

Abstract of the PhD Thesis

Impact of coronary artery lesion complexity on the results of mechanical reperfusion in acute myocardial infarction

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Background

Coronary artery disease (CAD) is the leading cause of death worldwide, including Europe and Romania. ST-segment elevation myocardial infarction (STEMI) is the most acute clinical form of this condition. Commonly, it is caused by the acute thrombotic occlusion of a coronary artery after the rupture of an inflamed, thin-capped atherosclerotic plaque. With the widespread implementation of emergent myocardial reperfusion using primary percutaneous coronary intervention (PCI) as a standard of care, the in-hospital mortality rates of STEMI have fallen to 7% from the historical 30% of a more conservative management.

However, the incidence of post-PCI adverse events is not uniform after an acute myocardial infarction. The short- and long-term clinical outcomes depend on various patient- and procedure-related factors. Advanced age, left ventricular dysfunction, multivessel CAD, late presentation after symptom onset and comorbidities such as diabetes mellitus or renal failure are the main patient-dependent determinants of poor prognosis. The modality of treatment, as well as immediate procedural results and possible complications could also have a major prognostic impact. On the basis of these variables, numerous risk-stratification models have been developed and successfully applied in clinical practice to identify patients with higher risk for adverse events, who may need supplementary peri- and postprocedural diagnostic and/or therapeutic measures.

Although multivessel disease is an important prognostic factor and it is described in approximately 50% of the emergent coronary angiographies performed for STEMI, this condition could have a very different significance. Accordingly, both the focal stenosis of a coronary branch, other than the culprit vessel, and the severe, calcified left main stem disease associated with chronic total occlusion(s) represent multivessel involvement, but the latter carries a much worse prognosis. To emphasize such differences, a new “angiographic tool” was recently developed: the SYnergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score. Initially conceived to guide revascularization decisions in stable CAD, this angiographic scoring system has been shown to be an independent predictor of adverse clinical events after PCI for chronic and acute coronary lesions: the higher the score, the greater the possibility of poor outcomes. This concept was recently validated in STEMI cases, too. However, the exact mechanisms behind this observation are still poorly understood. Thus, the present work evaluated the impact of complex coronary artery disease on the clinical and angiographic results of primary PCI.

Study objectives

Five specific objectives were defined: *a.* to identify the clinical and angiographic predictors of reperfusion success after primary PCI; *b.* to describe the relationship between myocardial reperfusion and the complexity of CAD; *c.* to evaluate the possible associations between the SYNTAX score and creatinine clearance, as well as (*d.*) carotid intima-media thickness in patients with STEMI and *e.* to test the Clinical SYNTAX Score (CSS), which incorporates angiographic and clinical data, in the setting of STEMI.

Methods and results

A prospective clinical study was performed during a one year period, including all patients admitted for primary PCI in the Centre of Cardiovascular Diseases of Tîrgu Mureş Emergency Clinical County Hospital, who met the following criteria: acute chest pain lasting ≥ 30 min; ≥ 1 mm ST-segment elevation in ≥ 2 contiguous electrocardiographic (ECG) leads; PCI performed within the first 12h (24h if ischemia was still present) from symptom onset. Subjects were not enrolled in the study if these conditions were present: thrombolysis prior

to PCI, previous coronary artery by-pass graft surgery (CABG), uninterpretable ECG (ST-elevation) findings, such as left bundle branch block, paced rhythm, pre-excitation syndrome, important left ventricular hypertrophy, or if they refused to participate.

The following clinical parameters were evaluated: age, sex, body mass index; presence of arterial hypertension, diabetes mellitus, dyslipidemia, smoking; familial occurrence of myocardial infarction; Killip class at presentation, cardiac arrest before PCI; duration of the ischemic period; glycaemia, serum creatinine level and estimated creatinine clearance (eC_{cr}) according to the Cockcroft-Gault equation at hospital admission; maximum creatin kinase (CK) level during hospitalization; electrocardiographic localization of STEMI and ST-segment elevation resolution; left ventricular ejection fraction (LVEF) and carotid intima-media thickness (IMT) determined by ultrasonography. The analyzed angiographic and procedural aspects included: the SYNTAX score before PCI; number of diseased coronary arteries, presence of chronic total occlusions, culprit lesion localization, pre- and post-intervention TIMI flow; TIMI thrombus grade before and after wire passage; intraprocedural use of: balloon pre- and postdilatation, manual thrombus aspiration, glycoprotein IIb/IIIa receptor blocking agents; number of implanted stents; intervention at a bifurcation site; occurrence of distal embolization. Angiographic no-reflow was considered in case of suboptimal (i.e. <3) final TIMI flow.

The SYNTAX score was calculated prospectively, on the basis of emergency coronary angiography, using the 2.11 version of the on-line calculator available at <http://www.syntaxscore.com/calc/start.htm>. All lesions causing stenosis of $\geq 50\%$ in any coronary branch with the reference diameter of ≥ 1.5 mm were scored separately. The score was multiplied by 2 for 50-99% lumen stenosis and by 5 for total occlusions. Other important adverse characteristics had an additive value: challenging localizations – ostium/bifurcation/trifurcation, side-branch angulation, vessel tortuosity, long-, calcified-, thrombus-containing lesions and diffusely narrowed segments.

