

The Effect of Symptom Onset-to-needle time on Ischemic Outcomes in Patients Treated with Primary Angioplasty in the Era of Potent Antiplatelets

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Abstract

Purpose: Based on previous studies with clopidogrel, the time between onset of symptoms and primary PCI was proven as an important prognostic factor. Our aim was to assess the effect of symptoms onset to needle time (SNT) on procedural results and on the occurrence of ischemic endpoints in primary angioplasty patients treated with potent P2Y₁₂ inhibitors.

Methods: A total of 1,131 out of 1,230 patients randomized to the PRAGUE 18 study (prasugrel vs. ticagrelor in primary angioplasty) were divided into a high and a low-risk group. The effect of defined SNT on patients' ischemic endpoints and prognosis by their risk status at admission was tested.

Results: The median SNT was 3.2 hours. Longer SNTs resulted in a more frequent incidence of TIMI flow < 3 post PCI ($p = 0.015$). There were significant differences in the occurrence of the combined ischemic endpoint among the compared SNT groups at 30 days ($p=0.032$), and 1 year ($p=0.011$), with the highest incidence in the ≤ 1 h SNT group of patients. "Latecomers" (SNT > 4 hs) in the high-risk group experienced more reMI within 1 year [OR (95% CI) 3.23 (1.09–9.62) $p = 0.035$]; no difference was found in the low-risk group.

Conclusion: In the era of intense antithrombotic medication, stratification of STEMI patients undergoing primary angioplasty, based on initial ischemic risk assessment affected prognosis more than symptom onset to needle time. Longer time delay significantly increased the incidence of ischemic events and all-cause mortality only in patients with high ischemic risk.

Introduction

The duration of ischemia is a major determinant of the extent of necrosis in patients with ST elevations acute myocardial infarction (STEMI) who are referred for primary percutaneous coronary intervention (PCI), and therefore, a rapid diagnosis followed by urgent revascularization is crucial to reduce morbidity and mortality [1-6]. Minimizing the time between the onset of symptoms and initiation of reperfusion therapy is a key indicator of the quality of care for patients with STEMI or with a newly formed bundle branch block [7-9]. A marked reduction in symptom-to-balloon time or symptom-to-needle time (SNT), which is achieved by early pre-hospital ECG registration and immediate transport to a Cath lab facility in cases with ongoing myocardial ischemia, is associated with a survival benefit for AMI patients [8-10]. Direct transport to the nearest Cath lab (i.e., bypassing emergency or coronary units) cuts down the total time delay [11]. Given the importance of PCI in improving the survival of STEMI patients, clinical studies have focused primarily on the evaluation of door-to-balloon time [12,13] as an indicator of hospital care. Nevertheless, studies have shown that symptom-to-balloon time is a better predictor of outcomes, especially in patients with early STEMI presentations [14]. Symptom-to-balloon time, like symptom-to-needle time, reflects not only the quality and efficacy of medical care but also awareness and education of the public.

Studies evaluating the effect of longer SNTs on patient outcomes were performed when clopidogrel was the dominant P2Y12 inhibitor [1-6]. Administration of new P2Y12 inhibitors like prasugrel or ticagrelor, compared to clopidogrel, leads to an earlier onset and stronger antiplatelet effects. The aim of this study was to examine whether the total duration of ischemia, evaluated using the SNT parameter, has any effects on PCI success rate and long-term ischemic outcomes in patients with AMI referred to primary PCI and treated with either prasugrel or ticagrelor, and analyze the prognostic impact of SNT according to patient profile at admission.

Methods

Our population was represented by 1,131 out of 1,230 patients from 14 PCI centers randomized into the PRAGUE-18 Study (Prasugrel vs. Ticagrelor in Patients with Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention; NCT02808767[15,16]) in whom the data of symptom onset were available.

