atrial fibrillation	1 (1%)	1 (1%)	0
Permanent atrial fibrillation	1 (1%)	0	1 (1%)
Average left ventricular ejection fraction (%)	60 ± 9	59 ± 10	61 ± 8
Median left ventricular ejection fraction (%)	65 (52-65)	65 (52-65)	65 (65-65)
Segmental wall motion abnormalities index	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3
Median segmental wall motion abnormalities index	1.2 (1-1.3)	1.2 (1-1.4)	1.2 (1-1.3)
Number of coronary arteries involved			
0	18 (7%)	10 (8%)	8 (6%)
1	114 (45%)	54 (43%)	60 (47%)
2	66 (26%)	37 (29%)	29 (23%)
3	56 (22%)	26 (21%)	30 (24%)
Infarct-related coronary artery	42 (17%)	20 (16%)	22 (17%)
Left anterior descending	74 (29%)	39 (31%)	35 (28%)
Circumflex/obtuse marginal artery	48 (19%)	23 (18%)	25 (20%)
Right	87 (34%)	44 (35%)	43 (34%)
Ramus	1 (0.4%)	0	1 (1%)
Saphenous vein graft	1 (0.4%)	0	1 (1%)
Infarct type			
Anterior myocardial infarction	79 (32%)	40 (32%)	39 (31%)
Nonanterior myocardial infarction	169 (68%)	83 (67%)	86 (69%)

No statistical difference between study groups was observed.

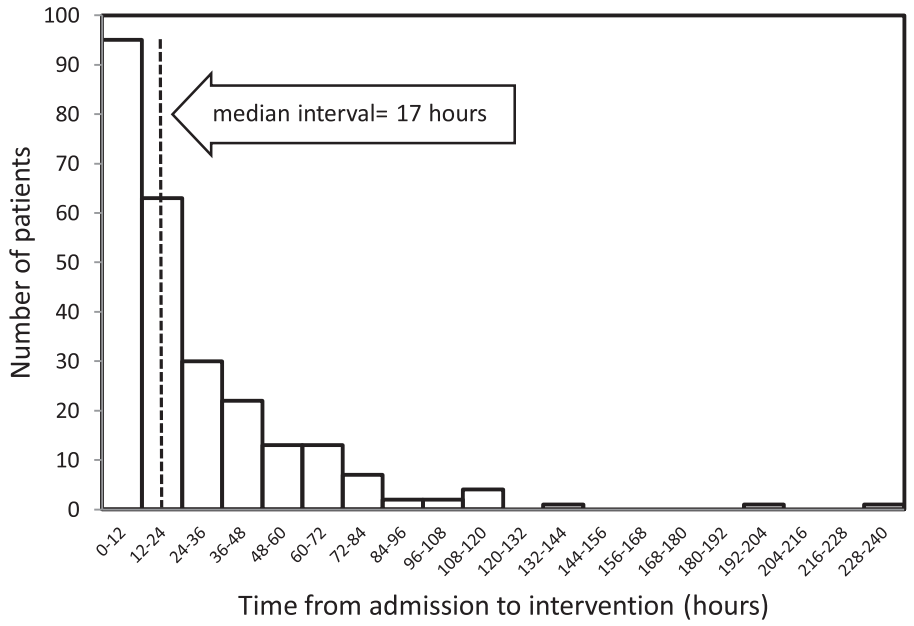

Figure 2. The distribution of the admission-to-intervention time intervals by 12-hour brackets with most TSTEMI patients clustered earlier in accord with the early invasive approach.

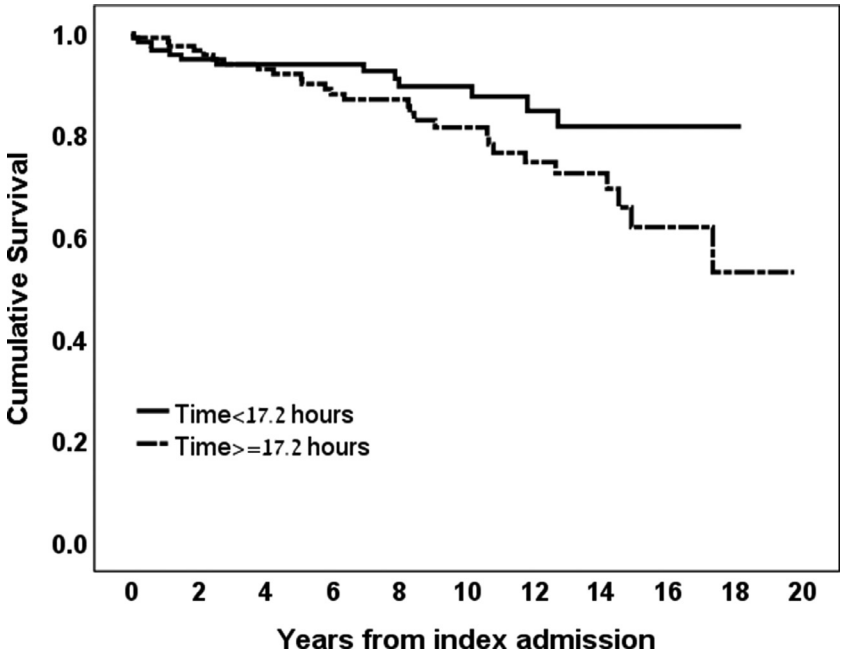

Figure 3. The Kaplan-Meier survival curve of study groups according to the timing of coronary intervention [earlier (solid line) or later than the median time interval of 17 hours (broken line), p <0.09].

and is not influenced by the timing of invasive strategy.[4] These workers have also observed that the short-term rate of major adverse coronary events was low in TSTEMI patients and similar between treatment approaches.

