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Novel insights in reperfusion therapy and stent thrombosis in the drug eluting stent era

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Summary, conclusions and Future perspectives

The aim of this thesis was: (1) to evaluate the immediate, short and long term outcomes of early abciximab administration prior to primary percutaneous coronary intervention (PPCI) in ST-segment elevation myocardial infarction (STEMI) patients, (2) to study the incidence of aborted infarction in the current PPCI era and its prognostic value, (3) to evaluate the prognostic importance of the early peak of cardiac troponin T in patients with first acute myocardial infarction treated with PPCI, (4a) to review the prevalence of late acquired stent malapposition in drug eluting stents compared with bare metal stents implantation and, (4b) to investigate its possible association with (very) late stent thrombosis.

SUMMARY

The introduction and outline of this thesis (**chapter 1**) describe current insights in PPCI as the treatment of choice for STEMI patients, role of platelets inhibitors as an adjunctive therapy, stent thrombosis as a major complication after stent implantation, and its possible association with late stent malapposition.

PPCI, usually combined with stenting, has become the standard treatment for STEMI. During this procedure, trauma commonly occurs to the arterial endothelium that, among other effects, causes the activation and aggregation of platelets. Because platelet aggregation may lead to coronary thrombosis in a patient already vulnerable to it, antiplatelet agents are essential adjunctive therapies in patients with STEMI undergoing PPCI. The goal of antiplatelet therapy is to provide maximal protection against thrombosis without increasing the risk of bleeding. The use of abciximab as an adjunctive therapy with PPCI is recommended by current guidelines. Still there are several unresolved issues in the era of PPCI such as the timing of abciximab administration, the incidence and predictors of aborted infarction and, the prognostic importance of cardiac troponin T release after PPCI. These are the main topics of this thesis. Stent thrombosis is one major complication after stent implantation. It can occur early (within < 30 days), late (between 30 days and 1 year) and very late (> 1 year) after stent implantation. Late stent malapposition has been accused to be one of the underlying mechanisms for late stent thrombosis. This is another point that we have explored in this thesis.

In **Chapter 2**, we evaluate the effects of early abciximab administration in the ambulance on immediate, short and long term outcomes within a fixed protocol for PPCI (Leiden MISSION! Project). 179 consecutive patients with STEMI were enrolled, 90 patients received abciximab bolus in the hospital (late group) and 89 patients received abciximab bolus in the ambulance (early group). December 2006 was the cut-off point for this prospective study. The two groups were well matched for baseline and angiographic characteristics. The early group received abciximab within the golden period (median 63 min vs. 136 min in late group). The infarct related artery (IRA) patency at onset of the PCI was 4 times higher in the early group than in late group (odds ratio = 4.9, 95% CI 2.4-10.1). Enzymatic infarct size was smaller in the early group (cumulative 48-h CK release 8011 vs. 11267 U/L, $p = 0.004$). This was associated with higher left ventricular ejection fraction (LVEF) at 90 days post-PPCI by myocardial scintigraphy (59% vs. 54%, $p = 0.01$), and lower incidence of heart failure through a median of 210 days of clinical follow-up (3% vs. 11%, $p = 0.04$). Thus, early abciximab administration in the ambulance significantly improves early reperfusion in STEMI

patients treated with PPCI. Moreover this is associated with a smaller infarct size, improved LV function at 3-months and a lower risk of heart failure through 7-months follow-up.

Chapter 3 describes the incidence, patient's characteristics and predictors of aborted myocardial infarction (MI) in patients with STEMI undergoing PPCI. 179 consecutive patients with STEMI were enrolled within a fixed protocol for PPCI (Leiden MISSION! project), 90 patients received abciximab bolus in the hospital (in-hospital group) and 89 patients received abciximab bolus in the ambulance (pre-hospital group). 32 patients (18%) fulfilled the criteria for an aborted MI. The incidence of aborted MI was 4 times higher in the pre-hospital abciximab group compared to in-hospital group (OR = 4.2, 95% CI = 1.7-10.3). The median time between symptoms onset and abciximab bolus administration was significantly shorter in the aborted MI compared to established MI patients (70 vs. 115 min, $p = 0.005$). Multivariable analysis identified pre-hospital abciximab administration as the main predictor of aborted MI (OR = 2.86, 95% CI = 1.1-7.5). Thus, Pre-hospital abciximab administration was the main predictor of aborted MI in STEMI patients treated with PPCI, and this effect was related to the initiation of treatment within the first 2 hours after symptoms onset and to the higher IRA patency at presentation.

In **Chapter 4** we present the prognosis of patients with aborted MI after PPCI.

Left ventricular function at 3 months follow-up measured by myocardial scintigraphy and one year incidence of major adverse cardiac events were investigated. Left ventricular ejection fraction at 3 months was higher in the aborted MI group compared to the established MI group (62.3% vs. 55.3%, $p = 0.001$). The cumulative incidence of mortality, recurrent MI, revascularization procedures and heart failure was lower in the aborted MI group than in the established MI group (16% vs. 36%, $p = 0.02$). Thus, patients with an aborted MI had a better left ventricular function at 3 months and superior prognosis than those with established MI.