Two major analyses related to time delay were performed. Firstly, the patients were divided into the following groups according to the length of SNT: (1) SNT \leq 1.0 hour, (2) SNT 1.1-3.0 hours, (3) SNT 3.1-6.0 hours, and (4) SNT > 6 hours. Post-PCI outcomes (i.e., stent insertion success rate, lateral branch patency, and final TIMI flow in the culprit artery), occurrence of the defined ischemic endpoints used in the PRAGUE-18 Study (i.e., death, reinfarction, urgent target vessel revascularization, and stroke) and presence of cardiogenic shock were analyzed and compared between the groups.

In the second analysis, the patients were divided into 2 groups according to the degree of the initial risk of ischemic complications as proposed by the Thrombolysis In Myocardial Infarction (TIMI) investigators [17]: (1) a high-risk group (presence of at least one of the following criteria: age > 70 years, STEMI of the anterior wall or LBBB, Killip II-IV, history of MI or CABG, systolic blood pressure < 100 mmHg and heart rate > 100/min), and (2) a low-risk group (all others). According to the TIMI Risk Score parameter "time-to-treatment," using a cut-off value of 4 hours, patients were subsequently divided into "early comers" (SNT \leq 4 hours) and "latecomers" (SNT > 4 hours). An occurrence of ischemic endpoints at 30 days and 1 year was evaluated and compared between the groups.

Statistical analysis

Absolute and relative frequencies were used to describe the categorical parameters. Continuous characteristics were described by N and medians (5th and 95th percentiles). Differences between categorical parameters were tested using the Fisher's exact test, and differences between continuous characteristics were tested using the Mann-Whitney test (when comparing two groups) and the Kruskal-Wallis test (when comparing multiple groups). A p-value < 0.05 was considered statistically significant. The relationship between SNT in high and low-risk patients and the occurrence of the combined ischemic endpoint (i.e., cardiovascular death, non-fatal myocardial infarction, and stroke), recurrent AMI, cardiovascular death, and all-cause mortality at 30 and 365 days were computed using logistic

regression and described using odds ratios and 95% confidence intervals. The analysis was performed using IBM SPSS Statistics 25.0.0.1.

Results

The median SNT was 3.2 hours (1.1; 34.3). Women had significantly longer SNTs than men (median 3.8 vs. 3.1 hours, $p < 0.001$). Hypertension was associated with longer SNTs in both men and women (median 3.4 vs. 3.1 hours, $p = 0.008$). Obesity was a factor that prolonged SNT in women (median 5.3 vs. 3.5 hours, $p = 0.001$). A history of previous MI or CABG did not significantly affect time delay.

Post-PCI TIMI flow < 3 (suboptimal flow) in the culprit artery was significantly more frequent in subjects with longer SNTs ($p = 0.015$) (Table 1). The incidence of ischemic endpoints was low in our patient cohort. CV death and the combined ischemic endpoint occurred in 1.8% ($N = 20$) and 3.0% ($N = 34$) at 30 days, and in 2.9% ($N = 33$) and 5.9% ($N = 67$) at one year.

Table 1
Patient characteristics and intervals from symptoms onset to coronary angiography

Symptom onset to needle time (hours)						P-value
	≤ 1.0 h	1.1 – 3.0 h	3.1 – 6.0 h	> 6.0 h		
Characteristics						
Numer of patients	48	476	307	300		
Age (years)	61.7 (35.9; 78.7)	61.4 (43.4; 77.4)	62.1 (43.1; 79.7)	61.9 (44.2; 80.8)	0.314	
Men	43 (89.6%)	375 (78.8%)	229 (74.6%)	206 (68.7%)	0.001	
Admission						
STEMI	43 (89.6%)	461 (96.8%)	287 (93.5%)	255 (85.0%)	< 0.001	
LBBB	0 (0.0%)	4 (0.8%)	4 (1.3%)	9 (3.0%)	0.124	
RBBB	1 (2.1%)	10 (2.1%)	5 (1.6%)	5 (1.7%)	0.909	
NSTEMI	4 (8.3%)	9 (1.9%)	13 (4.2%)	34 (11.3%)	< 0.001	
Killip classification	I	32 (66.7%)	417 (87.6%)	284 (92.5%)	< 0.001	
	II	4 (8.3%)	39 (8.2%)	13 (4.2%)		22 (7.3%)
	III	1 (2.1%)	6 (1.3%)	4 (1.3%)		5 (1.7%)
	IV	11 (22.9%)	14 (2.9%)	6 (2.0%)		9 (3.0%)
Ischemic risk stratification						
High risk patients	37 (77.1%)	300 (63.0%)	178 (58.0%)	194 (64.7%)	0.046	
History						
Hyperlipidemia	11 (22.9%)	159 (33.4%)	118 (38.4%)	102 (34.0%)	0.157	
BMI ≥ 30	7 (14.6%)	76 (16.0%)	59 (19.2%)	81 (27.0%)	0.002	
Hypertension	22 (45.8%)	234 (49.2%)	160 (52.1%)	168 (56.0%)	0.247	
Current smoker	33 (68.8%)	308 (64.7%)	188 (61.2%)	196 (65.3%)	0.621	

