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

Final Report Summary - CULPRIT-SHOCK (Multivessel versus culprit lesion only percutaneous revascularization in patients with acute myocardial infarction complicated by cardiogenic shock)

Executive Summary:
Cardiogenic shock (CS) complicating acute myocardial infarction (AMI) represents a major European health care concern with mortality rates between 40-70%. Approximately 70-80% of these patients present with multivessel disease defined as coronary lesions in more than one vessel. The clinician has previously been faced with the decision to either 1) intervene only on the culprit lesion acutely responsible for the initiation of cardiogenic shock, or 2) treat additional lesions considered hemodynamically significant but not acutely triggering the CS cascade as well. Previous guidelines recommended percutaneous coronary intervention (PCI) of all critical lesions. However, due to a lack of randomized trials, these recommendations were solely based on registry data, pathophysiological considerations and expert
Aim of the randomized CULPRIT-SHOCK trial was therefore to compare a) immediate multivessel PCI versus b) culprit lesion only PCI in patients with AMI complicated by CS. A total of 706 CS patients have been randomized in several European countries and 83 centers. The primary endpoint was 30-day all-cause mortality and/or severe renal failure requiring renal replacement therapy which was significantly lower in the culprit-lesion-only PCI arm in comparison to the immediate multivessel PCI arm. These results have been presented in September 2017 during the annual congress of the TCT in Denver, USA and simultaneously published in the New England Journal of Medicine. CULPRIT-SHOCK therefore determined the optimal percutaneous revascularization strategy in patients with AMI and multivessel disease complicated by CS. The 30-day results led to a chance in current European Society of Cardiology (ESC) revascularization guidelines, published in the end of August 2018, with the new recommendation to not perform immediate multivessel PCI in the setting of CS. In addition, a comprehensive array of efficacy, safety and socio-economic parameters for the chosen population has been assessed. Multiple secondary endpoints and several substudies (microcirculation, biomarkers, angiography) served to further understand the presumed differential effects of the 2 treatment arms and to understand the underlying pathophysiology and prognostic markers. From these parameters a multivariable regression model and a risk score for the prediction of clinical prognosis and a cost-effectiveness model in AMI and CS has been developed. Furthermore, CULPRIT-SHOCK obtained data on CS patients not meeting inclusion criteria by instituting a separate registry. The 1-year follow-up data have been presented in August 2018 during the annual congress of the ESC in Munich and once again simultaneously published in the New England Journal of Medicine underlining the importance of the trial. The results at 1 year could confirm the 30-day results and support also the change in the ESC guidelines. With the final inclusion of 706 patients, CULPRIT-SHOCK is the largest randomized trial in cardiogenic shock that has ever been performed. To be able to publish in the best medical journal within less than one year with the same clinical trial is not only very honorable, but it especially underlines the impact the CULPRIT-SHOCK trial has made within the internal medicine and also cardiac society.

Project Context and Objectives:
Background and Aims
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),2 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),3 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 before finalization of CULPRIT-SHOCK 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 g) increase the need for subsequent revascularization procedures due to in-stent restenosis.

Work strategy and general description
Beside CULPRIT-SHOCK, 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.10 The uncertainty regarding patient management is reflected in current guideline recommendations for cardiogenic shock in AMI. While ESC guidelines so far recommended PCI of all critical or highly unstable lesions in patients with AMI complicated by cardiogenic shock,11 the current German/Austrian S3-guideline recommends multivessel PCI only in selected individual cases.12

In light of the conflicting arguments and a lack of randomized data, reperfusion strategies differ widely among countries and institutions worldwide. In the German IABP-SHOCK II multicenter trial, multivessel PCI was performed in only 37% of the patients despite its Class IIa Level of Evidence B recommendation in current ESC guidelines. Beside the CULPRIT-SHOCK trial, there are currently 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, multicenter trial (CULPRIT-SHOCK) to compare both strategies. The consortium with its partners and the location of participating and enrolling countries is shown on the website.

