Polish trials influencing 2017 European Society of Cardiology guidelines on acute myocardial infarction in patients presenting with ST-segment elevation

Małgorzata Ostrowska, Piotr Adamski

Department of Principles of Clinical Medicine, *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

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During the latest annual European Society of Cardiology Congress in Barcelona, new guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation (STEMI) were presented [1]. It is noteworthy that, apart from international, multicenter studies involving sites from Poland, the results of three Polish trials had a significant impact on the shape of the current recommendations on the management of STEMI patients [2–4].

Alleviation of chest pain is one of the main therapeutic targets in patients presenting with STEMI, and titrated intravenous morphine is a routinely administered analgesic in this setting. However, a recent paper by Kubica *et al.* revealed that morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction [2]. The randomized, double-blind, placebo-controlled IMPRESSION trial, conducted in the Department of Cardiology and Internal Medicine, *Collegium Medicum*, Nicolaus Copernicus University in Bydgoszcz, aimed to evaluate the influence of infused morphine on pharmacokinetics and pharmacodynamics of ticagrelor and its active metabolite in patients with acute myocardial infarction. Seventy patients were assigned in a 1 : 1 ratio to receive either morphine (5 mg) or placebo intravenously followed by a 180 mg loading dose of ticagrelor. Morphine lowered the total exposure to ticagrelor and its active metabolite by 36% ($AUC_{(0–12)}$: 6307 vs. 9791 ng * h/ml; $p = 0.003$) and 37% ($AUC_{(0–12)}$: 1503 vs. 2388 ng * h/ml; $p = 0.008$), respectively. Moreover, a delay in maximal plasma concentration of ticagrelor (4 vs. 2 h; $p = 0.004$) was observed in patients receiving morphine. Multiple regression analysis showed that lower $AUC_{(0–12)}$ values for ticagrelor were independently associated with the administration of morphine ($p = 0.004$) and the presence of STEMI ($p = 0.014$). In pharmacodynamic assessment up to three platelet reactivity tests were used – the vasodilator-stimulated phosphoprotein phosphorylation assay, multiple electrode aggregometry and VerifyNow – and all of them revealed a stronger antiplatelet effect in the placebo group and a greater prevalence of high platelet reactivity in the morphine arm. Despite the results of the IMPRESSION study clearly showing a negative impact of morphine on bioavailability and antiplatelet action of ticagrelor, due to lack of effective alternative, titrated intravenous opioids should be considered to relieve pain in STEMI patients. Nevertheless, the class of recommendation for use of morphine in STEMI has been lowered from I to IIa with a level of evidence C [1, 5]. In everyday clinical practice morphine should not be routinely used in all STEMI patients together with antiplatelet agents, but this decision should be made individually after thorough evaluation to ensure that morphine is restricted to patients who actually need it [1, 2, 6].

It is a clear recommendation that reperfusion therapy is indicated in all STEMI patients with symptoms of ischemia lasting less than 12 h; however, it is still a class I recommendation to perform primary percutaneous coronary intervention (PCI) also in those with symptom onset > 12 h, but < 24 h and presence of ongoing symptoms suggestive of ischemia, hemodynamic instability, or life-threatening arrhythmias [1]. Evidence for such an approach comes from a prospective national observational study (PL-ACS) published by Gierlotka *et al.* from the Silesian Center of Heart Diseases in Zabrze [3]. The aim of this study was to evaluate whether primary PCI improves 12-month survival in those presenting with STEMI between 12 to 24 h from the onset of symptoms. The analyzed data concerned 2036 patients included in the Polish Registry of Coronary Syndromes. Patients with pulmonary edema, cardiogenic shock or initially treated

Corresponding author:
Małgorzata Ostrowska MD, PhD, Department of Principles of Clinical Medicine, *Collegium Medicum*, Nicolaus Copernicus University, 9 Skłodowskiej-Curie St, 85094 Bydgoszcz, Poland, phone: +48 52 585 40 23, fax: +48 52 585 40 24, e-mail: ostrowska.go@gmail.com
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with thrombolysis were excluded from the investigation. Coronary angiography was performed within 12 to 24 h from symptoms onset in 910 cases (44.7%), and 92.0% of them underwent primary PCI. Patients qualified for an invasive strategy had a lower mortality rate after 12 months than those treated with a conservative strategy (9.3% vs. 17.9%; $p < 0.0001$). Multivariate adjustment confirmed the benefit of an invasive strategy with a relative risk of 0.73 for 12-month mortality (95% confidence interval: 0.56–0.96). In conclusion, up to 10% of patients with STEMI present 12 to 24 h from the symptom onset and they should be considered for reperfusion by primary PCI, because an invasive strategy reduces the 12-month mortality rate as compared to a conservative strategy in this subpopulation of latecomers. The class of recommendation for such management has changed from IIb to IIa with the level of evidence C [1, 5].

Multivessel coronary artery disease is frequently found in coronary angiography in STEMI patients [1]. The aim of the study by Dziewierz *et al.*, from the 2nd Department of Cardiology, *Collegium Medicum*, Jagiellonian University in Krakow, was to evaluate the influence of multivessel coronary artery disease and noninfarct-related artery revascularization during the index PCI on outcomes of STEMI patients [4]. The authors analyzed data of 1598 patients with multivessel (≥ 1) coronary artery disease enrolled in the EUROTRANSFER Registry database. Out of identified patients, 51.5% of STEMI patients had a multivessel disease – 32% had 2-vessel disease and 19.5% had 3-vessel disease. Final Thrombolysis In Myocardial Infarction grade 3 flow was found in 93.6% of patients with 1-vessel disease, 89.3% in 2-vessel disease and 87.9% in 3-vessel disease ($p = 0.003$). ST-segment resolution > 50% within 60 min after PCI occurred in 80.9% of patients with 1-vessel disease, 77.5% in 2-vessel disease and 69.3% in 3-vessel disease ($p < 0.001$). Risk of 1-year death was the lowest in 1-vessel disease (4.9%), moderate in 2-vessel disease (7.4%) and the highest in 3-vessel disease (13.5%) ($p < 0.001$). In multivariate regression analysis 1-year mortality predictors besides multivessel disease were Killip class IV on admission and left anterior descending coronary artery as infarct-related vessel. Only 9% of patients had noninfarct-related artery revascularization during the index PCI, and they were at higher risk of both 30-day and 1-year mortality as compared with multivessel disease patients without noninfarct-related artery PCI. To conclude, patients with STEMI commonly present with multivessel disease (> 50%) and in the study by Dziewierz *et al.* they had a worse prognosis as compared with 1-vessel disease, which was even poorer when the noninfarct-related artery revascularization during index PCI was performed. Guidelines recommend noninfarct-related artery revascularization in patients with STEMI and multivessel disease before the hospital discharge (class of recommendation IIa, level of evidence A), while noninfarct-related artery revascularization during the index PCI should be reserved for those with cardiogenic shock (class of recommendation IIa, level of evidence C) [1].

In the recently published 2017 guidelines for the management of STEMI patients there are only three citations originating from Poland [1–4]. The impact of these studies was significant enough to influence the change in class of recommendation in the described clinical situations.

Conflict of interest

The authors declare no conflict of interest.

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