STEMI, ST-segment-elevation myocardial infarction; LBBB, left bundle-branch block RBBB, right bundle-branch block; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIMI, Thrombolysis in Myocardial Infarction; ACE Inhibitors, angiotensin-converting-enzyme inhibitors; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction; GP, glycoprotein

	Symptom onset to needle time (hours)				P-value
	≤ 1.0 h	1.1 – 3.0 h	3.1 – 6.0 h	> 6.0 h	
Diabetes mellitus	10 (20.8%)	86 (18.1%)	73 (23.8%)	65 (21.7%)	0.258
Previous MI	4 (8.3%)	50 (10.5%)	19 (6.2%)	22 (7.3%)	0.166
Previous PCI	2 (4.2%)	39 (8.2%)	22 (7.2%)	18 (6.0%)	0.652
Previous CABG	0 (0.0%)	7 (1.5%)	6 (2.0%)	6 (2.0%)	0.912
Chronic heart failure	0 (0.0%)	5 (1.1%)	2 (0.7%)	3 (1.0%)	0.903
Chronic renal failure	1 (2.1%)	7 (1.5%)	4 (1.3%)	3 (1.0%)	0.790
Peripheral arterial disease	1 (2.1%)	12 (2.5%)	10 (3.3%)	8 (2.7%)	0.934
Chronic therapy					
Aspirin	7 (14.6%)	68 (14.3%)	52 (16.9%)	49 (16.3%)	0.752
Beta-Blockers	3 (6.3%)	82 (17.2%)	68 (22.1%)	59 (19.7%)	0.034
ACE Inhibitors	4 (8.3%)	99 (20.8%)	68 (22.1%)	90 (30.0%)	0.001
ARB	6 (12.5%)	47 (9.9%)	42 (13.7%)	31 (10.3%)	0.373
Statins	4 (8.3%)	78 (16.4%)	57 (18.6%)	66 (22.0%)	0.067
Proton Pump Inhibitors	0 (0.0%)	29 (6.1%)	23 (7.5%)	21 (7.0%)	0.209
Procedure					
Pre-TIMI flow < 2	28 (58.3%)	287 (60.5%)	198 (64.9%)	201 (67.2%)	0.220
Post-procedural TIMI flow < 3	1 (2.1%)	13 (2.7%)	18 (5.9%)	22 (7.4%)	0.015
Number of diseased vessels > 1	26 (54.2%)	220 (46.3%)	149 (48.7%)	176 (58.7%)	0.007
Stem disease	2 (4.2%)	12 (2.5%)	8 (2.6%)	17 (5.7%)	0.092
Suboptimal or unsuccessful PCI	3 (6.3%)	16 (3.4%)	11 (3.6%)	25 (8.4%)	0.012
STEMI, ST-segment-elevation myocardial infarction; LBBB, left bundle-branch block RBBB, right bundle-branch block; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIMI, Thrombolysis in Myocardial Infarction; ACE Inhibitors, angiotensin-converting-enzyme inhibitors; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction; GP, glycoprotein					