Management structure and procedures
The Project Coordinator ensured the smooth operation of the project and guaranteed that all efforts were focused towards the objectives. He submitted all required progress reports, deliverables, financial statements to the European Commission, and, with the assistance of ARTTIC he was responsible for the proper use of funds and their transfers to participants. The CULPRIT-SHOCK office was established by and based at the coordinator in Lübeck as the Coordinating Institution and Leipzig location of the scientific coordinator and at ARTTIC in Munich. The Project Office at the Coordinator was concerned with the scientific management and the co-ordination of all research activities. The Project Office at ARTTIC was responsible for administrative, financial and contractual management and the organizational co-ordination of the project activities.

Objectives of CULPRIT-SHOCK:
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.

Project Results:
The CULPRIT-SHOCK study was conducted through 10 work packages.

WP01: Patient enrolment, randomization, and treatment
- Objectives
The objective of WP01 was to perform a prospective, randomized, controlled, multicenter, clinical trial comparing immediate multivessel PCI versus culprit lesion only PCI in patients with AMI and multivessel disease complicated by cardiogenic shock. The following specific tasks have been defined for WP01:
  - To set-up a multinational European collaborative network of tertiary care centers for enrolment of patients with multivessel disease and AMI with cardiogenic shock (Task 1)
  - To obtain ethical approval for all participating centers according to the respective laws and rules in all participating countries (Task 2)
  - To perform randomization of all eligible patients to either immediate multivessel PCI or culprit lesion only PCI and execute diagnostic and therapeutic measures according to study protocol (Task 3)
  - To perform clinical follow-up at 30 days (Task 4)
  - To perform intermediate and long-term follow-up at 6 and 12 months (Task 5)
Clearly the most significant result is the confirmation of the 30-day outcome at 1-year follow-up in the CULPRIT-SHOCK clinical trial. Immediate treatment of the primary lesion only does not increase the overall mortality rate at longer follow-up and the results remain nearly identical with a clear benefit of culprit-lesion-only PCI. The impact can be seen as the European revascularization guidelines were adapted and the highly ranked “New England of Medicine” published the 30-day follow up as well as the 1-year follow-up. Two publications within one year of the same clinical trial are extremely extraordinary.

WP02: Prospective CULPRIT-SHOCK registry
- Objectives
The principal objective of WP02 was to set-up a controlled, multicenter, prospective clinical registry for patients with AMI complicated by cardiogenic shock not eligible for the CULPRIT-SHOCK randomized trial in WP01. The following specific objectives have been defined for WP02:
  - To set-up a multinational European collaborative network of tertiary care centers for enrolment of patients with AMI and cardiogenic shock qualifying for the registry (Task 1)
  - To obtain ethical approval for all participating centers according to the respective laws and rules in all participating countries for registry patients (Task 2)
  - To include patients not eligible for randomization (WP01) into the registry (Task 3)
  - To describe the reasons for inclusion into the registry and the 30-day outcome of patients with cardiogenic shock after AMI non-eligible for the randomized CULPRIT-SHOCK trial (Task 4)
  - To perform intermediate and long-term follow-up at 6 and 12 months to further define the outcome of patients with cardiogenic shock in the registry (Task 5)
The significant results are related to WP01 and WP02.

WP03: Angiographic core lab
- Objectives
- To describe the coronary anatomy and procedural characteristics of patients enrolled in WP01 and WP02 (Task 1)
- To assess angiographic myocardial perfusion before and after PCI of patients enrolled in WP01 and WP02 as well as determination of any differential effects of the treatment strategies on angiographic perfusion parameters of patients enrolled in WP01 (Task 2)
- To calculate angiographic scores of patients enrolled in WP01 and WP02 (Task 3)
To analyze the correlation between specific angiographic assessments and clinical outcomes (Task 4).

To do some further substudies statistical analyses of the clinical database (Task 5)

A huge work was done to get all angiograms and to analyze them in order to report data as soon as possible. Specific CTO assessments were performed in order to answer the journal reviewers. The statistical analyses done will allow us to prepare multiple scientific articles which are under current preparation.

