Clinical outcome in high-risk STEMI patients with multivessel disease: towards recanalization of CTOs following primary PCI

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Chapter 11

Summary, future perspectives and concluding remarks

In **chapter 2**, we showed that even with the reperfusion therapy of choice, patients with diabetes mellitus (DM) have an increased long-term mortality when compared to patients without DM. Patients with ST-elevation myocardial infarction (STEMI) and diagnosed DM treated with primary percutaneous coronary intervention (PCI) constitute a high-risk patient group. DM patients have more severe coronary artery disease and present more often with shock and more often have PCI failure. After primary PCI for STEMI, one-year mortality is 7.2% in patients without DM and 17.8% in patients with DM. When stratified to treatment regimen, DM patients on oral medical therapy at time of admission for STEMI have a one-year mortality rate of 14.3% versus 27.1% in patients on insulin therapy. Preadmission therapy for diabetes is an independent predictor of one-year mortality. Even after primary PCI for acute STEMI, DM patients on insulin therapy are a subgroup with an approximately 4 times higher mortality rate compared with patients without DM and a 2 times higher mortality rate when compared with DM patients on oral therapy, in current daily "real life" clinical practice. Additional pharmacological and or other interventions should be studied to reduce PCI failure and improve clinical outcome in STEMI patients with DM.

In **chapter 3**, we report two novel findings on primary PCI for STEMI due to saphenous vein graft (SVG) occlusion. First, our data show that patients with STEMI due to SVG occlusion present either "early" or "late". The majority of patients with STEMI due to SVG occlusion present >10 years after coronary artery bypass grafting (CABG). Of the patients presenting <10 years after CABG, most of the acute SVG occlusions occur within one year after CABG. As a second finding we report equal angiographic success rates (70%) and comparable one-year mortality rates in patients treated with primary PCI for acute SVG occlusion with regard to time from bypass surgery. No difference in outcome was observed in patients presenting either <10 years or >10 years after CABG. Although different mechanisms may play a role, time from CABG does not affect outcome in patients with prior CABG treated with primary PCI for STEMI due to SVG occlusion.

Chapter 4, demonstrates that, compared with patients with single vessel disease (SVD), patients with multivessel disease (MVD) have a higher total mortality, after 8 years of follow-up in the Zwolle trial. This randomized trial compared clinical outcome in patients with acute myocardial infarction treated with a thrombolytic agent or with primary PCI. Although enzymatic infarct size was comparable between the patient groups, residual left ventricular ejection fraction (LVEF) was more often reduced in patients with MVD. This study is the first to demonstrate that the higher mortality rate was mainly driven by death due to heart failure during long follow-up. MVD was not found to be an independent predictor for total mortality, but a very strong and independent predictor of death due to heart failure. There was no difference in the incidence of sudden death between the patient groups.

In **chapter 5**, we confirmed that, despite the application of the reperfusion therapy of choice, primary PCI, patients with MVD have a higher one-year mortality rate compared with patients with SVD after primary PCI for acute STEMI. Moreover, we are the first to demonstrate that the higher one-year mortality rate in patients with MVD is determined by the presence of a chronic total occlusion (CTO) in a non-infarct related artery (IRA) and not due to the mere presence of MVD. Patients with a CTO therefore constitute the MVD patient group with a truly higher risk for death.

Chapter 6 extends the previous observation that the poor prognosis of STEMI patients with MVD is driven by the presence of a CTO in a non-IRA. For both early (within 30 days after STEMI) and late mortality (from 30 days up to five years after STEMI) the presence of a CTO in a non-IRA was identified as a strong and independent predictor. MVD without a concurrent CTO was found to be a relatively weak predictor for early mortality. After excluding patients who died within 30 days after STEMI, MVD without a concurrent CTO lost its independent predictive value for mortality. Furthermore, we found that a CTO, and not the mere presence of MVD, is associated with both a reduced residual LVEF after the index event and a further deterioration in LVEF during follow-up.

In **chapter 7** we show that, in the high-risk subgroup of STEMI patients presenting with cardiogenic shock (CS), mortality increased gradually with the extent of coronary artery disease. However, after correction for possible confounders by multivariate Cox regression analysis, the presence of MVD without a CTO was not an independent predictor of one-year mortality, whereas the presence of a CTO in a non-IRA was an independent predictor of one-year mortality. We are the first to demonstrate the prognostic importance of a CTO in a non-IRA in patients with STEMI complicated with CS.

Chapter 8 demonstrates the increased frequency of variables, all associated with adverse outcome after STEMI, in the subgroup of patients with DM. Still, the presence of a concurrent CTO, but not the mere presence of MVD, is an independent predictor of long-term mortality.