	Symptom onset to needle time (hours)				P-value
	≤ 1.0 h	1.1 – 3.0 h	3.1 – 6.0 h	> 6.0 h	
Only PTCA	1 (2.1%)	16 (3.4%)	8 (2.6%)	19 (6.4%)	0.100
Stent	47 (97.9%)	458 (96.6%)	296 (97.4%)	280 (93.6%)	
Manual aspiration thrombectomy	12 (25.0%)	189 (40.0%)	101 (33.1%)	80 (26.8%)	0.001
Bare-metal stent	12 (25.5%)	107 (23.4%)	89 (30.1%)	92 (32.9%)	0.029
Drug-eluting stent	32 (68.1%)	329 (71.8%)	192 (64.9%)	172 (61.4%)	0.023
Bioabsorbable v ascular scaffold	4 (8.5%)	39 (8.5%)	25 (8.4%)	18 (6.4%)	0.729
Antithrombotic therapy					
Aspirin	46 (95.8%)	466 (97.9%)	296 (96.4%)	288 (96.0%)	0.318
Prasugrel	23 (47.9%)	239 (50.2%)	160 (52.1%)	162 (54.0%)	0.717
Ticagrelor	25 (52.1%)	237 (49.8%)	147 (47.9%)	138 (46.0%)	
Unfractionated heparin	46 (95.8%)	463 (97.3%)	296 (96.4%)	283 (94.3%)	0.199
Enoxaparine	4 (8.3%)	41 (8.6%)	42 (13.7%)	32 (10.7%)	0.160
Fondaparinux	0 (0.0%)	8 (1.7%)	6 (2.0%)	8 (2.7%)	0.703
Glycoprotein IIb/IIIa bailout therapy	11 (22.9%)	103 (21.6%)	61 (19.9%)	56 (18.7%)	0.728
LV EF %	45.0 (25.0; 65.0)	50.0 (32.0; 65.0)	50.0 (30.0; 65.0)	48.5 (35.0; 65.0)	0.365
STEMI, ST-segment-elevation myocardial infarction; LBBB, left bundle-branch block RBBB, right bundle-branch block; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIMI, Thrombolysis in Myocardial Infarction; ACE Inhibitors, angiotensin-converting-enzyme inhibitors; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction; GP, glycoprotein					

Notably, the highest incidence of the combined ischemic endpoint was observed in patients with SNTs ≤ 1 hour compared to the patient groups with SNTs 1.1-3.0 hours, 3.1-6.0 hours, and > 6 hours both at 30 days (10.4% vs. 3.4%, 2.0%, and 2.3%, p = 0.032), and 1 year (16.7% vs. 4.8%, 4.6%, and 7.3%, p = 0.011) (Table 2, Fig. 1).

Table 2
Endpoints and intervals from symptoms onset to coronary angiography

Endpoints and intervals from symptoms onset to coronary angiography					
	Symptom onset to needle time (hours)				P-value
	≤ 1.0 h	1.1 – 3.0 h	3.1 – 6.0 h	> 6.0 h	
30 days					
Death from any cause	4 (8.3%)	11 (2.3%)	5 (1.6%)	6 (2.0%)	0.077
Cardiovascular death	3 (6.3%)	10 (2.1%)	2 (0.7%)	5 (1.7%)	0.055
Re-MI	3 (6.3%)	5 (1.1%)	4 (1.3%)	2 (0.7%)	0.053
Re-MI periPCI MI	3 (6.3%)	15 (3.2%)	15 (4.9%)	7 (2.3%)	0.194
Stroke	1 (2.1%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	0.103
Cardiovascular death Re-MI Stroke	5 (10.4%)	16 (3.4%)	6 (2.0%)	7 (2.3%)	0.032
Stent thrombosis	2 (4.2%)	4 (0.8%)	2 (0.7%)	2 (0.7%)	0.176
365 days					
Death from any cause	7 (14.6%)	17 (3.6%)	9 (2.9%)	14 (4.7%)	0.010
Cardiovascular death	5 (10.4%)	13 (2.7%)	5 (1.6%)	10 (3.3%)	0.024
Re-MI	4 (8.3%)	8 (1.7%)	8 (2.6%)	11 (3.7%)	0.042
Re-MI periPCI MI	4 (8.3%)	18 (3.8%)	19 (6.2%)	16 (5.3%)	0.249
Stroke	1 (2.1%)	3 (0.6%)	3 (1.0%)	2 (0.7%)	0.516
Cardiovascular death Re-MI Stroke	8 (16.7%)	23 (4.8%)	14 (4.6%)	22 (7.3%)	0.011
Stent thrombosis	2 (4.2%)	5 (1.1%)	3 (1.0%)	6 (2.0%)	0.205
MI, myocardial infarction; PCI, percutaneous coronary intervention					

