# Project Final Report

| | |
|---|---|
| **Grant Agreement number:** | **602202** |
| **Project acronym:** | **CULPRIT-SHOCK** |
| **Project title:** | **Multivessel versus culprit lesion only percutaneous revascularization in patients with acute myocardial infarction complicated by cardiogenic shock** |
| **Funding Scheme:** | **Collaborative project*** |
| **Date of latest version of Annex I against which the assessment will be made:** | **08.08.2018** |
| **Final report:** | |
| **Period covered:** | **From 2013-09-01 to 2018-08-31** |


**Name, title and organization of the scientific representative of the project's coordinator:**

**Prof. Dr. med. Holger Thiele, Universität zu Lübeck, University Hospital Schleswig-Holstein**

**Since 1st September 2017**

**Univ.-Prof. Dr. med. Holger Thiele**

**Director**

**Heart Center Leipzig - University Hospital, Department of Internal Medicine/Cardiology**

**Tel: +49 341 865 1428**

**Fax: +49 341 865 1461**

**E-mail: holger.thiele@medizin.uni-leipzig.de**


**Project website address: www.culprit-shock.eu**

# Table of Content

**Table of Content** ..... **2**
**Section 1 – Final publishable summary report** ..... **3**
1.1 Executive summary ..... 4
1.2 Summary description of project context and objectives ..... 5
1.3 Description of the main S&T results/foregrounds of CULPRIT-SHOCK ..... 7
1.4 The potential impact ..... 18
**Section 2 – Use and dissemination of foreground** ..... **24**
**Section 3 – Report on societal implications** ..... **25**

# Section 1 – Final publishable summary report

## CULPRIT SHOCK


**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):

The project is coordinated by Prof. Dr. med. Holger Thiele (Partner 01) UZL, Universität zu Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany, since 1st September located at (Partner 17) Heart Center Leipzig - University Hospital, Department of Internal Medicine/Cardiology, Strümpellstr. 39, D-04289 Leipzig

Other partners and team leaders:

| | |
|---|---|
| Partner 2 | IHF, Stiftung Institut für Herzinfarktforschung, Uwe Zeymer, Germany |
| Partner 3 | AMC, Academisch Medisch Centrum bij de Universiteit van Amsterdam, Jan J. Piek, The Netherlands |
| Partner 5 | VUHSK, Viesoji Istaiga Vilniaus Universiteto Ligonines Santariskiu Klinikos, Pranas Serpytis, Lithuania |
| Partner 6 | APHP, Assistance Publique - Hôpitaux de Paris, Gilles Montalescot, France |
| Partner 7 | ACTION, A.C.T.I.O.N Allies in Cardiovascular trials, Initiatives and organized networks Association, Vanessa Gallois, France |
| Partner 8 | UKC LJ, Univerzitetni Klinicni Center Ljubljana, Marko Noc, Slovenia |
| Partner 9 | ICTC, Instytut Kardiologii im. Prymasa Tysiaclecia Stefana Kardynala Wyszynskiego, Janina Stępińska, Poland |
| Partner 12 | UOG, University of Glasgow, Andrew Briggs, United Kingdom |
| Partner 13 | ASMN-IRCCS, Arcispedale Santa Maria Nuova Azienda Ospedamiera, Massimo Pantaleoni, Italy |
| Partner 15 | ULEI, Universitaet Leipzig, Joachim Thiery, Germany |
| Partner 16 | NWTCB, National Waiting Time Centre Board, Keith Oldroyd, United Kingdom |
| Partner 17 | ULEIHC, Herzzentrum Leipzig GmbH, Germany |
| Partner 18 | AOLC, Stefano Savonitto, Italy / Azienda Socio-Sanitaria Territoriale, Italy |
| Partner 19 | UZA, Antwerp University Hospital, Christiaan Vrints, Belgium |
| Partner 20 | ARTTIC S.A.S, Martin Dietz, France |
| Partner 21 | ATVB, Verein zur Foerderung der Forschung auf dem Gebiet der Arteriosklerose Thrombose, Kurt Huber, Austria |
| Partner 22 | INSEL Gruppe AG, Stephan Windecker, Switzerland |

## 1.1 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 consensus.

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

## 1.2 Summary description of 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%.[1] 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%).[1] 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).[4] **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. [5,6] [5,6] [5,6] [5,6] [5,6] [5,6] [5,6] [5,6] [5,6] [5,6] 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. [7-9] [7-9] [7-9] [7-9] [7-9] [7-9] [7-9] [7-9] [7-9] 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.

