PART III

CHAPTER 12

Summary,
future perspectives
and concluding remarks
Cardiogenic shock occurs in only 7% of all acute patients with acute ST elevation myocardial infarction (STEMI) but accounts for over 90% of all STEMI in hospital related deaths. Despite all current efforts, even in the era of early revascularization (ERV) in-hospital mortality for CS remains around 50%. We analysed our dedicated PCI database, in search of ways to improve prognosis of these critically ill patients. A total of 292 patients with STEMI and CS were treated with PCI in our Academic Medical Center during 1997 - 2005. It is one of the largest single center reported cohorts and in size comparable to the multicenter Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock landmark trial (the SHOCK trial). This trial was the first to compare medical treatment vs. early revascularization in acute myocardial infarction patients presenting with CS. The primary endpoint was set at 30 day mortality and this study failed to show a significant difference in survival at 30 days between the two treatment arms. Only after 6 months and up to ten years of follow up, patients with ERV had a significantly better clinical outcome. Although the difference was far less than initially planned at initiation of the trial, this trial is still a landmark trial in a patient population with very limited treatment options. Therefore, it is of paramount importance to identify factors associated with adverse clinical outcome. The goal of this thesis was to indentify easy clinically available parameters that may serve as tools for future research aiming to improve clinical outcome in these patients.

**PART 1 Biochemical parameters in cardiogenic shock complicating acute myocardial infarction**

In **CHAPTER 1** we assessed the relation between admission hemoglobin (Hb) concentration and one year mortality in STEMI patients with CS on admission and treated with PCI. Anemia is commonly observed in patients with cardiogenic shock. Mortality rates on average increased 17% for every 1.0 g/dL decrease in plasma Hb concentration. This might be due to a combination of decreased oxygen delivery due to lower Hb, a higher left ventricular end diastolic pressure in a CS state and compensatory tachycardia leading to a higher oxygen demand of the already ischemic myocardium and potentially to a larger infarct size. Additional bleeding and or overt fluid replacement therapy may lead to reduction of Hb but their individual role remains poorly understood. In any case a low Hb is associated with poor clini-
cal outcome in cardiogenic shock patients. **CHAPTER 2** we report on the strong correlation between admission glucose and 1-year mortality in our cohort excluding patients without prior diagnosis of diabetes mellitus. For every 1 mmol/L increase in plasma glucose concentration mortality rate increased by 16%. Hyperglycemia reflects a relative or absolute insulin deficiency which may lead to a lack of glycolytic substrate for the myocardium. Increased lipolysis and an excess of free fatty acids in the circulation has toxic effects on the ischemic myocardium and may reduce diastolic and systolic myocardial function. In addition, hyperglycemia has been associated with prothrombotic effects that may further affect the microcirculation resulting in no-reflow phenomenon. Further studies are warranted to determine whether concomitant glycometabolic regulation in patients with STEMI, particularly those with CS, is associated with a reduction of myocardial damage. Possibly future treatment with glucagon like peptide-1 (GLP-1), heralds a promising alternative approach for glycometabolic control in patients with STEMI. We further examined the influence of creatinine clearance CrCl at admission on 1-year mortality in our cohort which is presented in **CHAPTER 3**. The main finding was that mortality increased for each tertile of admission CrCl (from 24% to 30% to 45% respectively). Patients in the group with the lowest creatinine clearance were older and had more concomitant multi-vessel disease. In multivariable analysis creatinine clearance remained associated with mortality after correction for age above 60 years, gender, multivessel disease, left ventricular ejection fraction < 0.40 and TIMI less than 3 flow. It is well known that renal function substantially worsens with advanced age. In our study cohort, we found that advanced age was unequivocally associated with progressive renal dysfunction and henceforth with mortality. The presence of more extensive atherosclerosis may at least partially explain kidney dysfunction due to more diffuse athertherosclerotic disease of the renal arteries. Also, pre existing renal dysfunction may worsen from microcirculatory hypoperfusion in a CS state. Furthermore, contrast administration during PCI may worsen renal function. Kidney protection during PCI with a contrast removing device may prevent declining renal function and may improve clinical outcome. The three biomarkers (plasma Hb, glucose and renal function) showed prognostic associations with mortality in separate analysis. **CHAPTER 4** shows the results of a multivariable analysis of the three biomarkers in combination with age (in years), gender, diabetes mellitus, total
ischemic time, door-to-balloon time, left ventricular ejection fraction < 0.40 and TIMI less than 3 flow. Of the three biomarkers, plasma glucose concentration was the only statistically significant predictor of mortality in this analysis. Survival decreased by 11% for each 1 mmol/l increase in glucose. Besides the formerly described prothrombotic effects, one might speculate that hyperglycemia is only an utterance of stress and the result of an acute-phase reaction in the shock syndrome including proinflammatory effects as well. Hyperglycemia may serve as an important tool for risk stratification, although evidence is currently lacking that glycometabolic regulation as associated with myocardial recovery. It could potentially even be implemented in a prehospital triage setting.