WP04: Biomarkers and biobank

- **Objectives**
  - Standardized sampling, storage, shipment and cryoconservation of blood samples at pre-defined time points (Task 1)
  - Standardized analysis of established biomarkers in cardiogenic shock (Task 2)
  - Standardization of analytical procedures and analysis of novel biomarkers potentially suited to study pathophysiology and prognosis in cardiogenic shock (Task 3)

Multiple biomarkers are currently analyzed. A huge work was done to analyze a large array of new and also established biomarkers. The statistical analyses have been performed and all the will allow us to prepare multiple scientific articles on pathophysiology and prognosis of cardiogenic shock.

WP05: Microcirculation

- **Objectives**
  - To non-invasively assess systemic microvascular function in patients with AMI complicated by cardiogenic shock (Task 1)
  - To compare the prognostic implications of macrohemodynamic parameters or perfusion versus microhemodynamic parameters of perfusion (Task 2)
  - To identify possible differential effects of multivessel versus culprit-only primary PCI on myocardial and systemic microvascular functional status in patients with AMI complicated by cardiogenic shock, and its relationship to clinical outcome (Task 3)
  - To compare manual assessment of microhemodynamic parameters versus automated assessment of microhemodynamic parameters of perfusion, and its relationship to clinical outcome (Task 4)

The main conclusion of task 2 states there is a significant and independent association between microvascular perfusion parameters PCD and PPC and the combined clinical endpoint of all-cause death and renal replacement therapy at 30-days follow-up (table 2). When disagreement occurs with macrohemodynamic parameters, microvascular perfusion parameters confer dominant prognostic value (figure 1, figure 2)

Table 1: Univariate and adjusted Cox-regression for the combined clinical endpoint (all-cause death or renal replacement therapy)

<table>
<thead>
<tr>
<th>Study population (N=66)</th>
<th>Univariate analysis</th>
<th>Adjusted analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>HR (95%CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Macrocirculatory perfusion parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(at admission)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.985 (0.971 - 0.999)</td>
<td>0.031</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.989 (0.968 - 1.010)</td>
<td>0.295</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>0.984 (0.965 - 1.003)</td>
<td>0.096</td>
</tr>
</tbody>
</table>
Heart rate (beats/min) 1.006 (0.995 - 1.017) 0.260 Heart rate (beats/min) - -
Macrocirculatory perfusion parameters
(post PCI) Macrocirculatory perfusion parameters
(post PCI)
Systolic blood pressure (mmHg) 0.976 (0.957 - 0.995) 0.015 Systolic blood pressure (mmHg) 0.987 (0.966 - 1.007) 0.205
Diastolic blood pressure (mmHg) 0.996 (0.968 - 1.023) 0.752 Diastolic blood pressure (mmHg) - -
Mean arterial pressure (mmHg) 0.982 (0.957 - 1.009) 0.192 Mean arterial pressure (mmHg) - -
Heart rate (beats/min) 1.011 (0.992 - 1.030) 0.254 Heart rate (beats/min) - -
Microcirculatory perfusion parameters
(post PCI) Microcirculatory perfusion parameters
(post PCI)
de Backer's score (1/mm) 0.892 (0.798 - 0.997) 0.043 de Backer's score (1/mm) 0.893 (0.787 - 1.013) 0.079
Total capillary density (mm mm-2) 0.928 (0.862 - 0.999) 0.046 Total capillary density (mm mm-2) 0.934 (0.862 - 1.011) 0.090
Perfused capillary density (mm mm-2) 0.949 (0.906 - 0.994) 0.028 Perfused capillary density (mm mm-2) 0.948 (0.901 - 0.997) 0.037
Proportion perfused capillaries (%) 0.989 (0.980 - 0.999) 0.026 Proportion perfused capillaries (%) 0.987 (0.976 - 0.998) 0.020
Microvascular flow index 0.701 (0.510 - 0.963) 0.028 Microvascular flow index 0.615 (0.425 - 0.890) 0.010
*Adjusted for age, oliguria at admission, current smoking, mechanical circulatory support and duration of ICU treatment

Figure 1: Clinical outcome according to normal vs abnormal microvascular perfusion (proportion perfused capillaries) for normotensive patients after cardiogenic shock complicated acute myocardial infarction.

