Acute myocardial infarction treatment : from prehospital care to secondary prevention

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Summary

Summary and conclusions

Cardiovascular disease remains the leading cause of mortality in the western World, but significant improvements have been made in its treatment and prevention. This thesis shows that consistent implementation of a structured regional treatment and prevention program for acute myocardial infarction patients is feasible when health professionals of various disciplines collaborate (**Chapter 2**). Guideline-recommended time-to-treatment intervals were achieved for the entire region of Hollands-Midden.

PCI in the setting of AMI significantly reduces mortality. The introduction of DES has significantly improved one-year outcomes among patients undergoing elective PCI, primarily by reducing the need for repeat revascularization. Although DES are commonly used in AMI, there has been significant debate in the clinical community regarding their true efficacy and long-term safety. In **Chapter 3** results of the randomized MISSION!-intervention study demonstrates that safety of SES is comparable to BMS three years after the index event, in terms of death, stent thrombosis and nonfatal recurrent MI. The study also showed that the greatest efficacy of SES (compared to BMS) was achieved in the first year of follow-up after the AMI, by significantly reducing target vessel revascularizations. A similar need for target vessel revascularizations in SES and BMS treated patients was seen in the two subsequent years. It must be kept in mind though, that these results were achieved in the setting of the structured MISSION! AMI treatment protocol which ensured optimal treatment adherence and follow-up of patients.

In **Chapter 4** an effort was made to relate plaque characteristics at stent edges to clinical outcome at 9 months post PCI in 40 AMI patients by utilizing virtual histology intravascular ultrasound imaging (VH-IVUS). The technique allows for identification of four plaque components: fibrous, fibro-fatty, necrotic core and dense calcium. Plaque composition at 9 months follow-up was believed to be different in SES treated patients when compared to BMS treated patients due to the potent antiproliferative effects of sirolimus. However, against expectations, the study did not demonstrate any significant changes in plaque composition at stent edges after 9 month follow-up in either SES or BMS treated patients. At the same time an effect of sirolimus on vascular lumen dimensions at the distal stent edge and neointima volume inside the stent was clearly present. Because of the relatively small patient sample size and perhaps too short follow-up, it is not possible to definitely conclude that no differences exists in plaque composition between SES and BMS at stent edges, but it may be possible that these changes are of smaller magnitude than anticipated. Also, the complexity of the VH-IVUS analysis technique in the setting of a follow-up study may have made it difficult to detect such small changes at the present time.

It is thought that routine thrombus aspiration prior to DES implantation in STEMI may improve clinical outcome after such procedures. Given the association between large thrombus burden in STEMI and late stent thrombosis, debulking thrombus burden could reduce the occurrence of residual thrombus and stent malapposition. In the study presented in **Chapter 5**, a strategy of adjunctive thrombus aspiration before primary PCI in AMI patients

in combination with early (pre-hospital/in-ambulance) abciximab administration, was associated with a significant improvement in post-procedural ST segment resolution and with a lower mortality at one year follow-up.

In **Chapter 6** we evaluated the frequency and distribution of culprit lesions in patients presenting with ST-segment elevation myocardial infarction. This simple study demonstrated that the majority of occlusions occur in the proximal parts of the LAD and RCA with worse post-procedural LV-function in particular for LAD and LCX culprit lesions. The study shows that plaques in the proximal parts of the LAD and RCA are more prone to rupture. Knowledge of the distribution of vulnerable plaques may help in the identification of patients at risk of coronary events.