**PART II**

Angiographic predictors of clinical outcomes in cardiogenic shock complicating acute myocardial infarction

**CHAPTER 5** is a review on the role of revascularization in cardiogenic shock STEMI patients. Although in hospital mortality remains high, we have to bear in mind that long term outcome after hospital discharge is comparable to STEMI patients without based decision making towards cornerstone therapy of early revascularization, in various clinical presentations, is described. Choices between surgical or percutaneous ERV strategies, based on the extent of coronary artery disease are discussed. In this matter, two entities are of great interest. Unprotected left main coronary artery culprit lesions and/or a coexisting chronic total occlusion (CTO) in a non infarct related artery. Furthermore, the use of hemodynamic support with newly available percutaneous left ventricular unloading devices may herald a new era enabling preservation of CS with good quality of life. **CHAPTERS 6 and 7** describe different treatment modalities for unprotected left main coronary artery culprit lesions in the setting of acute myocardial infarction. In **CHAPTER 6** we discuss our systematic review and meta-analysis of the current literature on primary PCI of culprit unprotected left main disease in ST-segment deviation acute myocardial infarction patients. From 13 retrospective studies comprising a total of 977 patients an average mortality rate was calculated. Cardiogenic shock was present in 253 (26%) patients. The average calculated thirty day all-cause mortality was 15% in patients presenting without signs of cardiogenic shock and 55% in patients presenting with cardiogenic shock. These data may serve as benchmarks for future studies. In **CHAPTER 7** we
analyzed data on immediate revascularization of unprotected left main coronary culprit lesion in our single center experience. We analyzed overall data and compared clinical outcome after percutaneous or surgical coronary bypass grafting (CABG) revascularization for unprotected left main coronary related myocardial infarction. We also investigated the underlying decision making of the two treatment modalities. Fifty-five patients were initially treated with PCI (0.9% of total primary PCIs), whereas 29 patients were treated with CABG, which accounts for 9.5% of all emergency CABGs. All-cause mortality rates at 30-days were 67% in the PCI group and 24% in the CABG group. At 1-year follow-up, all-cause mortality rates were 73% and 24% respectively. In theory, patients could potentially benefit from a 'staged' approach. The first step would be to hemodynamically stabilize the patient either with or without inotropic and/or mechanical support device use. The second crucial step would be to restore TIMI 2/3 flow by means of PCI. Third in patients with multivessel disease complete revascularization with CABG or additional PCI should be considered in case of suitable coronary anatomy. In this respect it is important to realize that the SHOCK study aimed at complete revascularization rather than by treatment of the culprit lesion only. CHAPTER 8 describes the impact of multivessel disease (MVD) with and without a coexisting chronic total occlusion on short and long term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. A landmark mortality analysis up to 5-year follow-up with a landmark set at 30 days was performed. In non-CS STEMI patients with MVD, the presence of a coexisting CTO in a non-IRA drives early and late mortality. In patients with CS, not only CTO patients but also MVD patients with a CTO were associated with higher short term mortality, when compared with single vessel disease patients. In 30-day CS survivors, only MVD with a CTO was associated with a trend towards increased mortality. However, this analysis also reveals a potential benefit for additional revascularization of other significantly stenosed coronary arteries in CS patients.