Figure 2: Clinical outcome according to normal vs abnormal microvascular perfusion (perfused capillary density) in normotensive patients after cardiogenic shock complicated acute myocardial infarction.

The main conclusion of task 3 states that the magnitude of microvascular perfusion is not affected by culprit-only PCI compared to immediate multivessel PCI in patients with cardiogenic shock complicated acute myocardial infarction. Therefore, the clinical benefit of a culprit-only revascularization strategy compared to a multivessel revascularization strategy cannot be explained by a benefit in microvascular perfusion by the former revascularization strategy in this subgroup analysis of the CULPRIT-SHOCK study (table 2).

Table 2: Impact of culprit-only versus immediate multivessel PCI on systemic microvascular perfusion

<table>
<thead>
<tr>
<th>Immediate multivessel PCI</th>
<th>Culprit-only PCI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=33</td>
<td>N=33</td>
<td></td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) 66±10</td>
<td>68±10</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Male 25 (5.8) 19 (5.6) 0.18

cardiovascular risk factors
BMI 26.7 (24.2 29.4) 27.5 (25.6 29.6) 0.42
current smoking 15 (45.5) 8 (24.2) 0.55
hypertension 15 (45.5) 15 (45.5) 1.00
hypercholesterolemia 11 (33.3) 7 (21.2) 0.27
Diabetes mellitus 12 (36.4) 8 (24.2) 0.28
previous MI 6 (18.2) 4 (12.1) 0.49
previous PCI 9 (27.3) 2 (6.1) 0.02
previous CABG 4 (12.1) 1 (3.0) 0.16
previous stroke 0 (0.0) 3 (9.1) 0.08
Positive family history 3 (9.1) 5 (15.2) 0.48
peripheral artery disease 5 (15.2) 5 (15.2) 1.00
signs of impaired organ perfusion on admission
altered mental status 18 (54.5) 22 (66.7) 0.31
cold, clammy skin and limbs 20 (60.6) 17 (51.5) 0.46
Oliguria 7 (21.2) 9 (27.3) 0.61
pH level <7.36 23 (69.7) 26 (78.8) 0.40
arterial lactate >2.0mm/liter 24 (72.7) 25 (75.8) 0.78
ST-segment elevated myocardial infarction 20 (60.6) 18 (54.5) 0.61
Infarct-related artery
Left anterior descending artery 17 (51.5) 12 (36.4) 0.22
Left circumflex artery 9 (27.3) 11 (33.3) 0.59
Right coronary artery 7 (21.2) 8 (24.2) 0.77
Left main artery 0 (0.0) 2 (6.1) 0.15
Left ventricular ejection fraction, % 30 (20, 40) 40 (35, 50) 0.06
Two-vessel disease 11 (33.3) 17 (51.5) 0.14
Three-vessel disease 22 (66.7) 16 (48.5) 0.14

Procedural characteristics p-value
fibrinolysis <24 h before randomization 0 (0.0) 1 (3.0) 0.31
Resuscitation <24 h before randomization 17 (51.5) 18 (54.5) 0.81
Successful immediate complete revascularization 23 (69.7) - -
Mechanical circulatory support 5 (15.2) 5 (15.2) 1.00
Catecholamine therapy 30 (90.9) 29 (87.9) 0.69
Total dose of contrast material (ml) 240 (200, 330) 150 (120, 200) <0.01
Total duration of fluoroscopy (min) 18.8 (11.2 25.3) 12.0 (6.0 15.7) <0.01