Also, the all-cause mortality, cardiovascular mortality, and incidence of recurrent MI were more frequent in the SNT ≤ 1 hour group of patients at 1 year. However, patients with SNT ≤ 1 hour were in 22.9% cardiogenic shock (Killip IV) patients, compared to only 2.9%, 2.0%, and 3.0% in groups 1.1-3.0 hours, 3.1-6.0 hours, and > 6 hours ($p < 0.001$). The combined prevalence of resuscitation/out-of-hospital cardiac arrest (OHCA)/cardiogenic shock was 41.7% ($N = 20$) for the SNT ≤ 1 hour group. If these patients were excluded to avoid bias, no significant difference in the occurrence of any ischemic endpoint was found between the other SNT groups ($p = 0.177$).

High-risk vs. low-risk groups

Admission stratification relative to ischemic risk (according to the abovementioned TIMI criteria) revealed 62.7% ($N = 709$) high-risk patients and 37.2% ($N = 422$) low-risk patients. The proportion of high-risk

patients in the SNT < 1 hour group (77.1%) was significantly higher than in the patient groups with SNTs 1.1-3.0 hours, 3.1-6.0 hours, and > 6 hours ($p = 0.046$).

High-risk patients had a higher incidence of all-cause death, cardiovascular death, and combined ischemic endpoint both at 30 days (3.4% vs. 0.5%, $p = 0.001$, and 2.5% vs. 0.5%, $p = 0.010$, and 3.8% vs. 1.7%, $p = 0.047$) and at 1 year (6.1% vs. 0.9%, $p < 0.001$, and 4.1% vs. 0.9%, $p = 0.002$, and 7.5% vs. 3.3%, $p = 0.004$), irrespective of SNT duration (**Table S1 in Supplementary material**). Symptom-to-needle time analysis with a cut-off of 4 hours revealed that SNT > 4 hours in high-risk vs. low-risk patients was associated with more frequent all-cause death [OR (95% CI) 5.15 (1.17–22.70) $p = 0.030$], recurrent AMI [OR (95% CI) 3.23 (1.09–9.62) $p = 0.035$], and a higher incidence of the combined ischemic endpoint [OR (95% CI) 2.83 (1.14–7.03) $p = 0.025$] at 1 year (Fig. 1). For the high-risk patient group only, a comparison of “late comers” vs. “early comers” found a higher incidence of MI within one year ($p = 0.043$) for “late comers.” For the low-risk group, no differences in the incidence of ischemic outcomes were found.

Cardiogenic shock

Cardiogenic shock was present at admission in 3.5% of patients ($N = 40$). The 30-day mortality of patients with cardiogenic shock was 25% vs. 1.5% in patients with Killip I-III ($p < 0.001$), and the 1-year mortality was 40% vs. 2.8% ($p < 0.001$). Mortality and the incidence of combined ischemic endpoints were similar across the spectrum of patients categorized according to SNT groups. Thus, the SNT interval alone did not affect mortality of patients presenting in cardiogenic shock; however, the percentage of patients with cardiogenic shock was the highest in the SNT ≤ 1 hour group. (described in detail above) (Table 3).

