GENERAL CONCLUSION AND FUTURE PERSPECTIVES.
GENERAL CONCLUSION

In this thesis we describe the results of the VIAMI-trial. Patients admitted with acute chest pain caused by an acute myocardial infarction (AMI) were included and randomized after proven myocardial viability demonstrated with low dose dobutamine echocardiography. Eligible patients were initially treated with thrombolysis or were too late for reperfusion therapy. Half of the randomized patients were treated with culprit vessel coronary angioplasty with stenting and routine use of abciximab. The other half was treated non-invasively. After 1 year follow up, patients with viability in the infarct-area significantly benefit from an early invasive strategy of culprit vessel stenting. This invasive approach results in a clear reduction in ischemic events and an uneventful clinical course. In the patients without viability, the risk of recurrent ischemia remains low. After a median follow up of 8 years, the first year benefits are sustained. Revascularization of patients with viability in the early phase after AMI results in a significant improvement in LV function. Without revascularization these patients experience an increase in LV-volumes without change of ejection fraction. The absence of viability results in ventricular dilatation and deterioration of the LV ejection fraction, irrespective of revascularization status. The number of pathological Q waves, persistent ST-segment elevation with positive or negative T waves on discharge ECG were all strong independent predictors for the absence of myocardial viability. Our prediction-model for myocardial viability appears useful in clinical practice, especially in the high and low range scores.

FUTURE PERSPECTIVES

Viability after STICH in patients with ischemic cardiomyopathy

Much evidence, predominantly observational and retrospective, suggests that revascularization in patients with coronary artery disease (CAD) and left ventricular dysfunction (ischemic cardiomyopathy (ICM)), and proven viability is superior to optimal medical treatment (OMT)[1]. Therefore, in many centres viability testing has become a gatekeeper to revascularization. However, recent results of the Heart Failure Revascularisation Trial (HEART)[2], Positron emission tomography And Recovery Following Revascularization (PARR-2)[3] and, Surgical Treatment for Ischemic Heart Failure (STICH) trials [4,5] have all questioned the additional benefit of revascularization over OMT. Each of these studies, however, had significant methodological limitations resulting in considerable debates about the role of revascularization and viability testing in patients with ICM.[6] In the main STICH trial, most patients had angina and not dyspnea with the majority of patients in NYHA class I-II. Selection bias was present with an average recruitment rate of 2 patients per site per year. Left main stem patients were
excluded, a group in whom revascularization have shown survival benefit. There was significant cross over: 17% in OMT group and 9% in the CABG group. The outcome of screened and not included patients is unknown. The STICH viability substudy was nonrandomized and viability testing was left to the physician’s discretion. There were significant differences in baseline characteristics between those with and without viability, especially concerning the incidence of prior MI and LV volumes. Viability testing was performed with the use of controversial thresholds and different cut offs for SPECT or low dose dobutamine echocardiography (LDDE). Revascularization was not guided by the presence of myocardial viability. Only 19% of the tested patients were non-viable (114 patients out of 601 patients) limiting the power to detect a differential effect of CABG.

As a result of all these methodological flaws, the STICH trial did not cause a paradigm shift in clinical management of patients with ICM.

A recent single-centre nonrandomized study by Ling et al. [7] on 648 ICM patients clinically referred for cardiac PET found that it was myocardial viability, but not inducible ischemia, that identified patients who gain survival benefit with revascularization over OMT (21.6% vs. 30.4%, p=0.03). This survival benefit of revascularization was superior in patients with at least 20% viable myocardium. Compared to the STICH trial, these patients seemed to be sicker with more diabetes mellitus, older age, more prior revascularization, and ICD’s.

The ongoing Alternative Imaging Modalities in Ischemic Heart Failure (AIMI-HF) study is a randomized controlled trial comparing standard imaging (SPECT) with advanced imaging (PET and CMR) in ICM patients [8]. AIMI-HF hypothesizes that “advanced imaging-guided care” will be superior to “standard imaging-guided” care. Results are expected in 2016. Imaging is used as part of the management in both patient groups, a concept that is challenged by the STICH viability sub-study results.

In spite of the STICH (and HEART and PARR-2) trial results, testing for myocardial viability continues to be requested by clinicians in patients with ICM being considered for revascularization.

Therefore, a new randomized clinical trial is warranted comparing OMT with advanced imaging-guided care in patients with ICM, to elucidate optimal patient management and to evaluate the prognostic value of viability and ischemia to predict functional recovery, improvement of patient symptoms and/or survival.