Clinical outcomes Breslow p
Death or renal replacement therapy 51.5% 45.5% 0.61
Death 48.8% 45.5% 0.96
Renal replacement therapy 18.8% 6.3% 0.14

hemodynamic characteristics p-value
Macro-hemodynamics (at admission)
Systolic blood pressure (mmHg) 102 (87, 132) 94 (86, 114) 0.29
Diastolic blood pressure (mmHg) 70 (55, 78) 62 (49, 77) 0.28
Mean arterial blood pressure (mmHg) 80 (67, 95) 75 (61, 90) 0.22
Heart rate (N/min) 87 (71, 98) 83 (66, 101) 0.62
Microvascular perfusion parameters (post PCI)
de Backer score (n/mm) 11.5 (9.7 13.0) 12.2 (9.8 14.1) 0.48
TCD (mm mm-2) 18.0 (15.0 19.5) 18.7 (14.0 22.4) 0.64
PCD (mm mm-2) 14.1 (7.9 17.4) 13.9 (10.1 21.2) 0.39
PPC (%) 88.1 (44.3 94.5) 86.1 (65.8 93.5) 0.76
capillary MFI 2.3 (1.5 3.0) 2.5 (1.5 3.0) 0.68

numbers are given in n(%), mean ± standard deviation, median (Q1, Q3) or %

PCI=percutaneous coronary intervention, BMI-body mass index, MI=myocardial infarction, CABG=coronary artery bypass grafting, TCD=total capillary density, PCD=perfused capillary density, PPC=proportion perfused capillaries, MFI=microvascular flow index

The main conclusion of task 4 states that automated assessment of microvascular perfusion parameters using the Microvision AVA4.1 software package differs significantly from manual assessment of microvascular perfusion parameters using the Microvision AVA3.2 software package. This difference is driven by an underestimation of the vessel length and total vessel density by the automated software package, while it overestimates the proportion perfused vessels (table 4). Moreover, patients with an abnormal PPC or PCD assessed manually post-PCI associated with a significant worse clinical outcome compared to patients with a normal PPC or PCD assessed manually post PCI (figure 3a + b). In comparison, there was no difference in clinical outcome between patients abnormal versus normal PPC or PCD assessed with the automated software package post PCI (figure 4a + b).

Table 4: Automated versus manual assessment of microvascular perfusion

<table>
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<tr>
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<tbody>
<tr>
<td>N=98</td>
<td>N=98</td>
<td></td>
</tr>
<tr>
<td>Density data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessel length (mm)</td>
<td>5.2 (3.7 6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of grid crossings (N)</td>
<td>60 (54, 67)</td>
<td>0.007</td>
</tr>
<tr>
<td>De Backer score</td>
<td>12.1 (11.0 13.9)</td>
<td>0.562</td>
</tr>
<tr>
<td>Total vessel density (mm/mm2)</td>
<td>8.3 (6.0 10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perfusion data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion perfused capillaries (%)</td>
<td>100 (100, 100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion perfused all-vessels (%)</td>
<td>99.9 (96.0 100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perfused capillary density (mm/mm2)</td>
<td>6.1 (4.4 8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perfused all vessel-density (mm/mm2)</td>
<td>7.3 (5.5 9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>numbers are given as median (quartile 1, quartile 3)</td>
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Figure 3a: Clinical outcome of normal vs abnormal proportion perfused capillaries according manual assessment.

Figure 3b: Clinical outcome of normal vs abnormal perfused capillary density according manual assessment.
WP06: Data management and statistical analysis

- Objectives
  - Programming and providing an electronic CRF and electronic randomization system (Task 1)
  - Assure quality of data (Task 2)
  - Monitoring plan (Task 3)
  - On-site monitoring (Task 4)
  - Coordinate and perform statistical analyses (Task 5)

Data management and statistical analysis have been performed leading to the two major publications in the New England Journal of Medicine. Multiple subanalyses for all the sub-trials have been performed or will be performed. Unfortunately, financial support ended and prolongation of the funding period was not possible. Therefore, multiple subanalyses need to be funded by other institutions. We are currently working on getting additional funding.

WP07: Cost-effectiveness and health-economic analysis

- Objectives
  - Design data collection to support the economic analysis (Task 1)
  - Develop statistical analysis plan for the economic data for pre-specification of the analyses to be performed (Task 2)
  - Develop a pre-trial model based on the literature review representing the state of the art (Task 3)
  - Update the economic model with data from the trial and present final analyses (Task 4)

First, the use of a pre-trial model is a step forward with respect to the most extended practice in health economic evaluation. This approach enhanced the scientific quality by designing the analysis in advance of the availability of data. The pre-trial model was published in the peer-reviewed literature.

