Myocardial reperfusion in STEMI and the role of the antithrombotic/antiplatelet therapy

Summary of this thesis

The achievement of early myocardial reperfusion is one of the main goals in ST elevation myocardial infarction (STEMI) for reducing infarct size and improving prognosis. This thesis investigated the potential factors influencing myocardial tissue reperfusion before and after primary percutaneous coronary intervention (PCI) in the contemporary era of STEMI treatment. Moreover it focused on the role of different antithrombotic/antiplatelet therapies in STEMI patients for improving myocardial reperfusion and clinical outcomes. Finally it evaluated the optimal duration of dual-antiplatelet therapy (DAPT) after primary PCI investigating the safety and efficacy of a short DAPT duration after primary PCI.

In **chapter 2** we described how the angiography and serial electrocardiograms (ECG's) are important for the assessment of reperfusion, and in particular for the evaluation of microvascular and tissue-level reperfusion. The use of some angiographic parameters and ST-segment resolution (STR) are also useful tools to investigate the impact of therapies on myocardial reperfusion and they can be used as surrogate markers of clinical outcomes.

In **chapter 3** we identified the predictors of complete STR pre-primary PCI in patients enrolled in the ATLANTIC trial, a randomized study comparing pre-Hospital (pre-H) vs in-Hospital (in-H) treatment with ticagrelor loading dose in acute STEMI. We showed that complete STR (defined as ≥70%), which occurred pre-PCI in 12.8% of patients, predicted lower 30-days composite MACCE (OR=0.10, 95%CI 0.002-0.57; p=0.001) and total mortality (OR=0.16, CI 0.004-0.95;p=0.035). The independent predictors of complete-STR included the time from index event to pre-H ECG (patients delay) (OR=0.94, CI 0.89-1.00; p=0.035), use of heparins before pre-PCI-ECG (OR=1.75, CI 1.25-2.45; p=0.001) and time from pre-H-ECG to pre-PCI-ECG (OR=1.09, CI 1.03-1.16; p=0.005). Interestingly in the pre-H ticagrelor administration group, patients with complete STR had a significantly longer delay between pre-H-ECG and pre-PCI-ECG compared to patients without complete STR [median 53 (44-73) vs 49 (38.5-61) (mins);p=0.001]; however, this was not observed in the control group (in-hospital ticagrelor) [50 (40-67) vs 49 (39-61);p=0.258]. Therefore this study showed that short patient delay, early administration of anticoagulant and ticagrelor if long transfer delay is expected, may help achieve reperfusion prior to PCI and that pre-H treatment may be beneficial in patients with longer transfer delays allowing the drug to become biologically active.

In **chapter 4** we evaluated the predictors of complete STR after primary PCI in patients enrolled in the ATLANTIC trial. Complete STR occurred post-PCI in 54.9% of

patients and predicted lower 30-day composite MACCE (OR 0.35, 95% CI 0.19-0.65; p<0.01), definite stent thrombosis (OR 0.18, 95% CI 0.02-0.88; p=0.03), and total mortality (OR 0.43, 95% CI 0.19-0.97; p=0.04). Independent negative predictors of complete STR were the time from symptoms to pre-H ECG (OR 0.91, 95% CI 0.85-0.98; p<0.01) and diabetes mellitus (OR 0.6, 95% CI 0.44-0.83; p<0.01); pre-H ticagrelor treatment showed a favourable trend for complete STR (OR 1.22, 95% CI 0.99-1.51; p=0.06). These findings provide further insights into the potential optimization of STEMI treatment, indeed in the current era of STEMI reperfusion characterized by early pre-H drug administration and fast transportation, diabetic patients are still a subgroup who requires further approaches for improving outcomes and additional strategies are needed also to improve patient's delay.

In **chapter 5** we investigated the role of different pre-H hospital anticoagulation regimes. We specifically assessed the effect of bivalirudin compared to heparins with optional glycoprotein IIb/IIIa inhibitors (GPI) on 1-year mortality, a pre-specified outcome of the international, randomized EUROMAX trial. Complete 1-year follow up was available for 2164 patients. All-cause mortality at 1-year occurred in 5.4% of the patients. The number of all-cause deaths was the same for both treatment groups (59 deaths in each group, relative risk [RR]=1.02, 95% confidence interval [CI]: 0.72-1.45; p=0.92). No differences were noted in the rates of 1-year cardiac death (44 (4%) for bivalirudin, 48 (4.3%) for the control group, RR=0.93, 95% CI: 0.63-1.39; p=0.74) or non-cardiac death (15 (1.4%) for bivalirudin, 11 (1.0%) for the control group, RR=1.39 CI: 0.64, 3.01 p=0.40). Thus in patients with STEMI treated earlier in ambulance, with frequent use of radial access and novel P2Y12 inhibitors, bivalirudin, as compared with heparin with optional use of GPI, showed similar long-term mortality outcome.

