Proximal embolic protection and biomarkers of reperfusion in ST-segment elevation myocardial infarction
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Summary and conclusions

The goal of this thesis was to evaluate the effectiveness of combined proximal embolic protection and thrombus aspiration on surrogate end points and intermediate outcomes as well as the relationships between the biomarkers of reperfusion, intermediate and clinical outcomes. The first part (Chapter 2 to 5) comprises the results of a registry of Proxis-treated patients and the multi-center ‘PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation’ (PREPARE) study. The second part (Chapter 6 to 15) describes the relationships between cardiac serum biomarkers, angiographic outcomes, electrocardiogram (ECG) parameters, and intracoronary flow measurements with late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR)-derived and clinical outcomes.

Combined proximal embolic protection and thrombus aspiration in ST-segment elevation myocardial infarction

Over the last decade, numerous randomized controlled trials have been performed to study an array of adjunctive devices with different designs and mechanism of action to reduce or prevent microvascular injury in patients with acute myocardial infarction. In these studies, the use of distal embolic protection and thrombectomy devices in primary percutaneous coronary intervention (PCI) were tested. However, these studies showed mixed results. A potential interesting technique is the Proxis system, a combination of proximal embolic protection and thrombus aspiration. Although the effectiveness of the Proxis system in saphenous vein graft (SVG) intervention has been confirmed, the potential benefit of the Proxis system in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI was not studied. Thus, clinical investigation using this technique in STEMI patients was warranted.

In Chapter 2, we describe a study in which we tested the safety and feasibility of the Proxis system in patients with STEMI undergoing primary PCI. In this single-center registry, 172 patients were treated with primary PCI with combined proximal embolic protection and thrombus aspiration. The results demonstrated good angiographic outcomes, excellent ST-segment resolution, and low one-year mortality. The Proxis
system was shown to be safe and feasible in the setting of primary PCI for acute myocardial infarction and suggested that the system is highly effective for aspirating embolic material. To answer whether these observations could be translated in improved measures of PCI effectiveness in the setting of STEMI and would ultimately contribute to clinical benefit, a randomized controlled trial was needed.

On the basis of these findings, the randomized controlled PREPARE study was designed to evaluate the effectiveness of combined proximal embolic protection with thrombus aspiration during mechanical reperfusion therapy in STEMI. As described in Chapter 3, we randomized 284 patients with STEMI to primary PCI with Proxis system versus primary PCI alone after angiography in the Academic Medical Center and the Montréal Heart Institute. The primary end point was the occurrence complete ST-segment resolution at 60 minutes determined by continuous ST Holter monitoring. Continuous ST Holter is a well-validated method to determine the effectuation of mechanical reperfusion. Continuous ST Holter data were analyzed by an independent core laboratory (Duke Clinical Research Institute – Duke University Medical Center). Although there was no significant difference in complete ST-segment resolution at 60 minutes in this proof-of-concept study, we observed a significant improvement in immediate complete ST-segment resolution (immediately after PCI) in Proxis-treated patients and a reduction of ECG injury current over time compared with the control patients. Our results suggest that primary PCI with the Proxis system may lead to better immediate microvascular flow in STEMI patients. The improved microcirculatory reperfusion within the first hours after the restoration of epicardial flow might translate into a clinically relevant smaller infarct size and preservation of left ventricular function and clinical outcomes.

Because LGE-CMR imaging has recently been considered to become the gold standard for accurate assessment of infarct size and left ventricular function, we performed an ancillary LGE-CMR study of the PREPARE trial to determine whether the use of the Proxis system in primary PCI in a smaller infarct size and preservation of left ventricular function at follow-up. In Chapter 4, the results of this ancillary LGE-CMR study are presented and discussed. The LGE-CMR study included 206 STEMI patients who were enrolled in the PREPARE study. LGE-CMR imaging was assessed between four and six months after the index procedure. There were no
significant differences in regional and global LGE-CMR parameters, such as infarct size, extent of transmural segments, left ventricular ejection fraction, left ventricular dimensions, and systolic wall thickening in the infarct area among both arms. Thus, primary PCI with combined proximal embolic protection and thrombus aspiration in STEMI patients did not result in significant differences in infarct size or left ventricular function at follow-up. Multiple explanations have been proposed why the Proxis system succeeded to enhance myocardial reperfusion success, as observed by more early ST-segment resolution and a reduction in ECG injury current over time, but failed to reduce infarct size or improve left ventricular function. One of the possible explanations for these findings is the necessity for a “landing zone” for the Proxis system. Patients with a myocardial infarction related to an ostial coronary artery occlusion were not included. This resulted in more myocardial infarctions related to a right coronary artery (RCA) compared with a “typical” STEMI population and led to exclusion of very proximal infarct-related left anterior descending artery (LAD) and left circumflex artery (LCx) lesions. The preponderance of RCA lesions and non-proximal lesions of the LAD and LCx with subsequent smaller myocardial infarctions may have diluted the effect size that might have been seen in proximal LAD and LCx lesions with larger amounts of myocardium at risk.