WP08: Predictive prognostic model and risk score

- Objectives
  - To develop a multivariable model for the prediction of clinical prognosis in AMI and cardiogenic shock by analysis of the patients enrolled in the CULPRIT-SHOCK trial and registry (Task 1)
  - To externally validate the prognostic model’s performance in a separate cohort of patients with acute myocardial infarction and cardiogenic shock (Task 2)
  - To develop an integer-based score to predict clinical outcome in cardiogenic shock secondary to AMI (Task 3)

One of the objectives of WP 08 was to create an easy-to-use, readily available risk prediction score for short-term mortality based on the multivariable logistic regression analysis described in the summary report on deliverable D8.02. Based on the regression analysis described in the summary report on...
deliverable D8.02 an integer-based score system was developed. Integers were chosen to be approximately proportional to the estimated continuous β coefficient of each covariate from the logistic model. The overall score for each patient was calculated as the sum of the covariate weighted scores. Finally, risk categories were defined according to score results.

The score was validated externally in an independent cohort of patients from the IABP-SHOCK II trial.[1] The IABP-SHOCK II trial was a large-scale multicenter study of 600 patients with acute myocardial infarction and cardiogenic shock which randomized participants to intraaortic balloon pump counterpulsation (IABP group, 301 patients) or no IABP (control group, 299 patients). There was no significant difference in the primary endpoint of 30-day all-cause mortality between the groups. Both randomization groups of the IABP-SHOCK II trial and patients from an accompanying registry were combined for the purpose of external validation.

Six variables emerged as independent predictors for 30-day mortality and were used as score parameters:

1. Age >73 years
2. Altered mental status
3. Heart rate before percutaneous coronary intervention >100 beats per minute
4. Systolic blood pressure at admission <100 mmHg
5. Culprit lesion in left anterior descending
6. TIMI (Thrombolysis In Myocardial Infarction) flow after percutaneous coronary intervention <3

Either 1 or 2 points were attributed to each variable, leading to an integer-based prognostic score in 3 risk categories: low (0 to 2), intermediate (3 to 5), and high (6 to 9) [Fig. 1 and 2]. Mortality at 30 days differed markedly according to score category (p<0.0001 Fig. 3).

Fig. 1 Point score for prognostication in infarct-related cardiogenic shock

Abbreviations: PCI=percutaneous coronary intervention; BP=blood pressure; LAD=left anterior descending; TIMI=Thrombolysis In Myocardial Infarction.

Fig. 2 Risk grouping according to score result

Fig. 3 All-cause mortality at 30 days according to score category (Kaplan-Meier analysis)

External validation of the derived score in the independent population of the IABP-SHOCK II study revealed a stepwise increase in mortality across the different score categories (0 to 2: 28.7%; 3-5: 40.8%; 6-9: 62.2%, p<0.0001).

In summary, the CULPRIT-SHOCK risk score can be easily calculated in daily clinical practice and is strongly correlated with mortality in patients with infarct-related CS. It may help stratify patient risk for short-term mortality and might, thus, facilitate clinical decision making.
Potential Impact:
Socio-economic impact and the wider societal implications of the project
Contribution to Community and Social Objectives

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 were previously – before CULPRIT-SHOCK - largely left to the individual physicians. This was especially true for patients with AMI and cardiogenic shock who present with multivessel disease, the cohort studied in CULPRIT-SHOCK.

Randomized data were practically non-existent and therefore the present situation was characterized by a distinct absence of clear scientific evidence. This was in large part 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) offered theoretical benefits as well as risks before the start of the trial. The interventional cardiologist was formerly left alone and found 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 formerly mainly made decisions based on personal experience. CULPRIT-SHOCK did clarify the way patients with AMI-related cardiogenic shock and multivessel disease should be revascularized. This has been largely underlined by two publications in the New England Journal of Medicine (both publications including the accompanying editorial attached to this final report.13,14,16,17

Even more important is the direct change in the ESC revascularization guidelines 2018. A trial which leads to a change in guidelines within less than a year after publication is very rare.

