Section 1 - Publishable summary

Project title: Multivessel versus culprit lesion only percutaneous revascularization in patients with acute myocardial infarction complicated by cardiogenic shock

Website: www.culprit-shock.eu

Contractors involved (CULPRIT-SHOCK consortium):

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1.1 Summary description of project context and objectives

Cardiovascular disease is the leading cause of mortality in the European Union (EU) and direct and indirect costs of cardiovascular diseases to the EU amount to 300 billion Euros per year. Great progress has been made in treating cardiovascular disease by therapeutic interventions including drugs and devices. However, cardiogenic shock complicating acute myocardial infarction (AMI) remains a major European health care concern with mortality rates between 45-70%. Of estimated 910,000 patients with AMI admitted to hospitals in Europe per year, approximately 60,000 to 70,000 will result in cardiogenic shock (7-8%). Cardiogenic shock in AMI is therefore a prominent cause of death among European citizens.

The most important therapeutic measure in cardiogenic shock complicating AMI is early reperfusion of the infarct related artery. The landmark SHOCK trial is one of the rare adequately powered randomized trials in cardiogenic shock complicating AMI. Although it failed to meet the primary endpoint - reduction of 30-day mortality by an early revascularization-based management either by PCI or coronary artery bypass grafting (CABG) - (46.7% versus 56.0%, p=0.11), there was a significant mortality reduction at 6 months (50.3% versus 63.1%, p=0.027), 12 months (53.3% versus 66.4%, p=0.03), and long-term follow-up at 6 years (67.2% versus 80.4%, p=0.03). To save 1 life, <8 patients need to be treated by early revascularization in comparison to initial medical stabilization. Based on the current evidence PCI plus stent implantation (or CABG) is recommended for all patients in particular those aged <75 years to allow recovery of stunned myocardium and prevention of life-threatening arrhythmias. For patients aged >75 years an early interventional treatment is recommended depending on patient condition and comorbidities. The more widespread implementation of early interventional treatment in cardiogenic shock was likely the most important factor for a reduction of mortality to 40-50% observed in recent years.

In general, clinical trials in the critically-ill population of patients with cardiogenic shock are difficult to perform which might be the most important reason why overall scientifically accepted and evidence-based strategies in cardiogenic shock are scarce. The largest randomized clinical trial to date enrolled 600 patients. Given the limited treatment options novel strategies suitable to reduce the unacceptably high mortality are urgently needed and would have great impact.

As outlined above, early mechanical reperfusion is the single most important therapeutic measure leading to a marked mortality reduction.

Approximately 70-80% of patients with cardiogenic shock complicating AMI present with multivessel disease defined as coronary stenoses/occlusions in more than one vessel. These patients have a higher mortality compared to patients with single vessel disease. Coronary lesions in these patients can usually be classified into

1) a single “culprit lesion” acutely responsible for the initiation of cardiogenic shock and
2) additional lesions considered hemodynamically significant but not acutely triggering the shock cascade.

While mechanical treatment of the culprit lesion is accepted standard practice, optimal management of additional non-culprit lesions in patients with multivessel disease is unclear.

Potential advantages of multivessel PCI

Theoretically, by improving myocardial perfusion acute treatment of hemodynamically significant non-culprit lesions could a) limit infarct size and b) preserve ventricular function, which are major prognostic factors. Furthermore, immediate multivessel PCI might c) prevent potentially hazardous early and late recurrent ischemic cardiac events. Complete revascularization at the time of infarction may also d) reduce overall hospital stay and e) total cost of care by obviating the need for additional interventional procedures.

Potential disadvantages of multivessel PCI

On the other hand, several concerns exist regarding prolonged interventions of non-culprit lesions in the cardiogenic shock setting. Coronary interventions in AMI are frequently accompanied by a) distal embolization of thrombotic material, the possibility of b) acute side branch or even main vessel occlusion, or other inherent technical problems. In the already highly unstable situation of cardiogenic shock, these detrimental effects can lead to c) further deterioration in hemodynamic status or d) induce life-threatening arrhythmias. Furthermore, multi-lesion intervention is inevitably associated with e) higher amounts of contrast dye administration. This can lead to acute volume overload of the left ventricle with subsequent hemodynamic compromise, and contrast-induced nephropathy, a known predictor of adverse clinical outcome. The f) additional risk of stent thrombosis in the thrombogenic milieu of AMI also has to be taken into account with increasing numbers of implanted stents.
Finally, multiple interventions might increase the need for subsequent revascularization procedures due to in-stent restenosis.

There are no randomized clinical trials comparing a strategy of culprit lesion only treatment versus a strategy of acute treatment of all hemodynamically significant lesions in patients with AMI and cardiogenic shock presenting with multivessel disease and all guideline recommendations are based on registry data or pathophysiological considerations. However, non-randomized observational studies and registries are prone to treatment-selection bias precluding definitive conclusions. The uncertainty regarding patient management is reflected in current guideline recommendations for cardiogenic shock in AMI. While European Society of Cardiology (ESC) guidelines recommend PCI of all critical or highly unstable lesions in patients with AMI complicated by cardiogenic shock, the most recent German/Austrian S3-guideline recommends multivessel PCI only in selected individual cases.

