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Biochemical Validation of Patient-Reported Symptom Onset Time in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

OBJECTIVES This study evaluated a biochemical validation of patient-reported symptom onset time in patients with ST-segment elevation myocardial infarction (STEMI).

BACKGROUND Symptom onset time is an important metric but has never been formally validated.

METHODS The Mayo Clinic Percutaneous Coronary Intervention (PCI) Registry was interrogated to obtain baseline, procedural, and outcome data on 607 STEMI patients undergoing primary PCI. Biochemical onset time was determined by backward extrapolation of serial increasing cardiac troponin T (cTnT) measurements.

RESULTS The median patient-reported onset time was 12 min later than the calculated time of first cTnT increase and was therefore estimated to be 4.2 h later than the biochemical onset time (interquartile range: 1.9 to 11.1 h; $p < 0.001$), assuming a 4-h interval between coronary occlusion and first cTnT increase. Conventional ischemic time showed no association with infarct size (correlation with peak cTnT: $r = 0.023$; $p = 0.61$) or 1-year mortality (hazard ratio: 0.97 per doubling; 95% confidence interval: 0.68 to 1.40; $p = 0.88$). However, after recalculation of ischemic time with biochemical onset time, significant associations with infarct size ($r = 0.14$; $p = 0.001$) and 1-year mortality (hazard ratio: 1.70 per doubling; 95% confidence interval: 1.20 to 2.40; $p = 0.003$) were found. When underestimation of ischemic time by patient-reported onset time increased, so did the risk of mortality.

CONCLUSIONS Although our point estimate should be interpreted with caution, our study indicates that the actual onset of STEMI is likely to be earlier than the patient-reported onset time. Recalculation of ischemic time with biochemical onset time greatly enhanced its prognostic value. Underestimation of ischemic time by patient-reported onset time occurred more often in high-risk patients. (J Am Coll Cardiol Intv 2015;8:778–87) © 2015 by the American College of Cardiology Foundation.

Patients with ST-segment elevation myocardial infarction (STEMI) require rapid reperfusion therapy of the infarct-related coronary artery (1). In this context, patient-reported symptom onset time is a key metric. Symptom onset time is used in conjunction with time of treatment to determine the total ischemic time, which has been associated with myocardial reperfusion, infarct size, and mortality at short- and long-term follow-up (2–4). In addition, symptom onset time may aid in selecting a

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reperfusion strategy in patients with STEMI. Observational studies and a recent clinical trial have suggested that a pharmacoinvasive approach consisting of (pre-hospital) fibrinolysis with timely angiography may result in a superior outcome compared with primary percutaneous coronary intervention (PCI) in STEMI patients presenting within 3 h of symptom onset in whom delays to primary PCI are expected to be substantial (5–7). Similarly, current guidelines do not recommend routine reperfusion therapy in stable STEMI patients without clinical and electrocardiographic evidence of ongoing ischemia when time from symptom onset to presentation is more than 12 to 24 h (1).

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Despite this growing importance of symptom onset time, previous reports have pointed out that reported symptom onset time is subjective information and is likely to be an inaccurate measure of true time of onset of myocardial infarction (8,9). Some subgroups of patients are known for their often atypical symptoms such as women, those with diabetes, and elderly patients (10,11), which may further jeopardize the accuracy of reported symptom onset time. Furthermore, patients may report an episode of angina before coronary artery occlusion as the time of symptom onset. To the best of our knowledge, symptom onset time in STEMI has never been formally validated. In the present study, we validated patient-reported symptom onset time with biochemical onset time, which was estimated using cardiac troponin T (cTnT) concentrations. We determined the accuracy of patient-reported symptom onset time in the overall population and in relevant subgroups. Furthermore, we assessed the prognostic value of ischemic time using reported symptom onset time versus ischemic time using biochemical onset time.

METHODS

STUDY DESIGN. The Mayo Clinic PCI Registry was interrogated to obtain baseline, procedural, and outcome data on consecutive patients with STEMI undergoing primary PCI between 2004 and 2012 at the Mayo Clinic, Rochester, Minnesota. For this registry, data are prospectively collected by experienced interventional cardiology data technicians. After discharge, follow-up data are collected by a periodic standardized telephone survey with the patient. All adverse events are confirmed by reviewing the medical records of the patients followed at our institution and by contacting the patients' physicians and reviewing the hospital records of patients treated elsewhere. The database supervisor randomly audits 10% of the records for quality control purposes. STEMI was defined as symptoms suggestive of myocardial ischemia and an electrocardiogram with either new or presumed new ST-segment elevation or left bundle branch block. ST-segment elevation was defined as an increase of 1 mm or more in ST segments in 2 or more limb leads or an increase of 2 mm or more in 2 or more contiguous precordial leads. Patients were included if they had at least 2 increasing cTnT measurements within 24 h of patient-reported symptom onset time. Furthermore, the peak cTnT concentration had to be at least 5 times greater than the minimal value to allow for an accurate calculation of biochemical onset time. Exclusion criteria were moderate to severe renal disease (defined as creatinine >265 μmol/l [>3.0 mg/dl] or on dialysis or previous kidney transplantation), a previous PCI procedure within 7 days of the primary PCI procedure, unreported symptom onset time, and patient refusal to have their medical records reviewed for research. The study protocol was approved by the institutional review board.