## 1.3 Description of the main S&T results/foregrounds of CULPRIT-SHOCK

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.[13,14] 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.[13,14] 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.[13,14] 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)

| Study population (N=66) | | | | | |
|---|---|---|---|---|---|
| univariate analysis | | | Adjusted analysis* | | |
| Variable | HR (95%CI) | P-value | Variable | HR (95%CI) | P-value |
| Macrocirculatory perfusion parameters (at admission) | | | Macrocirculatory perfusion parameters (at admission) | | |
| Systolic blood pressure (mmHg) | 0.985 (0.971 - 0.999) | 0.031 | Systolic blood pressure (mmHg) | 0.999 (0.984 - 1.014) | 0.927 |
| Diastolic blood pressure (mmHg) | 0.989 (0.968 - 1.010) | 0.295 | Diastolic blood pressure (mmHg) | - | - |
| Mean arterial pressure (mmHg) | 0.984 (0.965 - 1.003) | 0.096 | Mean arterial pressure (mmHg) | - | - |
| 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.

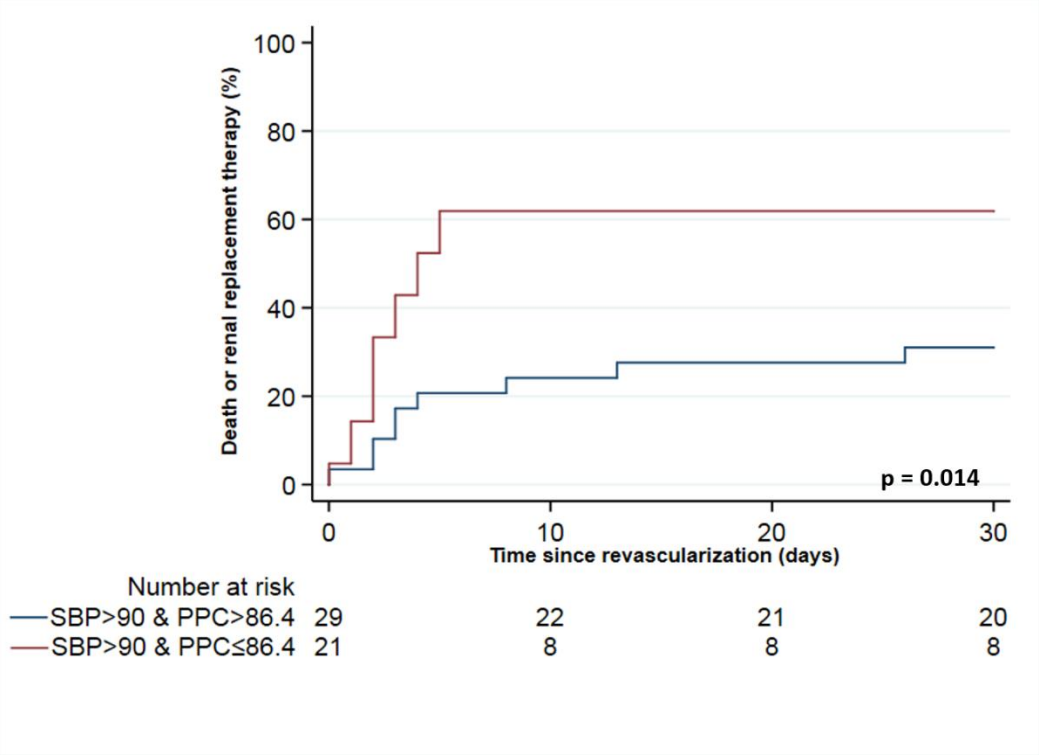
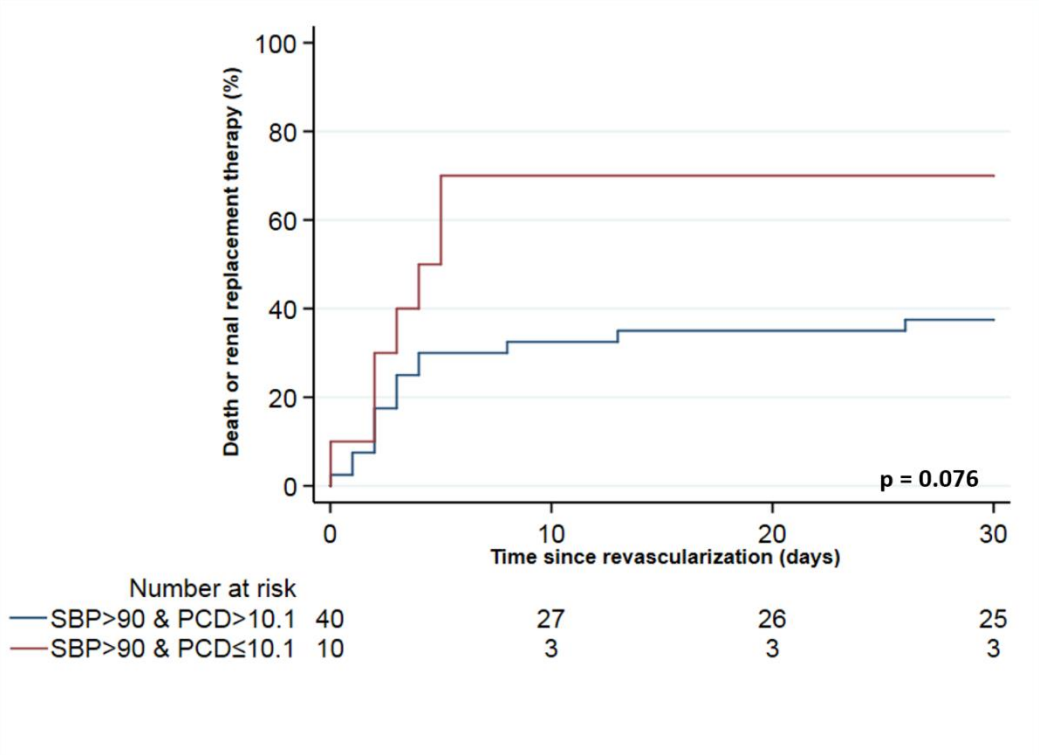


Figure 2: Clinical outcome according to normal vs abnormale microvascular perfusion (perfused calippary density) in normotensinve patients after cardiogenic shock complicated acute myocardial infarction.