Because of our conflicting findings, we additionally performed in Chapter 5 a re-evaluation of the angiographic outcomes. In this study, all post-procedural coronary angiograms were re-evaluated by the core laboratory (University Medical Center Groningen) blinded for treatment allocation and clinical data. In addition, analysis of myocardial perfusion was performed by computer-assisted quantitative blush evaluation (QuBE). High QuBE has been significantly associated with more ST-segment resolution, higher visually assessed myocardial blush grade, and lower one-year mortality. These post-hoc analyses did not reveal any significant differences in core laboratory adjudicated angiographic outcomes, such as TIMI-graded flow or myocardial blush and QuBE values.
Future perspective of proximal embolic protection

Prevention of embolization of atherothrombotic material during PCI is definitely “intuitively attractive” for every interventional cardiologist working in this field. Although some progress has been achieved, mechanical and pharmacological prevention and treatment of distal embolization remains challenging. Ideally, patients who are suffering from an acute myocardial infarction should be pre-treated with pharmacological agents aiming to prevent or dissolve potential emboli. Furthermore, the dislodgement of atherothrombotic material during PCI caused by wires, balloons, stents, and devices, should be prevented by an ‘ideal-world device’. The ‘ideal-world device’ should be able to prevent distal embolization during every step of the procedure, but simultaneously needs to be feasible and safe. Despite the fact that the ‘ideal world device’ does not yet exist, as they do not prevent embolization completely and may inflict additional damage to the vessel wall, the technical developments of embolic protection devices and thrombectomy devices in the last few years have been remarkable. It could be expected that the performances of the devices will further improve by current and future research. Although Proxis-treated patients had faster and more complete ST-segment resolution compared with control patients, the use of combined proximal embolic protection and thrombus aspiration during primary PCI did not translate into a clinically relevant smaller infarct size and less impairment of the left ventricular function at follow-up. In addition, recent data did not show any benefit of the use of distal embolic protection devices in patients with STEMI on surrogate end points, intermediate or clinical outcomes.

Recent data demonstrated the benefit of the use of a thrombus aspiration device (Export, Medtronic, Santa Rosa, CA, USA) in the setting of STEMI. However, future randomized trials should confirm these findings before thrombus aspiration in primary PCI may become a routine clinical practice. Although certain subgroups of patients with acute myocardial infarction have been identified to benefit from thrombus aspiration (e.g. high thrombus burden, right coronary artery-related myocardial infarction), other patients subsets, for example myocardial infarction patients with ‘spontaneously reperfused arteries’, may also benefit from thrombus aspiration. Furthermore, it seems conceivable that patients with stable coronary artery disease may have benefit of preventing embolization during elective PCI.
Summary and conclusions