METHODS OF MEASUREMENT. All patient baseline data were documented on admission. Hypertension was defined as a documented history or treatment with medication. Current smoking was defined as having smoked cigarettes within the past 6 months. Diabetes was defined as a documented diagnosis requiring treatment with medication or diet. Hypercholesterolemia was defined as total cholesterol >6.2 mmol/l (>240 mg/dl) or on drug therapy. Positive family history was defined as a family history of premature coronary heart disease (55 years of age or younger). Pre-procedural shock was defined as a systolic blood pressure <95 mm Hg or <110 mm Hg on inotropic support. Multivessel disease was defined as a stenotic lesion of ≥50% in a vessel other than the culprit coronary artery. Symptom onset time was defined as patient-reported date and time of onset of symptoms. In case of atypical or stuttering symptoms, the most likely time of onset of myocardial infarction was determined by the attending physician in discussion with the patient. To calculate biochemical onset time, serial blood levels of cTnT were used. cTnT levels are routinely measured in all STEMI patients following a standardized protocol on admission and at 3 and 6 h on an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Indianapolis, Indiana) with a coefficient of variation <10% at 0.035 ng/ml, a lower limit of

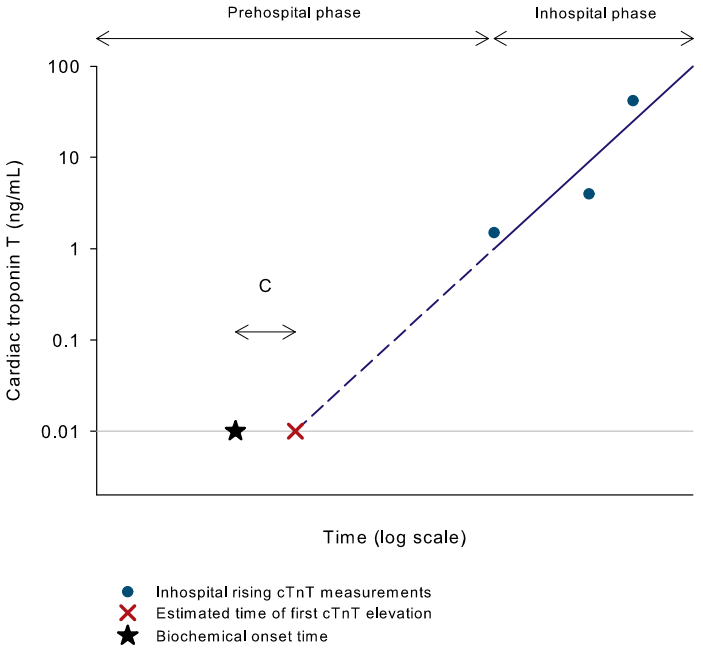
ABBREVIATIONS AND ACRONYMS

BMI = body mass index
cTnI = cardiac troponin I
cTnT = cardiac troponin T
IQR = interquartile range
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

detection of 0.01 ng/ml, and a 99th percentile reference limit <0.01 ng/ml in accordance with current guidelines for the diagnosis of myocardial infarction (12). Treatment time was the date and time documented in the catheterization procedure note as the time of first device used to open the coronary artery including a balloon, stent, or thrombectomy device. Conventional ischemic time was derived from reported symptom onset time and treatment time, whereas biochemical ischemic time was derived from biochemical onset time and treatment time. Thrombolysis In Myocardial Infarction (TIMI) flow grade was scored by the operator during the PCI procedure. Outcome measures included peak cTnT, which is a validated measure of infarct size (13,14) and all-cause mortality during hospitalization and at 1-year follow-up. One-year follow-up was completed in 93% of the included patients.

STATISTICAL ANALYSIS. Continuous variables were summarized as mean ± SD or median and interquartile range (IQR). Discrete variables were presented as numbers and percentages. Bivariate associations were assessed with Spearman's correlation, group differences were tested with the Mann-Whitney *U* test, and differences between paired observations were tested with the Wilcoxon signed rank test. To calculate the biochemical onset time, we adopted an approach as reported in a historical study that validated the circadian variation in acute myocardial infarction with creatine kinase myocardial band levels (15). Assuming a monoexponential increase in cTnT in STEMI patients, a regression line was fitted to the increasing cTnT levels in each patient after logarithmic transformation of both time and cTnT. By using a Tobit model, cTnT levels below 0.01 ng/ml could be considered as censored data in the modeling process (16). Backward extrapolation of the regression function allowed us to estimate the time of initial elevation of cTnT (defined as cTnT = 0.01 ng/ml). We then subtracted a predefined constant term from this time point, to account for the time between coronary occlusion and initial elevation of cTnT (Figure 1). On the basis of on previous studies, we chose a constant term of 4 h for all patients (17,18). Reported symptom onset time was compared with biochemical onset time in the overall population and in pre-specified subgroups on the basis of age (65 years of age and older), sex, body mass index (BMI) (above the median), hypertension, diabetes, hypercholesterolemia, current smoking, positive family history, previous myocardial infarction, previous PCI, previous coronary artery bypass grafting, reported symptom onset at night (midnight through 05:59), congestive heart failure on admission, pre-procedural shock, multivessel disease, and pre-procedural TIMI flow grade (>0). After logarithmic transformation of ischemic time, we used univariable Cox proportional hazards models to assess the association between ischemic time and 1-year mortality. For this analysis, ischemic time was calculated both with reported symptom onset time and biochemical onset time. In sensitivity analyses, the study results were recalculated with the following modifications: 1) selection of a constant factor of 2 h between coronary occlusion and initial elevation of cTnT; 2) exclusion of patients with post-procedural TIMI flow grade <3; and 3) exclusion of patients with only 2 cTnT measurements when 1 of these measurements was <0.01 ng/ml. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina), and statistical significance was set at $p < 0.05$ (2-tailed).