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

| | Immediate multivessel PCI | Culprit-only PCI | |
|---|---|---|---|
| | N=33 | N=33 | p-value |
| Baseline characteristics | | | |
| Age (years) | 66±10 | 68±10 | 0.29 |
| Male | 25 (75.8) | 19 (57.6) | 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 of differs significant 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 (figure3a + 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

| | Automated assessment of microvascular perfusion N=98 | Manual assessment of microvascular perfusion N=98 | p-value |
|---|---|---|---|
| Density data | | | |
| Vessel length (mm) | 5.2 (3.7, 6.2) | 11.7 (9.6, 13.1) | <0.001 |
| Number of grid crossings (N) | 60 (54, 67) | 56 (48, 63) | 0.007 |
| De Backer score | 12.1 (11.0, 13.9) | 12.2 (10.5, 14.4) | 0.562 |
| Total vessel density (mm/mm2) | 8.3 (6.0, 10.4) | 21.0 (17.9, 23.0) | <0.001 |
| Perfusion data | | | |
| Proportion perfused capillaries (%) | 100 (100, 100) | 91.7 (78.3, 98.4) | <0.001 |
| Proportion perfused all-vessels (%) | 99.9 (96.0, 100) | 92.8 (80.8, 98.5) | <0.001 |
| Perfused capillary density (mm/mm2) | 6.1 (4.4, 8.2) | 16.4 (11.6, 20.4) | <0.001 |
| Perfused all vessel-density (mm/mm2) | 7.3 (5.5, 9.9) | 18.6 (14.2, 22.4) | <0.001 |

numbers are given as median (quartile 1, quartile 3)