Chapter 7 aimed to provide more insight into the clinical profile, treatment delays, medication compliance and 12 month outcome of treatment in the elderly AMI patient population (≥ 75 years). Results showed that older AMI patients had significantly less modifiable risk factors of coronary artery disease than younger patients and had a significantly higher in-hospital mortality rate despite similar post-procedural TIMI flow grades. Most importantly, the study showed that after surviving the first 3 months post AMI, elderly patients had a similar potential for favorable clinical outcomes at 12 months to their younger counterparts when they were treated with equal consistency and intensity

In recent years heart rate has been described as an increasingly important risk factor for reinfarction, revascularization and heart failure in patients with left ventricular dysfunction. The study presented in **Chapter 8** investigated clinical relevance of resting heart rate in post AMI patients who were treated with primary percutaneous intervention and a relatively preserved LV-function. During a mean follow-up of 20 months a baseline heart rate (first electrocardiogram at admission) of 72bpm or higher was associated with a significantly increased risk of the composite endpoint of all-cause mortality, nonfatal reinfarction, coronary revascularization, and hospitalization for heart failure. In addition every 5bpm increase in baseline heart rate was associated with a further increase in risk for every one of those endpoints. Results of this study suggest that targeting heart rate in the currently growing population of post-AMI patients with preserved LV-function may also be of significant clinical importance.

Chapter 9 demonstrates that (1) left ventricular function can be preserved using an evidence-based protocol to manage AMI; (2), with preservation of left ventricular function, the proportion of post-MI patients fulfilling criteria for implantable cardioverter defibrillator (ICD) implantation is small; and (3), that relatively few of those patients who received ICDs receive appropriate ICD therapy delivery during follow-up. This last observation brings into question the current guidelines for the selection of patients for ICD implantation as primary prophylaxis against sudden cardiac death and should prompt a review of the evidence on which these guidelines are based.

Findings of the study described in **Chapter 10** suggest that properties of the baseline stimulation threshold may be used clinically as an indicator of chronic changes caused by ischemic heart disease which increase the risk of arrhythmic events requiring ICD therapy and risk of mortality. A high right ventricular stimulation threshold was used as a marker of potentially arrhythmia-prone conditions. Although the simple uncontrolled measurement method in this retrospective observational study is by no means sufficient to suggest routine clinical use for assessment of arrhythmia risk or ICD eligibility at this time, the results indicate future potential in measuring and utilizing stimulation thresholds in a standardized prospective fashion, as clinical predictors for these patients.

Chapter 11 aimed to provide more long-term (mean 5±3 years) data on the characteristics of recurrent atrial tachyarrhythmias (AT) after ablation of post-operative AT in 53 patients with congenital heart defects (CHD). A number of conclusions could be drawn from the findings of this observational study: First, the data demonstrated that successive post-operative AT in CHD patients may be caused by different mechanisms, including focal and reentrant mechanisms. The complexity of the reentrant circuit was associated with the complexity of the underlying CHD and the extensiveness of the corresponding surgical procedure. Second, as recurrent AT originated from different locations, it seems unlikely that these new AT were caused by arrhythmogenicity of previous ablative lesions. Third, the long-term outcome was often complicated by development of atrial fibrillation. Finally, despite frequent need for repeat ablative therapy, most patients were in sinus rhythm by the end of follow-up.

The purpose of the observational study presented in **Chapter 12** was to provide more insight into long-term (median 40months) outcome of cavotricuspid isthmus ablation in terms of atrial flutter (AFL) recurrence and particularly in terms of atrial fibrillation (AF) occurrence in "real-practice" patients with electrocardiographically documented isthmus-dependent AFL with or without a preablation history of AF. The study provided several interesting findings. (1) The cumulative incidence of AF after successful AFL ablation procedures was high, with 57% during 5 year follow-up even in the patient group without preexisting AF (group 2), (2) that after 1.5 year post-AFL ablation patients with a history of AF had a similar AF occurrence rate compared to patients without a history of AF, and (2) a twofold and highly significant risk of AF occurrence was observed for patients with a diastolic blood pressure ≥90mmHg, independent of a pre-ablation history of AF.