FIGURE 1 Determination of Biochemical Onset Time



After logarithmic transformation of both axes, a regression line was fitted to the increasing cardiac troponin T (cTnT) values in each patient. Extrapolation of this line allowed estimation of the time of first cTnT increase. Finally, a constant factor (C) was added to account for time between coronary occlusion and first cTnT elevation.

RESULTS

There were 1,809 eligible primary PCI cases in patients with STEMI between January 1, 2004 and

December 31, 2012. Of these, we excluded 1,174 patients in whom cTnT measurements were not suitable for biochemical onset time calculation, 15 patients who had had a previous PCI procedure within the past 7 days, and 13 patients with moderate to severe renal failure (Figure 2). Thus, 607 STEMI patients were included in the present analysis. Baseline and procedural characteristics of the included and excluded patients are listed in Table 1. In the included patients, the mean age was 62.6 years, 23% were female, and the mean BMI was 28.9 kg/m^2. The rate of current smokers was 33%, diabetes was present in 17% of patients, and 19% of patients had a history of PCI. On coronary angiography, TIMI flow grade 0 was found in 62% of patients and multivessel disease in 65%. The average number of cTnT measurements was 3.2, of which an average of 2.7 measurements was increasing.

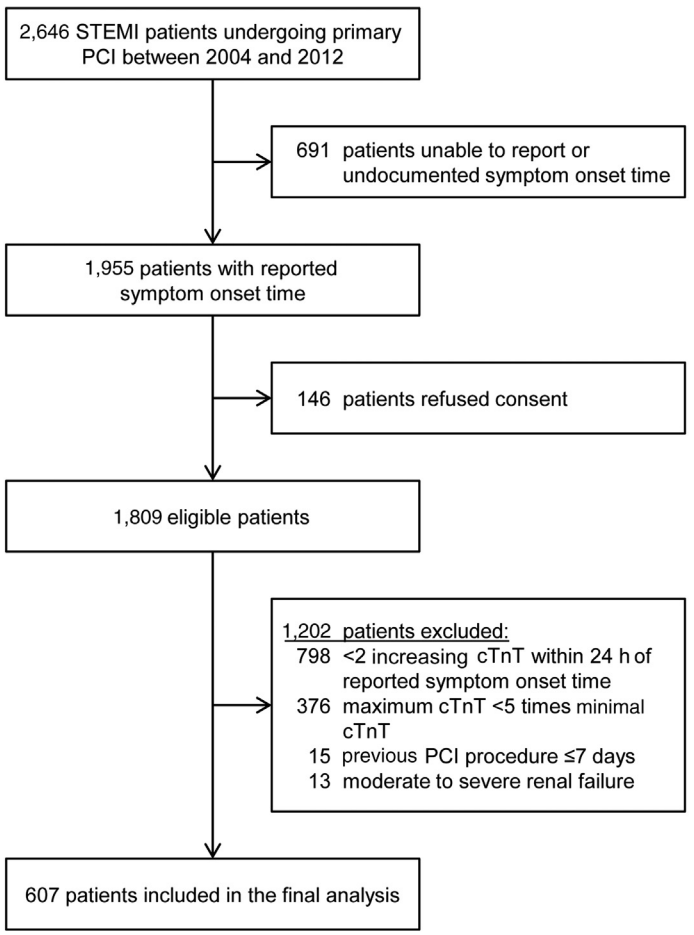
Patients excluded from this study were more likely to be female, to have higher rates of hypertension and longer ischemic time, but were less likely to have a positive family history (Table 1). Pre-procedural TIMI flow grade 0 was less often found in excluded patients. Treatment was similar in excluded patients, except for less right coronary artery interventions at the expense of more left anterior descending artery interventions. Mortality was higher in excluded patients.