Figure 3a: Clinical outcome of normal vs abnormal proportion perfused capillaries according manual assessment.

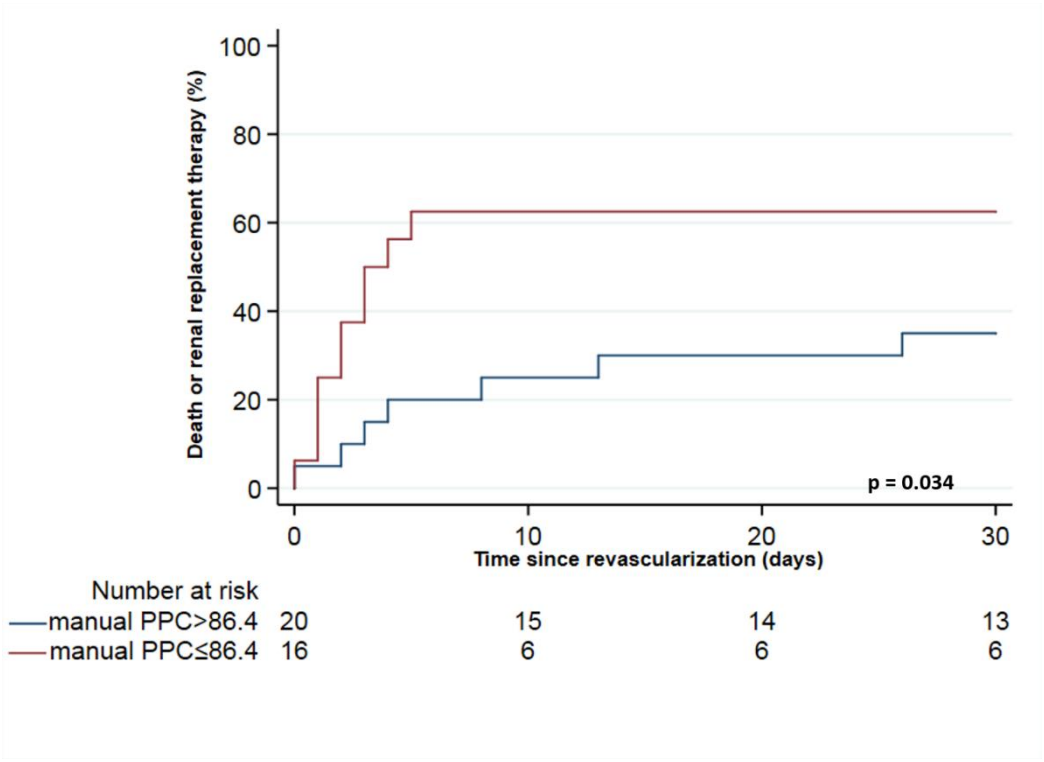



Figure 3b: Clinical outcome of normal vs abnormal perfused capillary density according manual assessment.