In light of the conflicting arguments and a lack of randomized data, reperfusion strategies differ widely among countries and institutions worldwide. In the most recent German IABP-SHOCK II multicentre trial, multivessel PCI was performed in only 37% of the patients despite its Class IIa Level of Evidence B recommendation in current ESC guidelines. Currently, there are no robust data available on the preferred revascularization method for patients with multivessel disease and cardiogenic shock across European countries and institutions.

Given these uncertainties, a prospective randomized clinical trial is warranted to determine the optimal revascularization therapy in patients with AMI-related cardiogenic shock and multivessel disease treated with early revascularization preferably by PCI.

We have therefore formed a collaborative consortium of highly experienced European partners to conduct a large-scale prospective, randomized, controlled, international, multicentre trial (CULPRIT-SHOCK) to compare both strategies. The consortium with its partners and the location of participating and enrolling countries is shown

The following major objectives have been defined in the CULPRIT-SHOCK project:

1) To determine the optimal percutaneous revascularization strategy in patients with AMI and multivessel disease complicated by cardiogenic shock.

2) To conduct a series of substudies (angiography, biomarkers, microcirculation) to further understand the presumed differential effects of the 2 treatment arms and to understand the underlying pathophysiology

3) To develop a multivariable regression model and a risk score for the prediction of clinical prognosis in AMI and cardiogenic shock.

4) To determine a cost-effectiveness model based on data from the trial and present final analyses from the overall European and also individual national perspectives.

5) To obtain data on patients and their treatment as well as their prognosis not meeting inclusion criteria by instituting a separate registry.

1.2 Work performed since the beginning of the project and the main results achieved so far

Since the start of the project in September 2013 a first 1 ½ day kick-off meeting with all partners has been arranged in Madrid. The different work packages have been described and the responsible persons for each of the WP presented their tasks and deliverables.

In the meantime an additional general consortium meeting took place in Barcelona in September 2014 reporting on the progress of the different WP and major deliverables have been reported. In Germany, a national investigator meeting was held during the annual autumn meeting of the German Cardiac Society in Düsseldorf, Germany in October 2014.

The major task for the overall project was to obtain ethical approval in all participating countries. One important aspect in cardiogenic shock patients is informed consent. The majority of patients is not able to give informed consent due to intubation, mechanical ventilation, and sedation. Another proportion of patients will have impaired peripheral and central perfusion induced by the cardiogenic shock itself and will be only partially able to give informed consent. Only a minority of patients will be able to give full informed consent in the acute setting. Therefore, a 4 version informed consent process according to circumstances has been validated and approved:
a) Patient not able to consent → 2 independent physicians assess supposed patient’s will (if possible by contact of relatives).

b) Patient with impaired ability to consent → Short version of informed consent

c) Patient with full consent → Long version of informed consent

d) Patient recovers to full consent → retrospective long version of informed consent

This scheme needed to be adapted in several countries and also according to multiple local ethical committee requirements such as in Germany and Austria where no central ethical committee decided on the ethical approval. Accordingly in all participating countries except for Belgium which was decided later to participate, the ethical approval has been granted. For further details see the Table 1 in the deliverables of WP01.

The first patient has already been randomized in 2013 and at the time of this first periodic report 176 patients have been randomized within WP01 and 104 patients been included in the accompanying registry of WP02. The majority of patients has been randomized currently in Germany with additional patients being included in Austria, Switzerland, Poland, UK, Italy, and Slovenia. Currently, the first patient is still pending in Lithuania where two sites are active, in The Netherlands where currently one site is active, and in France where the sites are just in the process of initiation. In France administrative issues were more complicated leading to a certain delay in the initiation of the sites.

A significant increase in patient inclusion in WP01 and WP02 is expected after full initiation of the sites in UK, France, The Netherlands, Poland, and also Belgium.

A monthly general newsletter is in place reporting on the progress of the trial. The individual national coordinators with Switzerland as pioneer also started to generate monthly national newsletters. The purpose of these national newsletters is to provide information on the progress in the individual countries and to report on national specialties in the countries also using the national languages.

To further advertise the trial, an award has been advertised and presented for the inclusion of the 100th randomized patient in WP01. Further awards will be advertised for the 200th, 300th, etc. patient. In addition, cups and pens with CULPRIT-SHOCK logo as well as a project flyer have been distributed to all participating countries and sites to increase the awareness of the trial.

The substudies of the different WP such as the biomarker, angiographic and microcirculation substudy are currently also enrolling patients into the project. The trial logistics are fully set-up but the number of patients needs to be increased which will be done along with the increase of the patient numbers within the WP01 and WP02.

The homepage www.culprit-shock.eu for the trial is in place since 06.06.2014 which is besides the newsletter and regular e-mail contacts the major platform for communication within the CULPRIT-SHOCK project. In addition, the homepage (https://studien.herzinfarktforschung.de/CulpritShock) of the IHF responsible for WP06 is available since the beginning of the project. This homepage is used for randomization, data entry as well as for data reporting and also the download of the newsletters.