REPORTED ONSET TIME VERSUS BIOCHEMICAL ONSET TIME. Overall, the median reported symptom onset time was 12 min later than the estimated time of first cTnT increase. As we assumed a time interval of 4 h from coronary occlusion to first cTnT increase, biochemical onset time tended to be earlier than reported symptom onset time, with a median difference of −4.2 h (IQR: −11.1 to −1.9 h; $p < 0.001$) (Figure 3). Subgroup differences are shown in Figure 4. Compared with the reference population, biochemical onset time was especially earlier than reported symptom onset time in patients aged 65 years of age and older (median: −4.8 h; IQR: −13.4 to −2.2 h; $p = 0.001$), in patients with a BMI <28 kg/m^2 (median: −4.7 h; IQR: −12.9 to −2.1 h; $p = 0.006$), in patients without a history of PCI (median: −4.3; IQR: −11.1 to 2.2 h; $p = 0.038$), and in patients with a pre-procedural TIMI flow grade >0 (median: −5.5; IQR: −15.3 to −2.0 h; $p = 0.001$). No differences were seen in subgroups on the basis of sex, diabetes, or reported symptom onset at night.

ASSOCIATION WITH ISCHEMIC TIME. When calculated using reported symptom onset time, median conventional ischemic time was 3.7 h (IQR: 2.4 to 6.1 h). Recalculation by using biochemical onset time resulted in a median biochemical ischemic time of 8.6 h (IQR: 5.1 to 17.4 h). Biochemical ischemic time tended to be longer than conventional ischemic time, although the 2 measures showed good agreement in patients with ischemic times >12 h (overall correlation, $r = 0.39$; $p < 0.001$) (Figure 5).

ASSOCIATION WITH OUTCOME. To verify the internal validity of biochemical onset time and compare the prognostic value of conventional ischemic time and biochemical ischemic time, their association with biochemical infarct size and mortality was assessed. Overall, the median peak cTnT was 3.7 ng/ml (IQR: 1.7 to 7.2 ng/ml). Although conventional ischemic time did not correlate with peak cTnT ($r = 0.023$; $p = 0.61$) (Figure 6A), there was a significant positive

FIGURE 2 Study Design and Participants



Flowchart of patient selection for this study. cTnT = cardiac troponin T; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 1 Baseline, Procedural, and Outcome Data

	Included Patients (n = 607)	Excluded Patients (n = 1,202)	p Value
Baseline			
Age, yrs	62.6 ± 13.4	64.0 ± 13.7	0.036
Female	140 (23)	355 (30)	0.004
Body mass index, kg/m^2	28.9 ± 5.3	29.1 ± 6.1	0.44
Hypertension	347 (62)	791 (69)	0.004
Diabetes mellitus	101 (17)	210 (18)	0.68
Hypercholesterolemia	372 (69)	755 (68)	0.61
Smoking status			0.52
Current	195 (33)	412 (35)	
Former	199 (34)	391 (33)	
Never	197 (33)	385 (32)	
Family history			<0.001
Positive	154 (25)	253 (21)	
Negative	260 (43)	673 (56)	
Unknown	193 (32)	276 (23)	
Previous myocardial infarction	96 (16)	206 (17)	0.47
Previous PCI	115 (19)	268 (22)	0.10
Previous CABG	32 (5)	79 (7)	0.29
Congestive heart failure			0.14
Current	46 (8)	110 (9)	
Previous	8 (1)	24 (2)	
Never	543 (91)	1,044 (89)	
Pre-procedural shock	74 (12)	129 (11)	0.34
Conventional ischemic time, h	3.7 (2.4–6.1)	4.8 (2.7–10.1)	<0.001
Procedural			
Multivessel disease	392 (65)	779 (66)	0.67
Pre-procedural TIMI flow grade 0	331 (62)	562 (52)	<0.001
Target coronary artery*			
Left anterior descending	208 (34)	522 (44)	<0.001
Right	320 (53)	486 (41)	<0.001
Circumflex	87 (14)	206 (17)	0.12
Left main	0 (0)	21 (2)	0.001
Graft	16 (3)	36 (3)	0.66
No. of segments treated	1.3 ± 0.6	1.4 ± 0.6	0.71
No. of stents placed	1.2 ± 0.7	1.2 ± 0.8	0.59
Use of drug-eluting stents	424 (70)	794 (66)	0.13
Periprocedural GP IIb/IIIa use	511 (84)	983 (82)	0.20
Outcome			
Post-procedural TIMI flow grade 3	531 (93)	1,050 (91)	0.26
Peak cardiac troponin T, ng/ml	3.7 (1.7–7.2)	1.3 (0.1–4.4)	<0.001
Death			
In-hospital	11 (1.8)	61 (5.1)	<0.001
1-year	34 (5.7)	119 (10)	<0.001

Values are mean ± SD, n (%), or median (interquartile range). *Sum is >100% because of multivessel procedures.

CABG = coronary artery bypass grafting; GP = glycoprotein; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

correlation between biochemical ischemic time and peak cTnT (r = 0.14; p = 0.001) (Figure 6B).