PART III Hemodynamic factors in cardiogenic shock
In CHAPTER 9 and 10 describe the impact of two easily available parameters on echocardiography. In chapter 9 we retrospectively assessed mitral regurgitation (MR) on early echocardiography in CS patients. For each grade (0 – 3) of MR inc-
increase, the odds for mortality increased with 71%. It is an important independent predictor of 1-year mortality in STEMI patients with CS on admission treated with primary PCI. It is hypothesized that mechanical unloading of the left ventricle may reduce mitral regurgitation and hence, improvement of clinical outcome. In **CHAPTER 10** we showed that RV dysfunction measured the tricuspid annular plane systolic excursion (TAPSE) $\leq 14$ mm was associated with adverse clinical outcome. Right ventricular dysfunction was present on early echocardiography in 38%. Overall 4-year survival was 57%. The right coronary artery was the infarct related artery in only 41% of all patients with RV dysfunction. RV dysfunction was an independent predictor for long term outcome. **CHAPTER 11** is a meta-analysis on Intra-aortic balloon counter pulsation (IABP) in ST-segment elevation myocardial infarction (STEMI) with and without cardiogenic shock. In the meta-analysis a total of nine cohorts of STEMI patients ($n = 10529$) were included. The meta-analysis of cohort studies in the setting of STEMI complicated by cardiogenic shock did not support IABP therapy adjunctive to primary PCI. Whether IABP therapy is of value in cardiogenic shock remains subject to debate. The IABP-SHOCK II trial will shortly provide a more definite answer.

**FUTURE CONSIDERATION**

One can only assume that the number of patients with complicated STEMI will increase due to an aging population with more co morbidity, i.e. more diffuse atherosclerotic disease. However, the absolute numbers of patients presenting with CS at PCI facilities will remain rather low. In our centre we perform on average 2000 PCI procedures of which 550 for acute STEMI per year. Of these STEMI patients, approximately 60-80 patients present with CS. In view of an increasing number of PCI centres in the Netherlands with different level of treatment possibilities, early triage might need to be expanded with a strategy for patients prone to develop cardiogenic shock. We should be aware that cardiogenic shock is a syndrome which requires more and a multidisciplinary clinical approach. It is not only the coronaries that need to be opened quickly but in cardiogenic shock the focus should be primarily to prevent multi organ failure. Therefore immediate triage of patients presenting with STEMI could be beneficial rather than to first go the nearest PCI-center. Patients presenting with STEMI complicated by cardiogenic shock or those prone
to develop cardiogenic shock might benefit from early transportation to a tertiary center with facilities such as a percutaneous LVAD or other mechanical support program. Although the role of mechanical support still needs to be further established as a routine strategy, the various available and future technologies warrant careful evaluation in an appropriate environment. These technologies require well trained and experienced personnel from various medical disciplines in order to achieve optimal effect.

It is therefore conceivable that so-called ‘cardogenic shock centers’ should be installed regionally for prompt CS treatment. In order to quickly identify patients at the highest risk for adverse clinical outcome, we demonstrated that in patients with CS a simple glucose measurement may further stratify patients. In the pre-hospital triage setting, this easily available tool could be used for additional decision making such as transfer to a ‘cardogenic shock center’. Especially in light of the Dutch geographic situation distribution of PCI centers. These proposed cardiogenic shock centers should define and implement clinical pathways that include early stratification, complete echocardiographic work-up and immediate revascularization upon hemodynamic stabilization.