Two types of ST-segment elevation resolution (STER) measurements were performed on a single ECG lead within the first hour after mechanical reperfusion. Relative STER was defined as the percent reduction of ST-segment elevation (STE) in the ECG lead with the highest preprocedural STE. Absolute STER was represented by the maximum residual single-lead STE (mm) on the post-PCI ECG. Both parameters had been validated as independent predictors of adverse events after primary PCI.

A complex statistical analysis was performed to examine possible associations between clinical and angiographic data, different complexity levels of CAD and markers of impaired reperfusion: abnormal, i.e. <3 Thrombolysis In Myocardial Infarction (TIMI) postprocedural flow, as well as incomplete STER.

In-hospital mortality was registered and analyzed as the main clinical outcome. The predictive power of the SYNTAX score and CSS was compared for this single endpoint.

One hundred and thirty-five patients were enrolled in the trial. The registered all-cause in-hospital mortality was 10.2%.

As a result of the first study – *Predictors of reperfusion success* (Chapter 4) – we identified the following parameters associated with poor epicardial (TIMI flow <3) and tissue reperfusion (incomplete relative and absolute STER): advanced age; low LVEF; renal dysfunction; high CK values; anterior STEMI localization; TIMI flow <2 before intervention; PCI at a bifurcation site; occurrence of the no-reflow phenomenon; distal embolization; high TIMI thrombus score after wire passage. In different multiple regression models, the most significant, independent predictors of poor reperfusion were anterior STEMI localization and the occurrence of distal embolization. Logistic regression analysis identified relative STER as an independent predictor of in-hospital mortality.

In Chapter 5: *Complex coronary artery disease, reperfusion and short-term prognosis after primary PCI*, subjects were stratified according to three different CAD complexity levels, as tertiles with low, medium and high SYNTAX score values. The markers of reperfusion success (post-PCI TIMI flow, absolute and relative STER), in-hospital mortality and the parameters associated with them were evaluated in these three patient groups. The calculated SYNTAX scores ranged between 3 and 42, with a nonparametric distribution and a median value of 16.0. A significant relationship was documented between CAD complexity and epicardial as well as tissue-level reperfusion: post-PCI TIMI flow was more frequently impaired in case of high SYNTAX score values and absent/partial absolute STER were more often documented. In-hospital mortality was also significantly increased in the high SYNTAX score group. Advanced age, non-smoking, anterior localization of

STEMI, renal dysfunction, high number of implanted stents, bifurcation culprit lesion and distal embolization were also found to be associated with complex CAD.

In chapters 6 (*Renal dysfunction at hospital admission, high complexity of coronary artery disease and short term prognosis in acute ST-segment elevation myocardial infarction*) and 7 (*SYNTAX score and global atherosclerotic burden in STEMI*) the same patient stratification was used. We tested the relationship between renal function and CAD complexity in STEMI patients treated by primary PCI. Kidney dysfunction was defined as eCr_{cr} of <60 ml/min. A significant, inverse proportional relationship was found between the complexity of CAD and the estimated GFR. This probably contributed to the increased mortality rates observed in patients with acute STEMI and high SYNTAX scores. The worse outcomes after primary PCI were also partially explained by the significantly increased global atherosclerotic burden. This condition is well characterized by the echographically measured carotid IMT. A positive correlation was documented between the absolute values of the IMT and the SYNTAX score – the main finding of the fourth study. However, the characteristics of the acute (culprit) lesion did not affect this relationship; it only depended on the extent and complexity of the chronic atherosclerotic process in epicardial vessels.

The final study – chapter 8: *Clinical SYNTAX Score in STEMI* – is, to the best of our knowledge, the first to evaluate this combined risk stratification model in acute myocardial infarction treated by primary PCI. Briefly, CSS is determined by “correcting” the angiographic SYNTAX score for three clinical variables: age, eCr_{cr} and LVEF. We based the current research on the hypothesis that this model would offer a better risk stratification for in-hospital mortality than the sole angiographic parameters. Receiver-operator characteristic (ROC) curve analysis evidenced a superior predictive power of the combined score. In fact, 3 of the 5 deceased patients with low risk according to the SYNTAX score, were reclassified in the high-risk subset on the basis of CSS. Although the inclusion of clinical variables significantly improved the ability of the SYNTAX score to predict short-term prognosis in the current research, further studies are needed to establish the exact role of CSS in the risk stratification after primary PCI.

Conclusions

Complex coronary artery disease (as defined by high SYNTAX score values calculated on the basis of emergency coronary angiogram) is associated with increased post-STEMI mortality, even if mechanical reperfusion therapy is applied. This is partially explained by the impaired epicardial and myocardial reperfusion (mainly mediated by the high incidence of distal embolization), but also by other clinical factors, such as the greater prevalence of advanced age and comorbidities in this patient group. The negative impact of distal embolization is amplified by the more frequent occurrence of left ventricular- and renal dysfunction, as well as by the more severe global atherosclerotic burden of the subjects with complex CAD. High values of the SYNTAX score (≥ 20 in the present work) could offer additive information for the optimal management of these patients. Accordingly, supplementary measures to improve myocardial reperfusion, followed by active searching for residual ischemia and early revascularization, would probably be welcomed in case of elevated SYNTAX score. The evaluation of the angiographic score to guide such decisions could be the subject of further research. Moreover, the use of the Clinical SYNTAX Score may prove superior to the SYNTAX score for this purpose.

Keywords: acute myocardial infarction, primary PCI, ST-segment elevation resolution, distal embolization, short-term prognosis, renal dysfunction, intima-media thickness, SYNTAX score, Clinical SYNTAX Score.