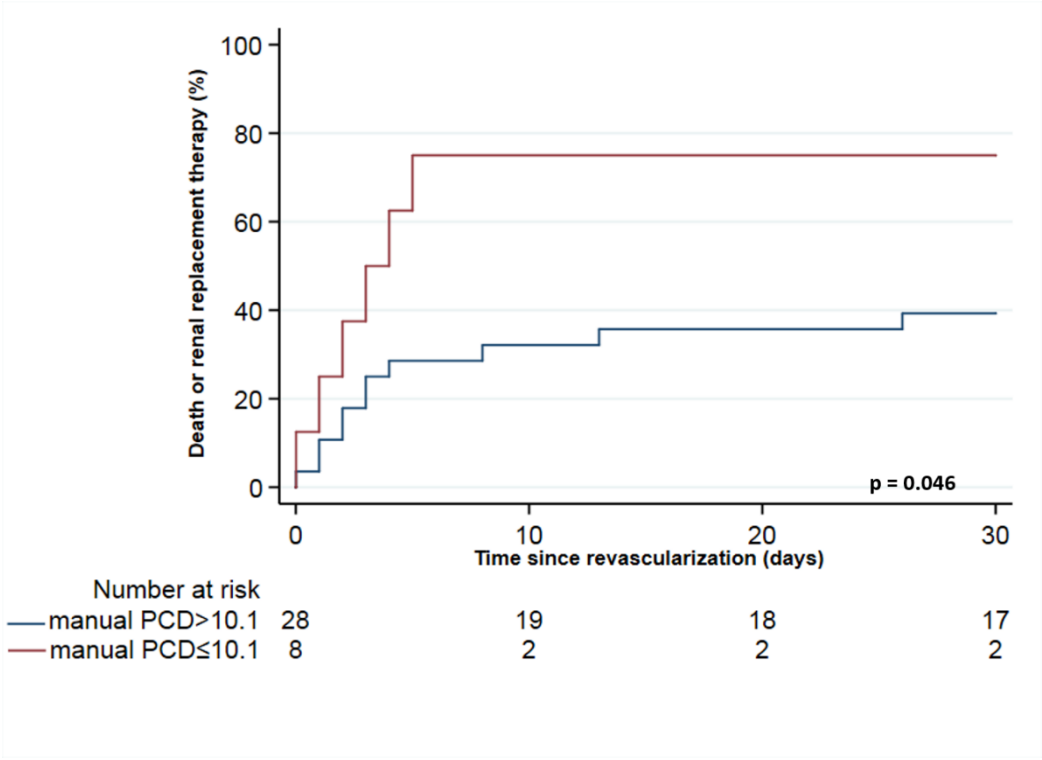



Figure 4a: Clinical outcome of normal vs abnormal proportion perfused capillaries according automated assessment.