The cost-effectiveness analysis and all subanalyses including the risk prediction model will provide valuable information for the medical decision making with respect to the optimal revascularization strategy for patients with multivessel disease complicated by cardiogenic shock. The choice of the optimal treatment will allow obtaining the maximum health output given the resources available by the European health systems.

Main dissemination activities and exploitation of results
At beginning of the project the clinical trial was registered and the protocols were published accordingly. Also the economic protocol was published including the pre-trial model.

Over the duration of the CULPRIT-SHOCK project, the partners constantly presented their results on international scientific congresses and poster sessions. Furthermore, with emerging results scientific publications were submitted and further approximately 30 manuscripts will be submitted in order to inform the scientific community.

In addition to the scientific publications, CULPRIT-SHOCK managed an own Twitter channel and informed via this channel over upcoming events, presentations on congresses or project news. Several partners, who also managed Twitter accounts had active dissemination activities via their own channels, e.g. the Health Economics and Health Technology Assessment (HEHTA) account.

To also inform lay public, several partners took the opportunities to represent CULPRT-SHOCK in public
Engagement stands, e.g. the European Researchers Night organized by the Health Economics and Health Technology Assessment (HAHTA) team in Glasgow September 2016 and 2017.

Outlook and future research
Until recently there were no randomized data on how to deal with non-culprit lesions in the setting of cardiogenic shock. This lack of evidence has also been reflected by divergent recommendations in current international guidelines. The European ST-segment elevation acute myocardial infarction (STEMI) guidelines - published in 2017 - recommended immediate PCI of non-culprit lesions in cardiogenic shock (class IIb, C), whereas the American STEMI guidelines give no specific recommendation. However, American appropriate use criteria - also published in 2017 - consider immediate revascularization of a non-culprit artery during the same procedure as appropriate if cardiogenic shock persists after treatment of the culprit artery.

After publication of the randomized, multicenter Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial, ESC guidelines have already been changed, but US guidelines and also US appropriate use criteria need to be reconsidered. To briefly recap, CULPRIT-SHOCK showed a significant clinical benefit of a culprit-lesion-only strategy with a reduction in the primary endpoint of 30-day mortality or severe renal failure requiring renal replacement therapy (45.9% culprit-lesion-only PCI versus 55.4% immediate multivessel PCI group; relative risk 0.83; 95% confidence interval 0.71-0.96; P=0.01) which was mainly driven by an absolute 8.2% reduction in 30-day mortality (43.3% versus 51.5%; relative risk 0.84; 95% confidence interval 0.72-0.98 P=0.03).

Are there specific situations where immediate multivessel PCI is still appropriate?
The results of CULPRIT-SHOCK were consistent across all predefined subgroups. This included sex, all age groups, presence/absence of diabetes, presence/absence of hypertension, STEMI or non-ST segment elevation myocardial infarction, anterior/non-anterior STEMI, previous/no previous infarction, double/triple vessel disease, or presence/absence of chronic total occlusion (CTO). Intuitively, some angiographic subgroups, such as occluded right coronary artery culprit lesion with a concomitant high-grade proximal left anterior descending coronary artery or additional non-culprit subtotal lesions with TIMI flow 1 or 2, may call for immediate multivessel PCI. However, this is not supported by the predefined subgroup analysis where culprit-lesion-only PCI in non-anterior infarctions had a hazard ratio of 0.67 (95% confidence intervals 0.48–0.94). Additional analyses based on findings of the central angiographic core laboratory will be performed aiming to identify angiographic predictors of outcome.

There were some cross-overs in the culprit-lesion-only PCI group to immediate multivessel PCI mainly based on individual decision of the interventionalist due to multiple reasons such as lack of hemodynamic improvement and plaque shifts. This suggests that the treatment strategy may require adaptation in certain circumstances. However, cardiogenic shock after PCI of the culprit lesion persists in the catheterization laboratory in nearly all patients and should not be used as a decision to perform immediate multivessel PCI.