Table 3

Endpoints and intervals from symptoms onset to coronary angiography in patients with Killip = 4; N = 40

	Symptom onset to needle time (hours)				P-value
	≤ 1.0 h	1.1 – 3.0 h	3.1 – 6.0 h	> 6.0 h	
30 days					
Death from any cause	2 (18.2%)	3 (21.4%)	2 (33.3%)	3 (33.3%)	0.786
Cardiovascular death	2 (18.2%)	3 (21.4%)	1 (16.7%)	2 (22.2%)	0.999
Re-MI	1 (9.1%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0.290
Re-MI periPCI MI	1 (9.1%)	0 (0.0%)	1 (16.7%)	1 (11.1%)	0.428
Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Cardiovascular death Re-MI Stroke	2 (18.2%)	3 (21.4%)	2 (33.3%)	2 (22.2%)	0.909
Stent thrombosis	1 (9.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0.999
365 days					
Death from any cause	5 (45.5%)	5 (35.7%)	2 (33.3%)	4 (44.4%)	0.970
Cardiovascular death	4 (36.4%)	5 (35.7%)	1 (16.7%)	3 (33.3%)	0.901
Re-MI	2 (18.2%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0.134
Re-MI periPCI MI	2 (18.2%)	0 (0.0%)	1 (16.7%)	1 (11.1%)	0.301
Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Cardiovascular death Re-MI Stroke	5 (45.5%)	5 (35.7%)	2 (33.3%)	3 (33.3%)	0.938
Stent thrombosis	1 (9.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0.999
MI, myocardial infarction; PCI, percutaneous coronary intervention					

Discussion

Our study found, based on patient medical histories and characteristics, that the most significant factor related to a longer SNT was gender. A possible cause and explanation of longer SNTs in women may be the more frequent occurrence of atypical symptoms, resulting in significant delays from symptom onset to contacting the emergency system [18,19]. Women often have no chest pain [20] or consider the pain to be insignificant or not life-threatening [21]. In the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), only half of patients < 55 years of age presenting with an acute myocardial infarction considered themselves at risk for heart disease before their event, despite having several cardiac risk factors [19]. Women were less likely than men to be told by their physician that they were at risk of cardiovascular disease or to have conversations about risk reduction.

Significantly longer SNTs were found in patients treated for arterial hypertension and in obese females, but not males. These findings are consistent with previous studies [22-24].

A negative trend toward longer delays (thus not statistically significant) was observed in patients with a history of CABG, and in diabetic patients while a trend toward shorter delay was seen in patients with a history of prior MI. Prolongation of time delay in diabetic patients has been consistently reported across studies, and related to atypical signs and symptoms of MI in this population [25–27]. Studies investigating pre-hospital delay in patients with prior CABG or MI reported conflicting results of whether patients with these comorbidities present earlier or not. In The Worcester Heart Attack Study, the researchers found that previous MI was associated with longer delays [27], other investigators [25,26,28,29] reported significantly shorter pre-hospital delays in these patients. In a prospective cohort study performed by Coventry et al. the patients with previous MI had shorter time delay than patients without previous MI or CABG, but patients with previous MI and CABG compared with previous MI alone had longer time delays [30]. The probable reason for these findings is that some patients perceive seriousness of the disease and potential threat after the first event while others think it is not likely to have a second MI after a successful CABG operation. Moreover, socio-demographic factors (e.g. marital status), cognitive (higher educational level [28,31]) and behavioral factors play a role when deciding to call emergency system or come to a hospital to seek help [32]. There is limited evidence that community media-based MI-awareness campaigns lead to shortening time delays [30,33], therefore a face-to-face educational intervention in selected high-risk patients (post MI/CABG, with diabetes) was proposed to be more beneficial. Despite the fact that a randomized trial conducted by Dracup et al [34] failed to prove this concept, the MEDEA study demonstrated that patients with a knowledge of MI symptoms and treatment presented with shorter time delays [35]. Thus, continuous efforts need to be taken to educate high risk patients to further reduce pre-hospital delay.