At follow-up, in-hospital mortality was 1.8% and 1-year mortality was 5.7% (Table 1). No association was found between conventional ischemic time and 1-year mortality (hazard ratio: 0.97 per doubling; 95% confidence interval: 0.68 to 1.40; p = 0.88). In contrast, longer biochemical ischemic time was clearly predictive of 1-year mortality (hazard ratio: 1.70 per doubling; 95% confidence interval: 1.20 to 2.40; p = 0.003). To gain further insight into this pattern, we also assessed the predictive value of the ratio of biochemical ischemic time over conventional ischemic time. An increase in this ratio was also predictive of 1-year mortality (hazard ratio: 1.60 per doubling; 95% confidence interval: 1.18 to 2.18; p = 0.003), indicating that shorter conventional ischemic time relative to biochemical ischemic time was more common in patients at higher risk of 1-year mortality.

SENSITIVITY ANALYSES. Full results of the sensitivity analyses are listed in the Online Appendix. Adjustment of the constant factor between coronary occlusion and initial increase in cTnT to 2 h resulted in a median difference between biochemical onset time and reported symptom onset time of −2.2 h (IQR: −9.1 to 0.1 h; p < 0.001), but did not affect any of the other analyses substantially. Results were also similar after exclusion of patients with post-procedural TIMI flow grade <3 (n = 76), thus arguing against a significant bias in the modeling process due to cTnT washout after reperfusion. Finally, we recalculated our results after exclusion of patients with only 2 cTnT measurements when the first measurement was <0.01 ng/ml (n = 85). This represented the group of patients with the most scarce data to model cTnT, and the Tobit model showed a slight bias toward later biochemical onset time in these patients. In the remaining patients, the difference between biochemical onset time and reported symptom onset time was greater and the correlation between biochemical ischemic time and peak cTnT was weaker (r = 0.08; p = 0.081), although performance was still better than conventional ischemic time. Results were otherwise similar.

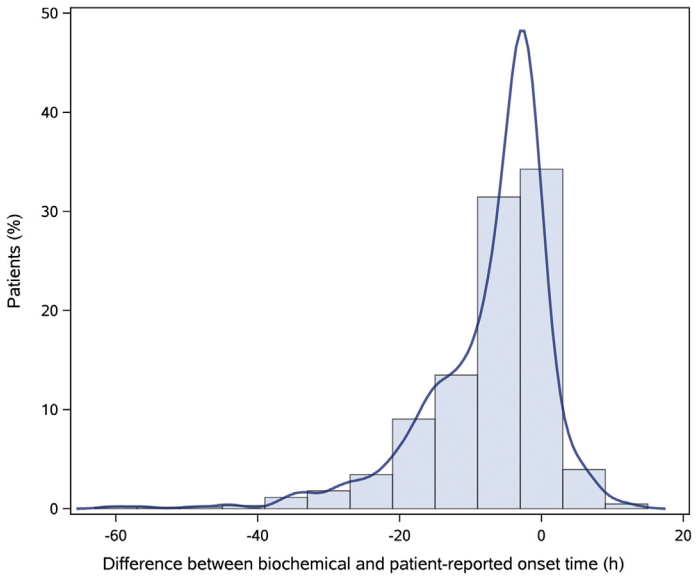
DISCUSSION

To the best of our knowledge, we are the first to validate symptom onset time in patients with STEMI. Patient-reported symptom onset time was compared with biochemical onset time, which was derived from serial cTnT measurements. We found that reported symptom onset time tended to be later than biochemical onset time and that this phenomenon was even more pronounced in elderly patients, in patients with a BMI <28 kg/m^2, in patients without a history of PCI, and in patients with residual flow in the culprit artery on coronary angiography. Conventional

ischemic time—reported symptom onset to treatment time—did not correlate with peak cTnT and mortality. Conversely, biochemical ischemic time—biochemical onset to treatment time—was associated with peak cTnT and mortality. An increase in the ratio of biochemical ischemic time over conventional ischemic time was also associated with mortality, indicating that larger differences between these measures were more frequent in patients at higher risk of death.

Although our findings are novel and compelling, a thorough understanding of the methodology applied to determine biochemical onset time is crucial to the interpretation of our results. As shown in **Figure 1**, backward extrapolation of serial increasing cTnT measurements was used to estimate the time of initial cTnT increase. From this time point, 4 h were subtracted in all patients to account for the time between coronary occlusion and first cTnT increase. This constant term was predefined and was based on the need for coronary perfusion for biomarkers to reach the peripheral circulation as well as the scarce data available from previous studies investigating this relationship (17,18). In 197 patients presenting with chest pain, Eggers et al. (17) demonstrated that 86% of patients ultimately classified as non-STEMI had increased cardiac troponin I (cTnI) levels within 4 h of symptom onset. In another study, cTnI measurements were performed on admission in patients presenting with chest pain. In this study, it was demonstrated that a second cTnI measurement performed at least 3 h after symptom onset identified 78% of patients who would have an increased cTnI value 6 h after admission (18). However, these studies relied on reported symptom onset time and are prone to the very bias that we tried to assess in this study. Furthermore, they were predominantly conducted in non-NSTEMI patients in whom the infarct-related artery is usually not fully occluded. Patient-reported symptom onset time is probably later than the thrombotic coronary event in these patients, as was the case in our study in STEMI patients with residual flow in the culprit coronary artery. Thus, the choice of the constant remains arbitrary to some extent because the true time of coronary occlusion cannot be known. Accordingly, the point estimate of the median difference between biochemical onset time and reported symptom onset time found in our study (−4.2 h) should be interpreted with caution. Still, regardless of the constant factor, the median reported symptom onset time in our study roughly coincided with the estimated time of first cTnT increase, thereby representing clear evidence that reported symptom onset time is later than the actual time of onset of STEMI. Moreover, a sensitivity analysis demonstrated that modification of the constant factor did not materially change the results of any of the other analyses reported in this study.