Future perspectives

In **chapter 9** we respond to an article, in which the authors report no improvement in in-hospital outcome after multivessel primary PCI for STEMI, even in patients with CS. Previously, there have been studies reporting no mortality benefit of multivessel PCI during and shortly after primary PCI in STEMI patients with MVD. Additionally, we identified patients with a CTO in a non-IRA as the subgroup with a truly high-risk for mortality after primary PCI for STEMI. Consequently, we suggest that a CTO in a non-IRA is a target for additional revascularization of STEMI patients with MVD.

To date, it is unclear whether STEMI patients with a CTO in a non-IRA should undergo additional PCI of the CTO on top of optimal medical therapy shortly after primary PCI. Possible beneficial effects of recanalization of a CTO include reduction in adverse left ventricular remodeling and preservation of global left ventricular function, increased electrical stability and protection against future events. Therefore we designed the investigator-initiated Evaluating Xience V and left ventricular function in PCI on occLusiOns afteR STEMI (EXPLORE) trial, which is presented in **chapter 10**.

The ongoing EXPLORE trial is the first randomized clinical trial powered to study clinical outcome after percutaneous treatment of CTOs. The Explore trial will determine whether recanalization of a CTO after primary PCI for STEMI improves LVEF and left ventricular end-diastolic volume. Three hundred patients after primary PCI for STEMI with a CTO in a non-IRA are randomized to either elective PCI of the CTO within seven days after primary PCI or standard medical treatment. When assigned to PCI of the CTO, the procedure is scheduled within seven days after primary PCI and an everolimus-eluting coronary stent is used to treat the CTO. Primary endpoints are LVEF and left ventricular end-diastolic volume assessed by Magnetic Resonance Imaging at four months after STEMI. Clinical follow-up will continue until five years after randomization.

Concluding Remarks

Treatment of patients with STEMI aims at early restoration of antegrade flow in the infarct related coronary artery, to preserve myocardial function and to improve survival. Angiography after thrombolysis or before primary PCI has revealed that MVD is present in 40-65% of all STEMI patients. These patients were considered to be a subgroup with an increased risk for morbidity and mortality, compared with patients with SVD. An aggressive multivessel percutaneous revascularization strategy, during and after primary PCI for STEMI, has not demonstrated to improve outcome in MVD patients. In fact, studies reported that treatment of non-culprit lesions in STEMI patients with MVD is associated with a higher post-procedural morbidity rate without a benefit in mortality rate. In the setting of primary PCI we demonstrated that, compared with patients with SVD, the higher mortality in patients with MVD is mainly determined by the presence of

a CTO in a non-IRA. Therefore, STEMI patients with a CTO constitute the MVD patient group with a truly higher risk for death, even in patients with cardiogenic shoch or in patients with diabetes mellitus.

Left ventricular function and left ventricular end diastolic volume (LVEDV) are major prognostic determinants in patients with coronary artery disease. After primary PCI, patients with MVD have a more reduced LVEF at hospital discharge compared with patients with SVD. In addition, there is impaired recovery of left ventricular function, which is closely related to the extent of coronary artery disease.

Despite the relatively low initial success rates and high rates of restenosis, it is suggested that opening of CTO can be of benefit by restoring blood flow to non-contractile, but viable, myocardium and thus improving LV function. Improvement of left ventricular function and a reduction of both end-diastolic and end-systolic volume after recanalization of a CTO has been demonstrated in several studies, provided long-term patency could be achieved. PCI of CTO can be performed with a success rate of 70-80%, but with a higher rate of restenosis than after PCI of non-occluded vessels. Although coronary stenting has been shown to be superior to conventional balloon angioplasty, restenosis rates remain relatively high. Drug eluting stents are effective in decreasing the risk of restenosis in successfully treated CTO patients when compared with patients treated with bare metal stents. However, there have been concerns about long-term delay of arterial healing produced by both the sirolimus eluting stent and paclitaxel eluting stent and the associated risk of late stent thrombosis. Preclinical data for the everolimus eluting stent are encouraging in terms of arterial healing since rates of re-endothelialisation were examined. Everolimus eluting stents had superior endothelialization compared with paclitaxel eluting stents. The suggested good safety profile of everolimus eluting stents was confirmed in recent large clinical studies, which reported superior performance and safety of the everolimus eluting stent when compared with the paclitaxel eluting stent.

In conclusion, in the setting of primary PCI, the mortality risk in patients with MVD is determined by a CTO in a non-IRA. An active revascularization strategy, i.e. recanalization of a CTO, might improve function in non-infarcted hibernating myocardium and promote infarct healing at the border zones. These effects may attenuate the remodeling process, which may lead to improved global left ventricular function, decreased LVEDV, and improved survival.