In the patients with longer SNTs, there was a higher incidence of post-PCI suboptimal TIMI flow in the culprit vessel despite the fact, that all patients were given appropriate combined antithrombotic therapy including prasugrel or ticagrelor at a cathlab prior to revascularization. Our results are consistent with previous reports that found a positive correlation between shorter time delays and more favorable postprocedural findings on the infarct-related artery [36,37]. In the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study, early (pre-hospital) compared to in-hospital administration of ticagrelor in STEMI patients did not result in more frequent TIMI 3 flow prior to and post-PCI but reduced stent thrombosis rates, irrespective of initial TIMI risk score of the patients [38]. To sum up, the data suggest that affecting time delay is of higher importance than timing of the first (loading) dose of a potent P2Y12 inhibitor, as long as given prior to PCI.

The study found only a borderline relationship between longer SNTs (i.e., above the median value) and the occurrence of the composite ischemic endpoint when no risk stratification was applied. Despite a low incidence of endpoints both at 30 days and 1 year, the present data demonstrated that stratification of patients at admission, relative to ischemic risk using the TIMI Risk Score (including hemodynamic

parameters, disease-specific patient medical history, and age) is still the most important act the attending clinician must perform, and in high-risk patients to subsequently take actions in order to maximally shorten time delay to reperfusion. Such approach, together with the use of potent antiplatelet therapy including prasugrel or ticagrelor, resulted in a better survival and less ischemic events. In patients with a low-risk profile at admission, with the same antiplatelet therapy applied, the prognostic effect of short time delay was not pronounced.

Similarly to previous publications [39,40], the majority of cardiogenic shock patients enrolled in our study arrived early ($\text{SNT} \leq 1$ hour) after the onset of symptoms but still having the worst prognosis. These patients arrived in very poor condition, had been resuscitated, and on hemodynamic or ventilator support. The poor outcomes in these cases were likely determined before the patient ever reached a Cath lab and were independent of elapsed SNT.

Limitations

The study has specific limitations. Compared to some other studies, the sample size was relatively small. Moreover, it is important to note that number of patients in the group with $\text{SNT} \leq 1$ hour was markedly lower compared to the numbers in the other groups. However, it was a multicenter, investigator-initiated study in which data collection was closely monitored and endpoints confirmed by an adjudication committee. The statistical power of our analyses was reduced due to the small number of endpoints in the Prague 18 study. Due to regional health care differences, the results from this study may not be entirely comparable with STEMI management used in other countries.

Conclusion

In this study of patients referred to primary PCI and treated with prasugrel or ticagrelor, longer SNTs were associated with more frequent suboptimal PCI results. Stratification of patients based on their initial ischemic risk proved to have more prognostic power than SNT. Longer time delay only in high risk patients significantly increased the incidence of ischemic events and all-cause mortality, compared to low risk patients.

Abbreviations

AMI- acute myocardial infarction

CABG - coronary artery bypass grafting

LBBB - left bundle-branch block

OHCA - out-of-hospital cardiac arrest

SNT - symptoms onset to needle time

PCI - primary percutaneous coronary intervention

STEMI - ST elevations acute myocardial infarction

TIMI - Thrombolysis In Myocardial Infarction

Declarations

CONSENT TO PARTICIPATE

Patients signed informed consent to participate in the clinical study.

CONSENT TO PUBLISH

All authors agree with the publication.

ETHICAL APPROVAL AND INFORMED CONSENT

The study was conducted with approval of the trial design and protocol by the Ethics Committee for Multicenter Clinical Trials, University Hospital Kralovske Vinohrady, Prague, Czech Republic, and the local ethics committees at each participating site. The study conformed to the principles of the Declaration of Helsinki. Patients signed informed consent to participate in the clinical study.

DATA AVAILABILITY

Raw data available on request.

COMPETING INTERESTS

Dr. Motovska reports receiving speaking and advisory board fees from AstraZeneca and Eli Lilly. Dr Varvarovsky reports receiving honoraria from AstraZeneca and Eli Lilly. Dr. Rokyta reports receiving lecture fees from AstraZeneca. Dr. Widimsky reports receiving honoraria from AstraZeneca, Eli Lilly, and Daiichi Sankyo. The other authors report no conflicts.