FIGURE 3 Distribution of the Difference Between Biochemical Onset Time and Reported Symptom Onset Time

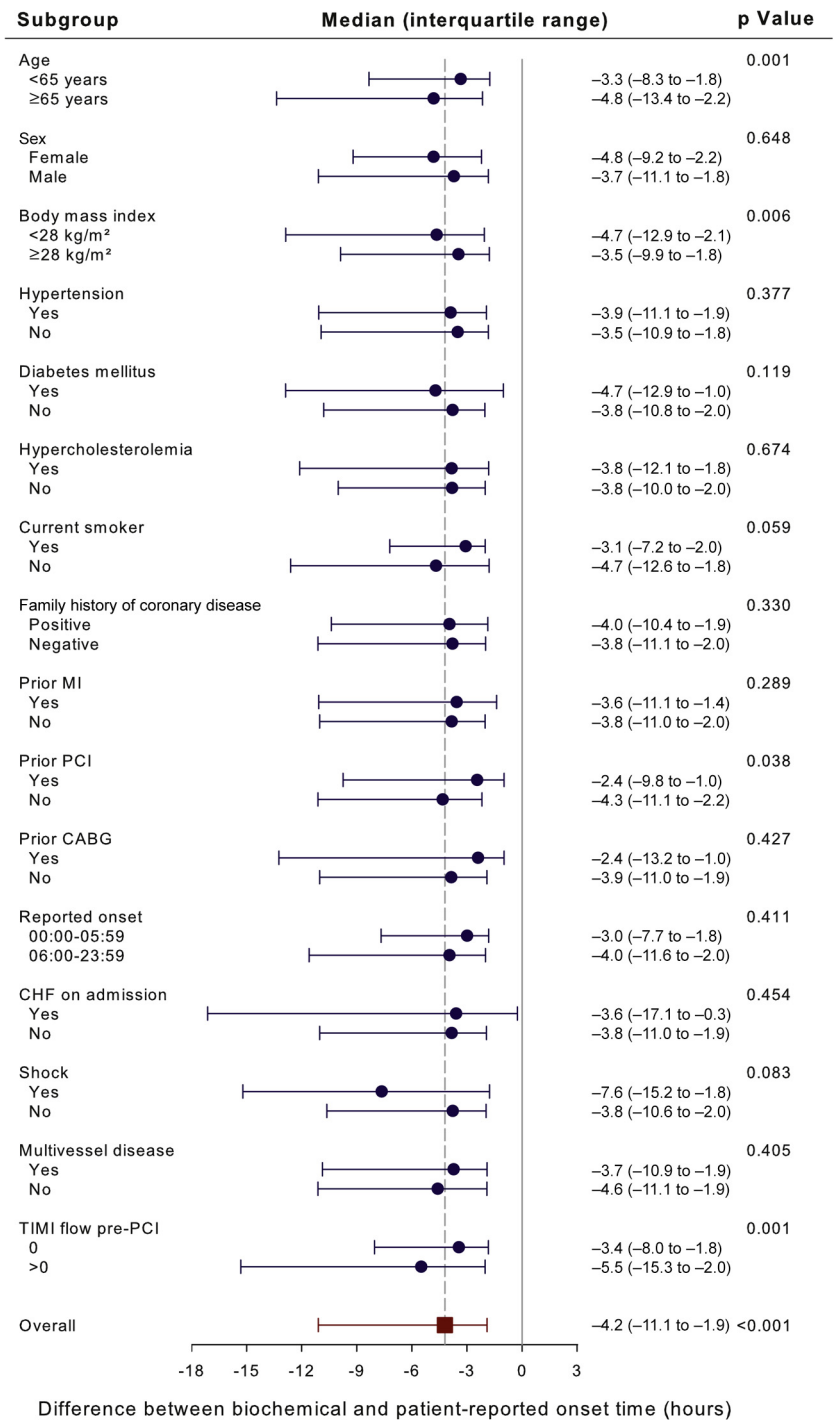


Median biochemical onset time was 4.2 h earlier than reported onset time (interquartile range: 1.9 to 11.1 h; $p < 0.001$). The **blue line** indicates the estimated density function using a kernel estimator.