Conclusions

Standardized protocols like the multidisciplinary MISSION! program contribute to improved adherence to evidence-based medicine in routine clinical practice and to the uniform implementation of structured care for patients with AMI. It is clear that a good collaboration between general practitioner, ambulance services and hospital is essential in achieving well-coordinated prevention, acute care and rehabilitation of (potential) AMI patients. Results

demonstrated in this thesis demonstrate the efficacy of a pre-hospital protocol in achieving predefined targets, stressing the importance of close collaboration with all partners. In a later stage of this thesis, it is additionally shown that by the rigorous adherence to this kind of AMI protocol, development of severe LV dysfunction post-MI can be prevented by focusing on minimal treatment delays, aggressive reperfusion therapy and the use of early and consistent optimal pharmacological therapy. This way, only a very small percentage of AMI patients eventually become candidates for primary prevention ICD implantation according to current guidelines which also helps contain the strain on financial resources.

Sirolimus-eluting stent implantation in acute ST-elevation myocardial infarction is associated with a significant benefit (compared to bare-metal stents) at 1 year follow-up in terms of target vessel revascularizations, but declines thereafter to some extent due to more similar target vessel revascularization rates during the 2 subsequent years. Rates of death and non-fatal recurrent MI remain comparable.

There is a trend towards positive remodeling at the distal stent edges in SES patients and a significant inhibition of neointimal hyperplasia within the stented segment at follow-up as compared to BMS treated patients. The effect on the distal stent edge suggests a down-stream effect of sirolimus elution, despite the fact that an effect on plaque composition is not visible with virtual histology IVUS at 9-months follow-up.

Among STEMI patients treated with primary PCI and receiving early (in-ambulance) abcix-imab, it appears that the adjunctive use of manual thrombectomy significantly improves post-procedural ST-segment resolution, and may be associated with a lower clinical event rate. Therefore, although no benefit was observed regarding the enzymatic infarct size or LV function as assessed by Gated-SPECT, it appears that a selective strategy of thrombus aspiration still has an additive benefit, even with adjunctive early abciximab administration. This needs further confirmation in appropriately powered randomized trials.

Patients with ST-segment elevation AMI who are candidates for primary PCI are more likely to have a RCA or LAD culprit lesion that tends to be clustered in the proximal or mid vessel segments.

Older patients surviving the first 3 months post-MI have similar outcomes to younger patients in terms of cardiac function. Age was not a significant risk factor of 1-year mortality in survivors three months after MI. Therefore, though conservative treatment may be the adequate choice for some patients, many older patients have the potential to gain significant advantage from aggressive and invasive AMI treatment which suggests that age alone should not preclude intensive treatment after an MI.

In patients after AMI treated with primary PCI and preserved left ventricular function, resting heart rate at admission is a strong independent risk factor for all-cause mortality, reinfarction, revascularization and hospitalization for heart failure. This emphasizes that achieving a lower heart rate should be a priority in the care for the currently growing population of post-AMI patients with preserved left ventricular function.

In a cohort of ICD treated patients with a primary prevention indication and ischemic heart disease the RV stimulation threshold at implantation has an independent prognostic value for the prediction of potentially life-threatening ventricular arrhythmia and death.

It may also have a predictive value when measured serially, but this requires further investigation in future studies.

Focal and reentrant mechanisms underlie late post-operative atrial tachycardia in patients with congenital heart disease (CHD). Successive atrial tachycardias developing over time may be caused by different mechanisms. The complexity of the reentrant circuit is associated with the complexity of the CHD and corresponding extensiveness of surgical procedures. In patients who had multiple ablation procedures, the atrial tachycardia originated from different atrial sites suggesting that these new atrial tachycardias were not caused by arrhythmogenicity of previous ablative lesions. Recurrent atrial tachycardia occurred frequently after successful ablation and occurred mainly in the first year after treatment. The long-term outcome is often complicated by development of atrial fibrillation. However, the majority of the patients are in sinus rhythm.

Despite the efficacy of cavotricuspid isthmus radiofrequency ablation in the treatment of atrial flutter, most patients cannot be considered completely cured, particularly with regard to atrial fibrillation (AF) occurrences. Patients with a preablation history of AF and high diastolic blood pressure are at significantly higher risk and should be monitored more closely and treated more aggressively for hypertension. However, preablation AF did not lead to an increased long-term (>1.5 year) risk after atrial flutter ablation. Patients in this subgroup therefore may expect the same long-term risk of AF as patients without pre-existing AF.