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AUTHORS' CONTRIBUTIONS

Z.M. had the original idea for the Prague-18 study. M.H., Z.M., O.H., P.K., I.V., J.D., F.T., P.J., S.S., M.B., J.M., R.M., R.R., P.W. were investigators, M.H., Z.M. designed the time delay substudy, M.H., Z.M. prepared the manuscript. J.J., M.S. analysed the data. Figures and Tables were created by J.J., M.S.

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Figures

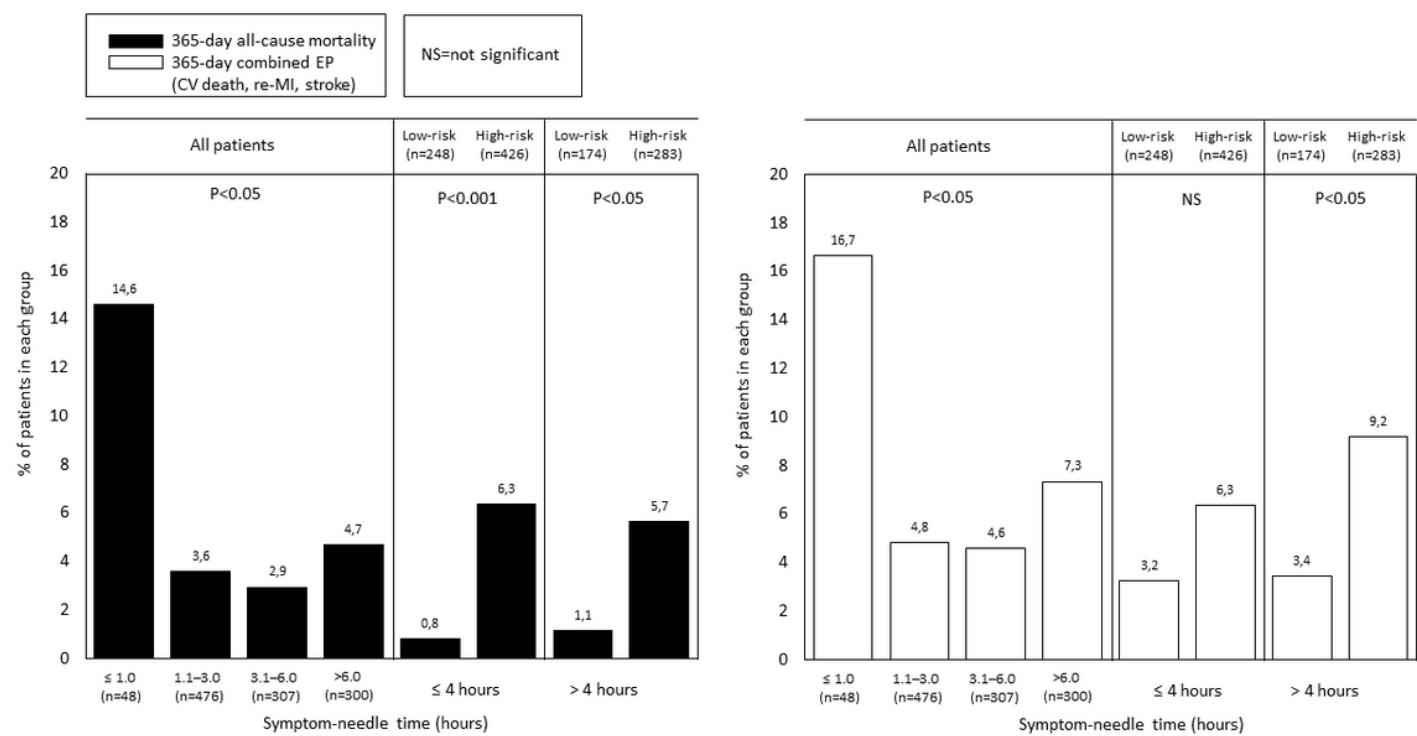


Figure 1

Incidence of all-cause mortality and the combined ischemic endpoint at one year in the cohort of 1131 patients.