In a sensitivity analysis, the association between biochemical ischemic time and peak cTnT was no longer significant after exclusion of patients with 1 undetectable and 1 increased cTnT value. Although this could be related to the modeling of cTnT, other explanations are also plausible. Clearly, a sample size reduction limits the statistical power to detect any association. More importantly, patients with initially undetectable cTnT values are likely to be early presenters and generally have a favorable outcome (19). Selective exclusion of these patients may compromise the association between ischemic time and outcome.

We found greater deviation between reported symptom onset time and biochemical onset time in elderly patients. This finding is consistent with findings of previous studies, showing that elderly patients with acute myocardial infarction more often present with atypical symptoms such as dyspnea and faintness (10). In addition, recollection of time of onset may be less accurate in elderly patients.

FIGURE 4 Subgroup Differences in Biochemical Onset Time Relative to Reported Symptom Onset Time

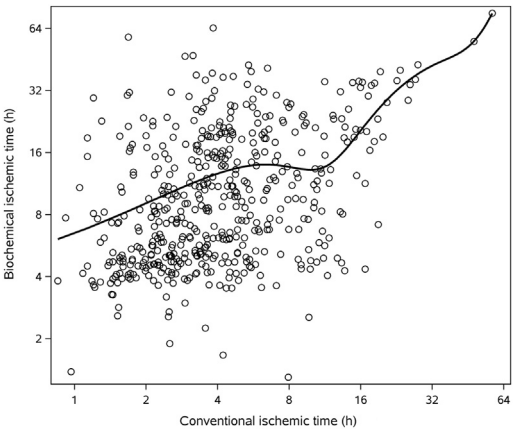


Biochemical onset time was particularly earlier in patients ≥65 years of age and patients with a preprocedural TIMI flow >0. CABG = coronary artery bypass grafting; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Reported symptom onset time also tended to be later than biochemical onset time in patients with TIMI flow grade >0 on coronary angiography. This group of patients may experience a "stuttering myocardial infarction," in which transient episodes of (sub)total coronary occlusion are accompanied by waxing and waning of ischemic symptoms, thereby complicating determination of actual time of onset of symptoms (20). Furthermore, reported symptom onset time was later than could be expected from biochemical onset time in patients with a lower BMI and patients without a history of PCI procedures. These patients have not been identified as subgroups with an atypical symptom presentation in previous studies. A possible explanation is that these patients were not made aware of the symptoms associated with myocardial infarction by their physicians because of their lower risk of cardiovascular events. Hence, they may not have attributed the initial symptoms as being cardiac. In this context, however, it should also be stressed that atypical symptoms such as dyspnea and nausea, although more difficult to attribute as cardiac, do not necessarily preclude adequate recollection of onset time. This may explain why we did not find differences in other subgroups known for their atypical symptom presentation such as women and those with diabetes (10,11).

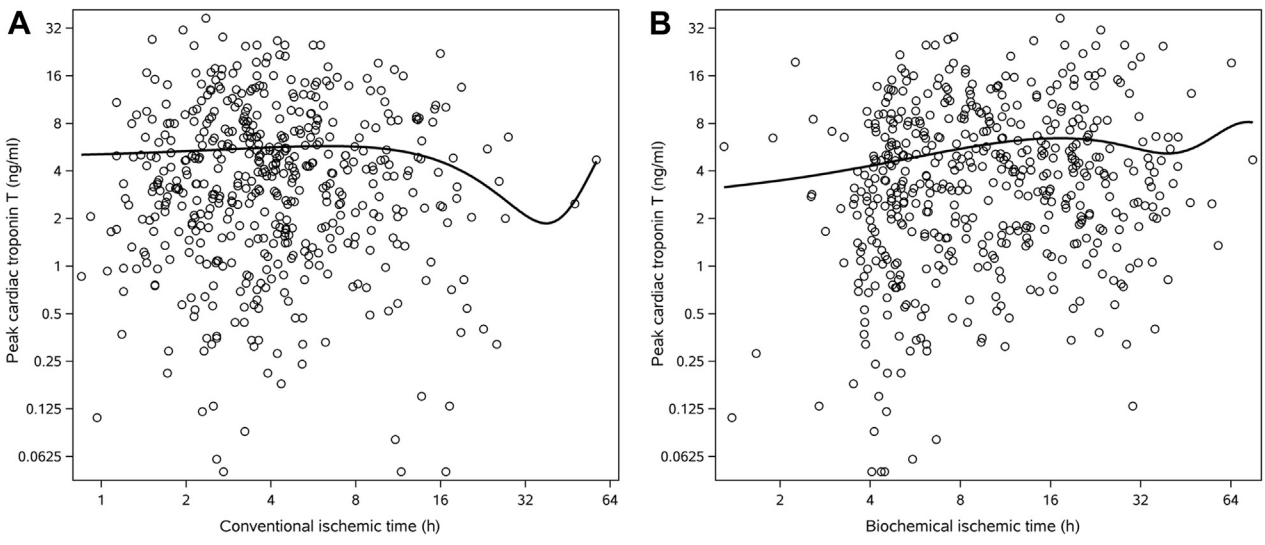
The pathophysiological importance of total ischemic time in patients with STEMI is well recognized (21). However, some previous studies in patients undergoing primary PCI failed to show associations between ischemic time and infarct size, myocardial salvage index, left ventricular ejection fraction, and mortality (8,9). Remarkably, associations with these outcome measures could be

FIGURE 5 Correlation Between Conventional Ischemic Time and Biochemical Ischemic Time



The **line** indicates a spline smoother to help visualize the trend ($r = 0.39$; $p < 0.001$).