A different mortality rate among TSTEMI patients depending on the time of the intervention was observed in the present study. The basis of this finding is unclear, but it could be speculated to be related to the long-term effect of extended untreated myocardial hibernation. The bulk of evidence indicates that a primary intervention approach is plausible but not imperative in TSTEMI patients and that some delay, if the circumstances demand, is feasible in these patients. Yet, the results of the present study demonstrate that there is a 17-hour time limit to such a delay, and that coronary intervention should be performed within this time frame in order to achieve optimal immediate results and salutary long-term outcome. Analysis of a larger patient population will, perhaps, show a statistically significant trend on the survival curve and may allow to pin-point the optimal therapeutic time-window of TSTEMI patients.

The present study is not a randomized trial. In the current registry assembled since 2000, patients with TSTEMI were usually treated by immediate intense pharmacological therapy combined with an early invasive approach,[1] though a small minority of TSTEMI patients was treated by primary PCI. In case of difference of opinion regarding the appropriate therapy, consensus opinion was sought.

In conclusion, few published studies have dealt specifically with TSTEMI patients. The current guidelines, as aforementioned, do not provide a clear evidence-based therapeutic recommendation regarding TSTEMI patients. Current results suggest that TSTEMI patients should undergo coronary angiography or intervention within 17 hours from admission.

Disclosures

The authors declare that they have no conflict of interest regarding the present paper.

1. Meisel SR, Dagan Y, Blondheim DS, Dacca S, Shochat M, Kazatsker M, Asif A, Frimerman A, Shotan A. Transient ST-elevation myocardial infarction: clinical course with intense medical therapy and early invasive approach, and comparison with persistent ST-elevation myocardial infarction. *Am Heart J* 2008;155:848–854.
2. Rimar D, Crystal E, Battler A, Gottlieb S, Freimark D, Hod H, Boyko V, Mandelzweig L, Behar S, Leor J. Improved prognosis of patients presenting with clinical markers of spontaneous reperfusion during acute myocardial infarction. *Heart* 2002;88:352–356.
3. Blondheim DS, Kleiner-Shochat M, Asif A, Kazatsker M, Frimerman A, Abu-Fanne R, Neiman E, Barel M, Levy Y, Amsalem N, Shotan A, Meisel SR. Characteristics, management, and outcome of transient ST-elevation versus persistent ST-elevation and non-ST-elevation myocardial infarction. *Am J Cardiol* 2018;121:1449–1455.
4. Lemkes JS, Janssens GN, van der Hoeven NW, van de Ven PM, Marques KMJ, Nap A, van Leeuwen MAH, Appelman YEA, Knaapen P, Verouden NJW, Allaart CP, Brinckman SL, Saraber CE, Plomp KJ, Timmer JR, Kedhi E, Hermanides RS, Meuwissen M, Schaap J, van der Weerdt AP, van Rossum AC, Nijveldt R, van Royen N. Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial. *Eur Heart J* 2019;40:283–291.
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267–315.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. ESC Scientific Document Group. *Eur Heart J* 2019;40:87–165.
7. de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. *J Am Coll Cardiol* 2001;38:1283–1294.
8. Bainey KR, Fu Y, Wagner GS, Goodman SG, Ross A, Granger CB, Van de Werf F, Armstrong PW, ASSENT 4 PCI Investigators. Spontaneous reperfusion in ST-elevation myocardial infarction: comparison of angiographic and electrocardiographic assessments. *Am Heart J* 2008;156:248–255.
9. Arroyo Úcar E, Domínguez-Rodríguez A, Juárez Prera R, Blanco Palacios G, Hernández García C, Carrillo-Pérez Tome M, Abreu-González P. Differential characteristics of patients with acute coronary syndrome without ST-segment elevation compared to those with transient ST-segment elevation. *Med Intensiva* 2011;35:270–273.
10. Badings EA, Remkes WS, The SH, Dambrink JE, Tjeerdsma G, Rasoul S, Timmer JR, van der Wielen ML, Lok DJ, Hermanides R, van Wijngaarden J, Suryapranata H, van 't Hof AW. Early or late intervention in patients with transient ST-segment elevation acute coronary syndrome: Subgroup analysis of the ELISA-3 trial. *Cath Cardiovasc Interventions* 2016;88:755–764.
11. Meneveau N, Seronde MF, Descotes-Genon V, Dutheil J, Chopard R, Ecarnot F, Briand F, Bernard Y, Schiele F, Bassand JP. Immediate versus delayed angioplasty in infarct-related arteries with TIMI III flow and ST segment recovery: a matched comparison in acute myocardial infarction patients. *Clin Res Cardiol* 2009;98:257–264.