In **chapter 6** we undertook a subgroup analysis of the On-TIME 2 trial a study that randomized patients undergoing primary PCI to pre-H tirofiban administration vs placebo.

We investigated the potential association between early tirofiban treatment and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level after primary PCI showing that pre-hospital tirofiban administration was independently associate with a lower risk of high NT-proBNP level after primary PCI (OR 0.71; 95% CI 0.51 to 0.99; p=0.045), supporting the potential benefit of early antithrombotic treatment administration in STEMI patients.

In **chapter 7** we explored the association between NT-proBNP levels and long-term mortality and the effect of pre-H tirofiban administration on mortality in relation NT-proBNP levels. NT-proBNP level above the median was an independent predictor

for 5-year mortality (HR 2.73 (95% CI 1.47 – 5.06; p = 0.002) and patients with values above the median who received early tirofiban treatment had significant lower mortality compared to patients treated with placebo at 30-days (2.7% vs 7.5% p=0.021) and 1-year (4.5% vs 9.4% p=0.043). At 5-years, a lower but non-significant mortality rate was maintained in the treatment group (18% vs 22.4% p=0.265). We have shown that a high-risk subset of STEMI patients, as identified by higher levels of NT-proBNP upon presentation, may derive particular benefit from early GPIs treatment in terms of reduced short term and long term mortality. Our findings may help to further refine the identification of patients likely to derive the greatest benefit from pre-hospital GPI administration. Early NT-proBNP measurement aimed at stratifying patients and guiding early antiplatelet therapy, could represent a possible new strategy to be tested in further studies.

In **chapter 8** we investigated the potential interactions between pre-H ticagrelor administration and thrombus aspiration (TA) in patients treated with primary PCI enrolled in the ATLANTIC trial.

A total of 941 (57.7%) patients underwent TA. In adjusted multivariate logistic model, pre-H ticagrelor treatment was significantly associated with less frequent new MI or definite stent thrombosis (ST) (OR 0.43, 95% CI 0.20-0.92, p=0.031), or definite ST (OR 0.26, 95% CI 0.07-0.91, p=0.036) at 30 days. Patients treated with TA had higher frequency of TIMI flow 0-1 compared to no-TA group (80.7% vs 51.9%, p<.0001). TA when also adjusted for TIMI flow 0-1 showed significant association only for higher bail-out use of GPI (OR 1.72, 95% CI 1.18-2.50, p=0.004) and more frequent 30-day TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, p=0.032). No significant interactions between TA and pre-H ticagrelor were present for the explored endpoints. TA when left to physicians discretion was used in high risk patients and was associated with bail-out use of GPI and TIMI major bleeding but had no impact on 30-day clinical outcomes. Conversely pre-H ticagrelor treatment predicted lower 30-day rates of ST or new MI without interaction with TA.

In **chapter 9** we have designed the Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In STEMI (DAPT-STEMI) trial, a randomized, multicentre, international, open label trial aimed to examine the safety (non-inferiority) of 6-month DAPT after Resolute Integrity stent implantation in STEMI patients compared to 12-months DAPT. Indeed the optimal DAPT after PCI with second-generation DES is unclear and because prolonged DAPT is associated with higher bleeding risk and health care costs, establishing optimal DAPT duration is of paramount importance.

In the trial event free patients on DAPT at 6-months are randomized (1:1 fashion)

between single (aspirin only) versus DAPT for an additional 6 months and followed until 2 years after primary PCI. The primary end point (PE) is a patient oriented composite endpoint of all-cause mortality, any myocardial infarction, any revascularization, stroke and major bleeding (net MACCE) at 18-months after randomization. To achieve a power of 85% for a non-inferiority limit of 1.66, a total of 1100 enrolled patients are required. No other dedicated randomized controlled trials have evaluated the safety of shorter DAPT duration in STEMI patients.

In **chapter 10** we reported the results of the DAPT-STEMI trial. 1100 patients were enrolled in the trial and 870 were randomized: 432 versus 438, in SAPT and DAPT, respectively. The PE occurred in 4.8% versus 6.6 %, in SAPT and DAPT respectively (HR 0.73; 95% confidence interval (CI), 0.41 to 1.27; P=0.26). Noninferiority was met (P for noninferiority =0.004), as the HR upper 95% CI of 1.27 was smaller than the pre-specified noninferiority margin of 1.66. Limiting DAPT duration to 6 months in event-free STEMI patients resulted in a non-inferior clinical outcome, as assessed by the patient-oriented composite clinical endpoint of safety, efficacy, and bleeding, versus the regimen of 12 months DAPT. This trial for the first time showed that if clinically mandated a shorter DAPT is safe and sets the stage for further dedicated research on DAPT duration in STEMI patients.