In our PREPARE study, distal embolization on the coronary angiogram was visible in 12% of the patients despite triple antiplatelet therapy, including heparin, aspirin, and clopidogrel before PCI and the use of abciximab at discretion of the operator at the start of the PCI procedure. Novel antithrombotic treatment strategies, such as intracoronary bolus of abciximab, could further reduce distal embolization and microvascular injury by suppression of platelet activity and lysis of embolized thrombus particles. Intracoronary administration of abciximab in patients undergoing primary PCI for STEMI may facilitate the diffusion of the antibody to platelets inside the flow-limiting thrombus, thus resulting in improved dissolution of thrombi and microemboli at the ruptured plaque and further downstream in the microcirculation. Other intracoronary pharmacological therapeutics, such as streptokinase, could also improve the outcomes of acute myocardial infarction patients. Furthermore, the delivery of the pharmacological agent in the periphery of the coronary artery by a micro-catheter could enable the pharmacological agent to act more effectively. New developments include the use of anticoagulation with bivalirudin alone in acute myocardial infarction and the thienopyridine prasugrel instead of clopidogrel. In patients with STEMI who are undergoing primary PCI, anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors resulted in significantly reduced 30-day rates of major bleeding and mortality. Nevertheless, at present the main clinical application of proximal and distal embolic protection devices still remains SVG interventions. The use of these devices is supported by randomized data and guidelines recommendations. Although the use of proximal and distal embolic protection devices reduces the major adverse event rate in SVG PCI patients, periprocedural adverse outcomes still occur in approximately 10% of patients, emphasizing the need for complementary device-based innovations and new pharmacologic regimes to additionally enhance the safety of SVG intervention in these high-risk patients. Studies that specifically address the role of adjunctive devices in SVGs during acute myocardial infarction are also required.

In conclusion, all these developments could lead to a better understanding of the crucial role of distal embolization in microvascular dysfunction and the ‘no reflow phenomenon’ and may further improve our mechanical and pharmacological strategies in preventing and treating distal embolization in PCI.
Biomarkers of reperfusion in ST-segment elevation myocardial infarction

The aim of the second part of the thesis was to assess the predictive value of reperfusion biomarkers in STEMI patients treated with mechanical reperfusion. Many studies have been conducted to investigate the relationship between various reperfusion biomarkers and their association with surrogate end points and clinical outcomes. Nevertheless, many of these reperfusion parameters have not yet been studied or extensively investigated to test their prognostic value in acute myocardial infarction patients.

Cardiac serum biomarkers before PCI have been shown to be prognostic in patients with acute coronary syndrome (ACS) and stable coronary artery disease. In Chapter 6, we sought to evaluate whether the plasma levels of admission N-terminal pro-brain natriuretic peptide (NT-pro-BNP) relates to left ventricular function and infarct size measured by LGE-CMR imaging during follow-up and compared NT-pro-BNP values with those of other serum biomarkers associated with prognosis, including cardiac troponin T, creatinine clearance rate, and CRP. The results of this analysis showed that an admission level of NT-pro-BNP higher than 260 pg/mL in patients with non-anterior wall myocardial infarction undergoing primary PCI is a strong and independent predictor of left ventricular function at 4 months. NT-pro-BNP was the strongest independent predictor of cardiac function of the other serum biomarkers.

Also, in Chapter 7 the effect of an elevated NT-pro-BNP level on incomplete ST-segment recovery is investigated. Because ST-segment recovery on the 12-lead ECG is a marker of microvascular reperfusion at the tissue level and accurately predicts final infarct size and clinical outcome, serum biomarkers at the start of PCI associated with incomplete ST-segment recovery could help identify patients at continued risk of impaired microvascular reperfusion. Again, NT-pro-BNP was the strongest independent predictor among the other serum biomarkers. Conclusively, NT-pro-BNP, a widely available biomarker, is a strong independent predictor for incomplete ST-segment recovery in acute myocardial infarction patients and cardiac function in non-anterior wall myocardial infarction patients and might be helpful in the early risk stratification of these patients.

Although several established measures assess the quality of myocardial reperfusion, new measures have been developed and tested. A new technique is a computer-assisted analysis of the myocardial blush on the coronary angiogram: the QuBE
program. It is an open source software program providing a practical and feasible and reproducible assessment of myocardial perfusion. Chapter 8 describes the evaluation of this computer-assisted myocardial blush quantification program on coronary angiograms assessed in other catheterization laboratories and whether the QuBE score could be associated with other measures of myocardial reperfusion. In addition, in Chapter 9, the predictive value of the QuBE program for intermediate outcomes of successful reperfusion as determined with the current golden standard LGE-CMR in STEMI patients at four to six months after primary PCI is studied. The QuBE program provided analyzable results from coronary angiograms recorded at the Academic Medical Center and the Montréal Heart Institute. In both studies, a higher QuBE value was associated with other measures of reperfusion (myocardial blush grade and complete ST-segment recovery) and improved functional and contrast-enhanced CMR outcomes including left ventricular ejection fraction and infarct size. Early identification of high risk patients by the QuBE program may select those who can benefit from adjunctive therapies targeted at sustaining myocardial function after mechanical reperfusion.