Chapter 5 describes the prognostic value of cTnT in patients with STEMI treated by PPCI. 168 consecutive patients with first acute MI were enrolled in the present study. Patients were eligible if STEMI symptoms started < 9 h before the PPCI. Patients had repeated measurements of cTnT and creatine kinase (CK) in the first 48 hour post PPCI, left ventricular ejection fraction (LVEF) assessment by myocardial scintigraphy at 90 days and clinical follow-up at 1, 3, 6 and 12 months post PPCI. Peak cTnT values were observed within the first 24 hours in all patients. Patients within highest peak cTnT tertile ($> 6.34 \mu\text{g/L}$) were more likely to be older and presenting with Killip class ≥ 2 . The enzymatic infarct size was positively correlated with peak cTnT ($r = 0.73$, $p < 0.001$). LVEF at 3 months was negatively correlated with peak cTnT ($r = -0.52$, $p < 0.001$). Multivariable Cox regression analysis identified peak cTnT as an independent predictor of incidence of major adverse cardiac events (HR = 1.07, 95% CI = 1.01-1.12) and heart failure (HR = 1.12, 95% CI = 1.05-1.20) assessed during clinical follow-up. The results indicate that peak cardiac troponin-T in the first 24 after primary PPCI offers a good estimation of infarct size and a long-term prognostic indicator in patients with first acute myocardial infarction.

In **Chapter 6** we present a meta-analysis and systematic review on the context of late stent malapposition (LSM) that may be acquired (LASM) or persistent. Our objective was to compare the risk of LASM in bare metal stents (BMS) with drug-eluting stents (DES) and to investigate the possible association of both acquired and persistent LSM with (very) late stent thrombosis (ST). Inclusion criteria for studies or expert presentations were: (1) Intravascular ultrasonography (IVUS) at both post-stent implantation and follow-up; (2) Follow-up IVUS performed within 6 to 9 months after stent implantation; (3) Implantation of either BMS or the following DES: sirolimus (SES), paclitaxel (PES), everolimus (EES) or zotarolimus (ZES) and, (4) Follow-up for LSM. Two investigators independently extracted all data, and disagreements were solved in consultation with a third investigator. Meta-analysis was conducted for IVUS and clinical outcomes. Of 295 potentially relevant articles identified, 33 were retrieved for detailed evaluation and, 17 met the inclusion criteria. The risk of LASM in patients with DES was 2.5 times higher compared to BMS (OR= 2.49, CI 95% 1.15-5.35) when all studies were used and was 4 times higher (OR= 4.36, CI 95% 1.74-10.94) when only data from randomized control trials (RCTs) were used. The risk of (very) late ST in patients with LSM (5 studies) was higher compared to the patients without LSM (OR= 6.51, CI 95% 1.34-34.91). Thus, the risk of late acquired stent malapposition is significantly higher after drug-eluting stent compared to bare-metal stent implantation. In our meta-analysis, late stent malapposition seems to be associated with (very) late stent thrombosis.

CONCLUSIONS

- Early abciximab administration in the ambulance compared to in-hospital abciximab administration, significantly improves early reperfusion in STEMI patients treated with PPCI. Moreover this is associated with a smaller infarct size, improved left ventricular function at 3-months and a lower risk of heart failure through 7-months follow-up.
- In patients with STEMI treated with PPCI, the incidence of aborted MI was 18%. Pre-hospital abciximab administration was the main predictor of aborted MI, and this effect was related to the initiation of treatment within the first 2 hours after symptoms onset and to the higher IRA patency at presentation.
- Patients with aborted MI had better left ventricular function at 3 months and superior prognosis compared to those with established MI.
- Peak cardiac troponin-T in the first 24 after primary PCI offers a good estimation of infarct size and a long-term prognostic indicator in patients with first acute myocardial infarction.
- The risk of late acquired stent malapposition is significantly higher after drug-eluting stent compared to bare-metal stent implantation. Late stent malapposition seems to be associated with (very) late stent thrombosis.

FUTURE PERSPECTIVES

1. Primary percutaneous coronary intervention treatment and follow-up

The optimal results of primary percutaneous coronary interventions (PPCI) requires a well developed system involving early diagnosis, rapid transportation, effective procedure and evidence based pharmacotherapy. This objective can only be achieved by implementing rigorously standardized protocols for management of patients with acute myocardial infarction concerning pre-, peri- and post-PCI treatment such as the MISSION! Protocol implemented at Leiden University Medical Center. Within a fixed protocol, early administration of abciximab prior to PPCI is recommended. Our results support early abciximab administration in the ambulance. However, the literature available on this subject is limited. Future large randomized control studies within a fixed protocol for early patient triage are needed to clarify the best time point for early abciximab administration.

The work presented in this thesis was aimed at clarifying the concept of aborted infarction in the current era of PPCI. Our study provides a clear novel definition of aborted infarction. Future research thus should aim at clarifying the utility of this definition in another population group. It might be of interest to develop new large prospective studies aiming at exploring the incidence of aborted infarction in the PPCI era in a large cohort of patients.

Cardiac troponin T (cTnT) is an essential component in the diagnosis and treatment strategy of acute coronary syndromes. However for STEMI, its role is limited. Future research should aim at clarifying the prognostic value of cTnT in this group of patients, especially on the issue of predicting incidence of heart failure.

2. Stent thrombosis and late stent malapposition

On the basis of the available data, late acquired stent malapposition appears to be a problem (1) that cannot be fully avoided by IVUS immediately after the procedure, (2) that occurs more frequent with drug-eluting stent implantation, and (3) that is associated with increased risk of late and very late stent thrombosis. Our findings demand a careful assessment of the intervention strategy and post intervention medical treatment since we may trade a benign complication of restenosis in bare-metal stents with the serious late acquired stent malapposition and the subsequent stent thrombosis in drug-eluting stents.

In the light of the most recent literature and insights of the present time we do not know whether the presence of late stent malapposition should be treated and how, since it is evident that many late stent malappositions may persist for years without leading to (very) late stent thrombosis, more research is needed to explore the underlying relation between late stent malapposition and stent thrombosis and for how long patients should receive thienopyridine therapy after drug-eluting stent implantation.