Viability in the current PCI era

According to current guidelines, direct percutaneous coronary intervention (PCI) is the preferred treatment for all patients with acute myocardial infarction (AMI) presenting within 12 hours of symptom onset and persistent ST-segment elevation or (presumed) new LBBB [9]. Although PCI is very effective in restoring epicardial patency, functional recovery of the myocardium is impaired in a significant part of patients due to the “no reflow” phenomenon. The exact mechanism of “no reflow” is poorly understood and still a matter of debate [10]. The concept of blockage of the coronary microcirculation by downstream embolization of micro thrombi or atheroma from the culprit lesion and edema is supported by substantial
evidence from different studies [11-14]. The effects of the no-reflow phenomenon on the myocardium can be visualized in cardiac MRI studies. The use of late gadolinium enhancement shows a hypo-enhanced core within a hyperenhanced region. This phenomenon on cardiac MRI was called “micro vascular obstruction (MVO)” reflecting the original hypothesis of microvascular blockage as the underlying cause of no-reflow [15]. Based on more recent data, the mechanism of this enhancement pattern is now believed to be myocardial tissue with vascular damage and extravasation of erythrocytes, rather than microvascular obstruction [16]. This specific finding on cardiac MRI is associated with major cardiac events (MACE), heart failure and cardiac death [17-19]. Preventing microvascular injury and intramyocardial haemorrhage to occur in the acute phase could benefit patients presenting with ST-segment elevation myocardial infarction (STEMI).

In patients with AMI, myocardial necrosis and intramyocardial haemorrhage expands as a wavefront from the subendocardium towards the epicardium [20]. For that reason, intramyocardial haemorrhage is only present in the core zone of the infarction. Reperfusion injury of the microvasculature could play an important role in the cause of intramyocardial haemorrhage. An old necropsy study showed only haemorrhage in patients treated with thrombolytic therapy and not in untreated AMI patients [21]. Importantly, MRI-studies performed early after primary PCI show that intramyocardial haemorrhage is observed in up to 50% of patients with STEMI [22].

In the border zone of the infarct where the microvasculature remains intact, no intramyocardial haemorrhage is seen. Nevertheless, in this border zone an increased influx of inflammatory cells is starting within 2 days after AMI accompanying the complex process of left ventricular remodeling [23]. This border zone is potentially salvageable and therefore considered viable.

Many experimental studies have been performed to minimize the extent of the core zone and to preserve the viable border zone of the infarction: ischemic preconditioning to prevent endothelial damage, blood-pressure lowering drugs to reduce the extent of intramyocardial hemorrhage, antiplatelet therapy, and pharmacological therapies to protect the microvasculature. Especially, pharmacological therapies to protect the microvasculature and prevent microvascular injury are promising (VEGF, angiopoietin-1, and MMP's inhibition)[24].

In summary, even in the current era of primary PCI the presence of myocardial viability needs special attention and treatment in order to prevent unfavorable myocardial remodeling and loss of initially saved myocardium.

**VIAMI in the current PCI era**

The results of the VIAMI trial suggest that routine angioplasty in the early post-MI period in stable patients (whether or not treated with thrombolysis) is not mandatory in every patient. Especially in patients for whom the transport time for primary PCI is exceeding 120 minutes as recommended by the AHA/ACC and ESC guidelines [9,25], thrombolysis could be an alternative with the VIAMI-trial approach as a second window of opportunity.

Nevertheless, current guidelines do recommend transfer to a PCI-centre in all
patients within 24 hours after fibrinolysis (class of recommendation (COR) I, level of evidence (LOE) A) based on several randomized clinical trials and meta-analyses [26-31]. In countries who cannot comply with these guidelines due to logistic problems to transport patients within 24 hours to a PCI-centre the VIAMI-approach could be a reasonable alternative.

There are more opportunities for a viability-guided approach in patients with a recent STEMI. The current guidelines do not provide strong and consistent recommendations for patients presenting between 12 and 48 hours after STEMI. A time period beyond the time window of expected myocardial salvage by “acute” coronary intervention. Even if pain-free and with stable hemodynamics, the guidelines state that these patients may still benefit from early coronary angiography and possible PCI (COR IIb, LOE B). In stable patients with a totally occluded infarct artery >24 h after STEMI, a delayed PCI is not recommended (COR III, LOE B)[9,25,32-35].

**Is there place for a second VIAMI-study?**

The VIAMI 2 study could be a randomized clinical trial comparing invasive with non-invasive therapy in stable patients presenting 12-48 hours after AMI and proven viability demonstrated with a dedicated cardiac MRI. All patients receive a cardiac MRI for viability testing 3-5 days after symptom onset. Patients with proven myocardial viability are randomized to an invasive (coronary angiography and possible PCI) or conservative strategy (OMT). After 6 months, all patients receive a cardiac MRI to investigate left ventricular improvement as primary endpoint. Secondary endpoints include composite of death, recurrent myocardial infarction or stroke at 6 months.

In a substudy it could be very interesting to investigate the effect of revascularization on the occurrence of microvascular injury and intramyocardial haemorrhage. A second cardiac MRI should than be performed 2-5 days after coronary intervention. In particular, for understanding the mechanism of left ventricular improvement or deterioration. It could be hypothesized that revascularization induces intramyocardial haemorrhage with failure of the viable myocardium to regain function. Limitation of such a study could be the small subgroup of suitable patients with consequently a slow inclusion rate. Therefore, a multicenter approach should be necessary. Only dedicated cardiac MRI centers could participate in the substudy.

**VIAMI 2**

STEMI; ST elevation myocardial infarction, OMT; optimal medical treatment
Reference List