Was there any influence of chronic total occlusion presence on outcome?
It is well known that presence of a CTO is frequent in cardiogenic shock and associated with high mortality. Therefore, CTO presence was not defined as an exclusion criterion in CULPRIT-SHOCK, which is different from all other STEMI trials without cardiogenic shock. This allowed for inclusion of a real-world cohort of patients. Exclusion of CTO would have led to a major selection bias and a lower-risk cohort. It was, therefore, also recommended to intervene on the CTO. However, technically CTO intervention needed to be deemed easily possible with a limit of contrast agent of 300 cc for the overall CTO intervention.
immediate multivessel PCI procedure. No retrograde or other complex interventional approaches were recommended. At least one CTO was present in 22.4% in the culprit-lesion-only arm and in 24.0% in the immediate multivessel PCI arm. In CULPRIT-SHOCK immediate CTO recanalization was attempted in roughly 50% of patients in the immediate multivessel PCI group and was successful in approximately one third of attempts. The results for the primary study endpoint were consistent for CTO presence or absence as shown in the predefined subgroup analysis (p-value for interaction 0.26). Thus, neither presence of CTO nor a CTO intervention did influence the overall outcome for both treatment strategies.

Impact of staged revascularization and timing of staged revascularization?
In contrast to many of the trials in STEMI without cardiogenic shock, in CULPRIT-SHOCK staged revascularization was encouraged and was not counted as a disadvantage for the culprit-lesion-only PCI strategy. In prior studies of stable STEMI patients, the differences between culprit-lesion-only PCI versus immediate multivessel PCI or early staged PCI were mainly driven by the difference in the rate of repeat revascularization, counted as part of a composite endpoint. In CULPRIT-SHOCK 21.5% of patients underwent staged or urgent repeat revascularization within 30-day follow-up. This rate appears to be higher as compared with stable STEMI revascularization strategy trials (COMPARE-ACUTE: 17.4% at 1-year follow-up; Complete versus Lesion-only Primary PCI trial [CvLPRIT]: 8.2% at 1-year follow-up; Primary PCI in Patients With ST-elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization [DANAMI-3-PRIMULTI]: 17% at 1-year follow-up; Preventive Angioplasty in Acute Myocardial Infarction [PRAMI]: 16% at 6-month follow-up) and might be related to the extent of coronary artery disease, the impaired left ventricular function and the nature of disease in cardiogenic shock.

Currently, the optimal timing of staged revascularization has not been adequately investigated and no recommendation can be formulated in favor of a staged multivessel PCI during the index hospitalization, after discharge or at longer follow-up only in case of symptoms or signs of ischemia. In general, patients with cardiogenic shock require much longer hospitalization and often also neurologic rehabilitation because of previous resuscitation (>50% of patients in CULPRIT-SHOCK). Thus, timing and also the requirement for staged revascularization may differ in cardiogenic shock in comparison to non-shock patients.

What are the reasons for the difference in outcome?
The higher 30-day mortality in the immediate multivessel PCI arm in CULPRIT-SHOCK might be related to the significantly higher dose of contrast medium (190 cc versus 250 cc; p<0.001) and a subsequent decline in renal function. There was a lower estimated glomerular filtration rate in the immediate multivessel PCI group in comparison to culprit-lesion-only PCI at days 3 and 4. However, the incidence of severe renal failure leading to renal replacement therapy did not differ significantly (11.6% versus 16.4%; p=0.07). The higher dose of contrast medium in the immediate multivessel PCI group may have also led to acute left ventricular volume overload with a negative effect on myocardial function and recovery. In addition, the prolonged duration of the multivessel PCI procedure may be hazardous at a time when the patient is hemodynamically compromised, leading to potentially more bleeding and inflammation.

Additional myocardial damage may also have been induced by PCI in stable lesions. Further subanalyses using biomarkers from the central core laboratory of renal function, inflammation, and myocardial damage as well as detailed angiographic analyses will be performed to elucidate potential underlying mechanisms for the difference in mortality.

References


Please look at the pdf file with publications attached

List of Websites:
www.culprit-shock.eu

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