1.3 The expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project so far)

The final results of CULPRIT-SHOCK are expected to clarify the role of different percutaneous revascularization strategies in patients with cardiogenic shock secondary to AMI and multivessel disease. Current evidence is characterized by a lack of randomized controlled clinical trials. Clinical practice is therefore based on observational studies and expert opinion. Recognition of the deficiencies of the current knowledge base and the perception that these can only be overcome through the acquisition of randomized data was the main impetus for foundation of the CULPRIT-SHOCK consortium. Upon completion, CULPRIT-SHOCK will be the largest randomized controlled clinical trial in patients with cardiogenic shock ever conducted and will inform patients, health care providers, and decision-makers about which percutaneous revascularization strategy is most effective.

Scientific impact

Cardiogenic shock in patients with AMI is associated with extremely high mortality. Occluded or severely stenosed coronary vessels leading to critical levels of myocardial oxygen supply are usually causative for the acute onset of the disease (most often secondary to long-standing atherosclerosis). Mechanical treatment of such coronary lesions ideally followed by full restoration of epicardial and microcirculatory blood flow directly interferes with the underlying mechanism. It is therefore at present the most important treatment step as detailed above. However, the exact modalities of how to perform mechanical reperfusion are largely left to the individual physicians. This is especially true for patients with AMI and cardiogenic shock who present with multivessel disease, the cohort studied in
CULPRIT-SHOCK. Randomized data are practically non-existent and therefore the present situation is characterized by a distinct absence of clear scientific evidence. This can in large part be attributed to the complexities of conducting randomized studies in this particular subset of patients. Both interventional strategies studied in the CULPRIT-SHOCK randomized cohort (culprit lesion only or immediate multivessel PCI) offer theoretical benefits as well as risks. The interventional cardiologist is left alone and finds her/himself in the unsatisfactory and stressful situation of having to acutely decide on how to perform mechanical reperfusion in a patient with a life-threatening condition and no clear evidence-based guidance on how to and to what extent to do this. In the acute setting and faced with the dilemma of a lack of any sound scientific evidence to draw from, the treating physician usually makes decisions based on personal experience. CULPRIT-SHOCK is expected to clarify the way patients with AMI-related cardiogenic shock and multivessel disease should be revascularized. Even if both percutaneous revascularization strategies should prove not to significantly differ with regards to the primary endpoint, the project will generate a myriad of additional data related to other aspects of cardiogenic shock. Underlying mechanisms and pathophysiology will be revealed by analysis of a multitude of biomarkers, microcirculatory function and angiographic parameters. Identification of predictors of clinical outcome followed by the development of a risk score will help patients and physicians make informed and reliable decisions about treatment escalation or discontinuation of therapy. Knowledge of prognostic factors will also likely influence future research directions. Taken together, CULPRIT-SHOCK will result in significant scientific advances in one of the most life-threatening diseases. Results will likely find their way into clinical practice guidelines and textbooks and lead to a change in the care of patients with cardiogenic shock secondary to AMI.

Economic impact
CULPRIT-SHOCK hosts an economic subproject and analysis of cost-effectiveness according to current scientific standards. The models obtained will provide the database for discussion about society’s willingness to provide financial resources in the population studied.

It is expected that the two revascularization strategies may differ in cost-effectiveness. While immediate complete revascularization at the time of infarction may reduce the overall hospital length of stay and avoid additional interventional procedures, this has to be weighed against the higher costs of human and technical resources at the time of the procedure itself and a possible higher incidence of complications (i.e. contrast-induced nephropathy). Based on the cost-effective model in WP07, CULPRIT-SHOCK will likely improve the selection of candidates for either strategy beyond current clinical practice, thereby minimizing ineffective, potentially costly or harmful use of resources. This might result in a consistent decrease of direct and indirect costs for the European health care systems and be of major importance for the insurances in the different participation European countries.

Impact for individual patients and societal benefit
AMI and cardiogenic shock in particular are frequent causes of death and disabling morbidity in the European population and are therefore a major individual and social burden. CULPRIT-SHOCK offers the realistic vision of reducing morbidity and possibly mortality by addressing an important unresolved issue in the management of cardiogenic shock. For individual patients the prospect of treatment optimization might be life-saving or prevent disabling morbidity. On a societal level, CULPRIT-SHOCK might influence the way how organizational networks in the management of acute cardiogenic shock are structured. For example, nation-specific outcome analyses might reveal significant inter-country variability in clinical results. In this scenario, the prediction model (WP08) might help to further define associated factors such as organizational differences between countries. By predicting the most likely clinical outcome, WP08 will also help to optimally structure social networks (e.g. relatives, family physician, and rehabilitation institutions) according to individual circumstances.

The above mentioned impact is also of relevant interest to patient organizations leading to the support by the German Heart Foundation (Deutsche Herzstiftung) with more than 75,000 members. This organization has taken patronage of the CULPRIT-SHOCK project and will also allow a rapid distribution of the results to a lay patient organization.