FIGURE 6 Correlation Between Ischemic Time and Biochemical Infarct Size as Assessed by Peak Cardiac Troponin T



(A) Correlation between conventional ischemic time and infarct size ($r = 0.023$; $p = 0.61$). **(B)** Correlation between biochemical ischemic time and infarct size ($r = 0.14$; $p = 0.001$). The line indicates a spline smoother to help visualize the trend.

demonstrated when ischemic time was replaced with a more objective measure such as system delay. Our findings help to explain these observations by showing that the prognostic value of ischemic time was greatly enhanced when it was systematically determined in a manner that was less prone to bias than the use of reported symptom onset time. Importantly, reported symptom onset time tended to underestimate ischemic time to a greater extent in patients at higher risk of mortality, thereby further obscuring the association between ischemic time and clinical outcome.

The retrospective methodology that we applied to determine biochemical onset time limits its applicability for reperfusion strategy selection in clinical practice. Nonetheless, the use of biochemical onset time in future studies may enhance our knowledge about the interaction between time from symptom onset, reperfusion strategy selection, and outcome in STEMI patients. In addition, clinicians should be aware that reported symptom onset time is typically later than the actual time of onset of STEMI, especially in the subgroups identified in this study and in high-risk patients. Our results suggest that other readily available measures that reflect time from onset of STEMI should also be considered when selecting a reperfusion strategy, such as the presence of Q waves on the baseline electrocardiogram (22,23). However, we do not argue against the current guideline recommendations to consider conservative management in stable STEMI patients without evidence of ongoing ischemia when the time from symptom onset to presentation is more than 12 to 24 h because conventional ischemic time correlated well with biochemical ischemic time in patients with ischemic time beyond 12 h (1).

STUDY LIMITATIONS. As stated earlier, the most important limitation of our study is the fact that true time of onset of STEMI cannot be known and that there is neither a gold standard for onset time nor one for ischemic time. Nonetheless, biochemical ischemic time greatly outperformed conventional ischemic time as a prognostic marker, thus showing good internal validity. Second, biochemical onset time could only be reliably calculated in patients with sufficient and increasing cTnT measurements. Exclusion of a substantial number of patients with inadequate cTnT measurements inadvertently resulted in selection of a lower risk population, as is reflected by the lower mortality rate in included patients. Third, the lack of routine cTnT sampling beyond 6 h after admission may explain the relatively low peak cTnT values seen in our study. However, it did allow us to have consistent timing for that evaluation, which is a strength. In addition, studies have suggested that any cTnT measurement beyond the value on admission shows a fair correlation with single-photon emission computed tomography–determined infarct size (14). Fourth, it is conceivable that a minor plaque disruption occurs in many patients before the total occlusion occurs, which may have caused cTnT release. If one is attempting to measure the onset of total occlusion, this may be a limitation, but from the point of view of pathobiology, it might indeed be a better estimate of onset. We corrected for the presence of persistent increased values in patients with renal failure by excluding those patients, but some of the included patients may still have had persistently increased cTnT levels due to other conditions such as left ventricular hypertrophy, heart failure, and diabetes, which could also introduce a bias toward an earlier biochemical onset time (24).

CONCLUSIONS

Our study provides evidence that patient-reported symptom onset time is later than the actual time of onset of STEMI in patients undergoing primary PCI. This phenomenon is especially pronounced in elderly patients, in patients with a lower BMI, in patients without a history of PCI, and in patients with residual flow in the culprit artery on coronary angiography. Unlike conventional ischemic time, biochemically determined ischemic time correlated well with peak cTnT and mortality. Compared with biochemical onset time, reported symptom onset time tended to underestimate ischemic time more in patients at higher risk of 1-year mortality. Our study shows that minimizing ischemic time should remain a key goal in STEMI care. Future studies are required to corroborate our findings and assess the association between biochemically determined ischemic time, preferably with prospectively collected cTnT samples, and infarct size measured by imaging modalities such as magnetic resonance imaging.

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PERSPECTIVES

WHAT IS KNOWN? Ischemic time is an important metric in ST-segment elevation myocardial infarction care. However, it relies on patient-reported symptom onset time, which has an uncertain validity.

WHAT IS NEW? Our study provides evidence that patient-reported symptom onset time is typically later than the actual onset of the thrombotic coronary event, especially in specific subgroups such as elderly patients.

WHAT IS NEXT? Further prospective validation of our findings is warranted. In the meantime, clinicians should be aware of this phenomenon and also take into account other factors that reflect ischemic time, such as Q waves on the baseline electrocardiogram.

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APPENDIX For supplemental material, please see the online version of this article.