Nowadays, ST-segment recovery after PCI is used to assess patient outcome. However, the impact of ST-segment recovery immediately after PCI, late ST-segment recovery, and no ST-segment recovery on outcomes remains unclear. The aim of the study, as described in Chapter 10, was to determine the predictive value of ST-segment recovery immediately after PCI, late ST-segment recovery, and no ST-segment recovery for left ventricular ejection fraction and infarct size by LGE-CMR at follow-up in patients with STEMI. Patients with ST-segment recovery immediately after PCI had more preserved left ventricular ejection fraction and smaller infarct size compared with patients with late ST-segment recovery or no ST-segment recovery. ST-segment recovery directly after PCI was independently predictive for left ventricular ejection fraction and infarct size and late ST-segment recovery was not predictive for left ventricular ejection fraction, but predictive for infarct size. In conclusion, patients with immediate complete ST-segment recovery after primary PCI have better preserved left ventricular ejection fraction and smaller infarct size. Patients with late complete ST-segment recovery do not have better preserved left ventricular ejection fraction, but smaller infarct size.
Most data on the prognostic value of ST-segment recovery after PCI are mostly coming from randomized controlled trials, with ST-segment recovery assessed at 30 min or later after completion of the PCI procedure. For that reason, we evaluated in Chapter 11 the predictive power of ST-segment recovery immediately after PCI in an unselected STEMI population treated with mechanical reperfusion at the Academic Medical Center. ST-segment recovery immediately after PCI was a strong predictor of one-, three-, and five-year mortality. Moreover, even when the analysis was restricted to six-month survivors, ST-segment recovery remained significantly predictive for five-year mortality. Therefore we concluded that ST-segment recovery directly after PCI has excellent prognostic value in a real-world STEMI population. Additionally, the study of Chapter 12 was performed to evaluate the predictive value of various measures of ST-segment recovery for one-year mortality in an all-comer STEMI population undergoing primary PCI. Of the several measures to assess ST-segment recovery, \( \Sigma ST-D \) resolution (comparing summed pre- and post-procedural ST-segment deviation) was the most excellent independent predictor for one-year mortality. Additionally, when a 50% cut-off is used, the ST-segment recovery measure was most outspoken. Furthermore, in Chapter 13 an analysis was performed to investigate the clinical and angiographic predictors of ST-segment recovery after primary PCI. In this study, the presence of age >60 years, no smoking, diabetes mellitus, anterior wall myocardial infarction, multi-vessel disease, and pre-procedural TIMI 3 flow were significantly associated with impaired microvascular reperfusion as measured by incomplete ST-segment recovery.

In summary, ST-segment recovery immediately after PCI, especially \( \Sigma ST-D \) resolution, has an outstanding prognostic value to identify STEMI patients with continued risk for adverse outcome. Therefore, absence of ST-segment recovery could be a reason to administer adjunctive therapy to enhance suboptimal microvascular reperfusion. Furthermore, assessment of ST-segment recovery may serve as an important performance measure to assess the quality of a primary PCI program. However, data regarding the value of ST-segment recovery immediately prior to primary PCI to predict infarct-related patency remains limited. Therefore, we performed in Chapter 14 a study to test whether ST-segment recovery prior to PCI is a reliable, non-invasive indicator of infarct-related artery patency in patient with STEMI. Although there was
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A correlation between ST-segment recovery prior to primary PCI and pre-procedural TIMI flow, the negative predictive value of incomplete ST-segment recovery for detection of TIMI 3 flow was moderate and therefore should not be a criterion to refrain from urgent coronary angiography in patients with STEMI.

Finally, microvascular injury in STEMI patients is often assessed by ST-segment recovery. Other measures of microvascular injury are intracoronary Doppler flow measurements and LGE-CMR imaging. In Chapter 15, we performed a study to investigate the relationship between microvascular injury by LGE-CMR and by intracoronary Doppler flow measurements. The extent and size of the microvascular injury as determined by LGE-CMR correlated well with Doppler flow measurements, such as the presence of early systolic retrograde flow, rapid deceleration of the diastolic flow velocity, and reduced coronary flow velocity reserve. LGE-CMR is thus an accurate non-invasive technique to quantify myocardial function, infarct size, and microvascular injury in patients with STEMI.