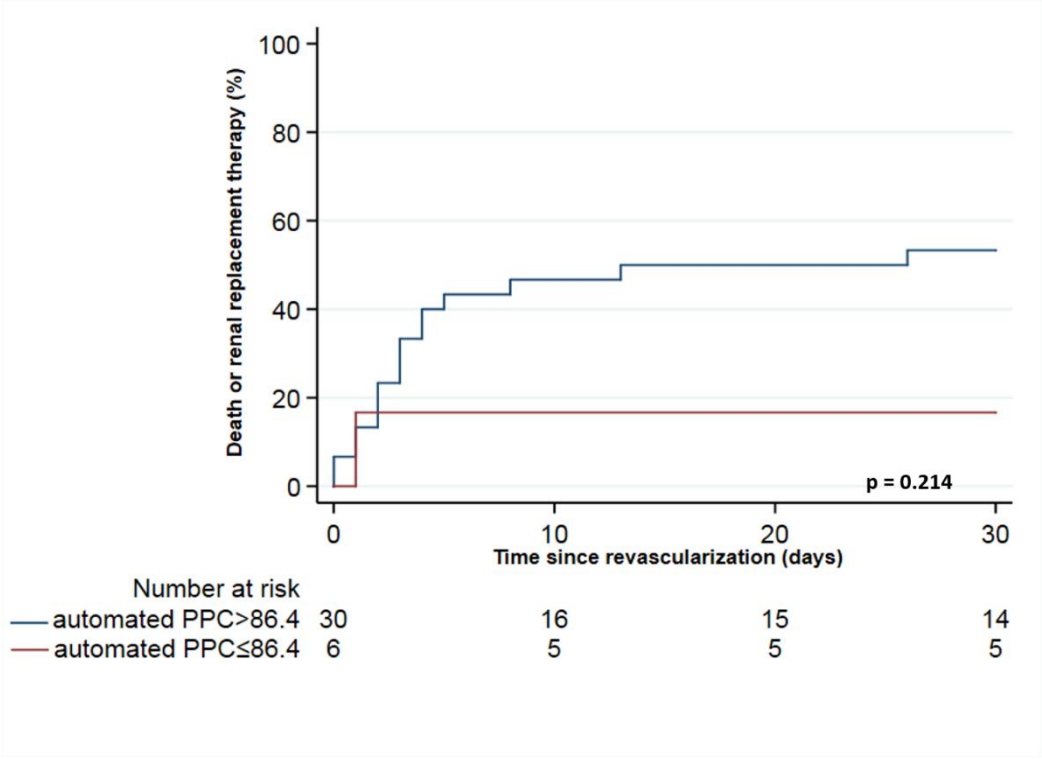
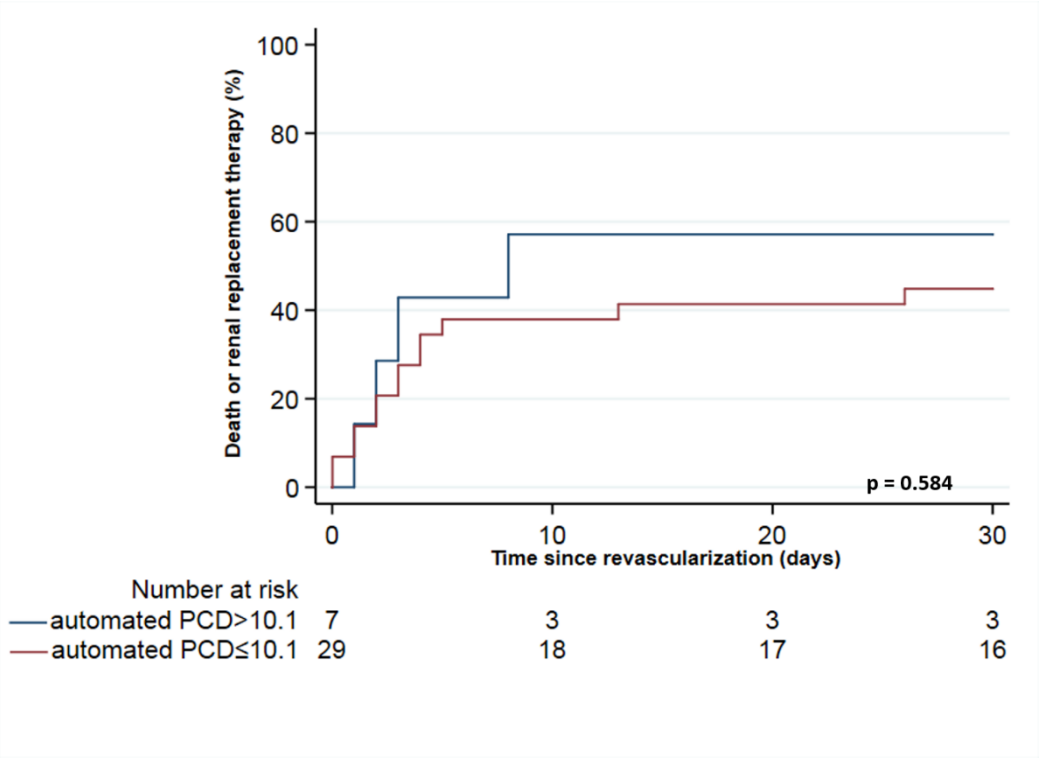



Figure 4b: Clinical outcome of normal vs abnormal perfused capillary density according automated assessment.




**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.[15]

**WP08: Predictive prognostic model and risk score**

- **Objectives**

The principal objective of WP08 was to create a model for the prediction of clinical prognosis in cardiogenic shock. The following specific objectives had been defined for WP08:

- 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 ß 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 is 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**

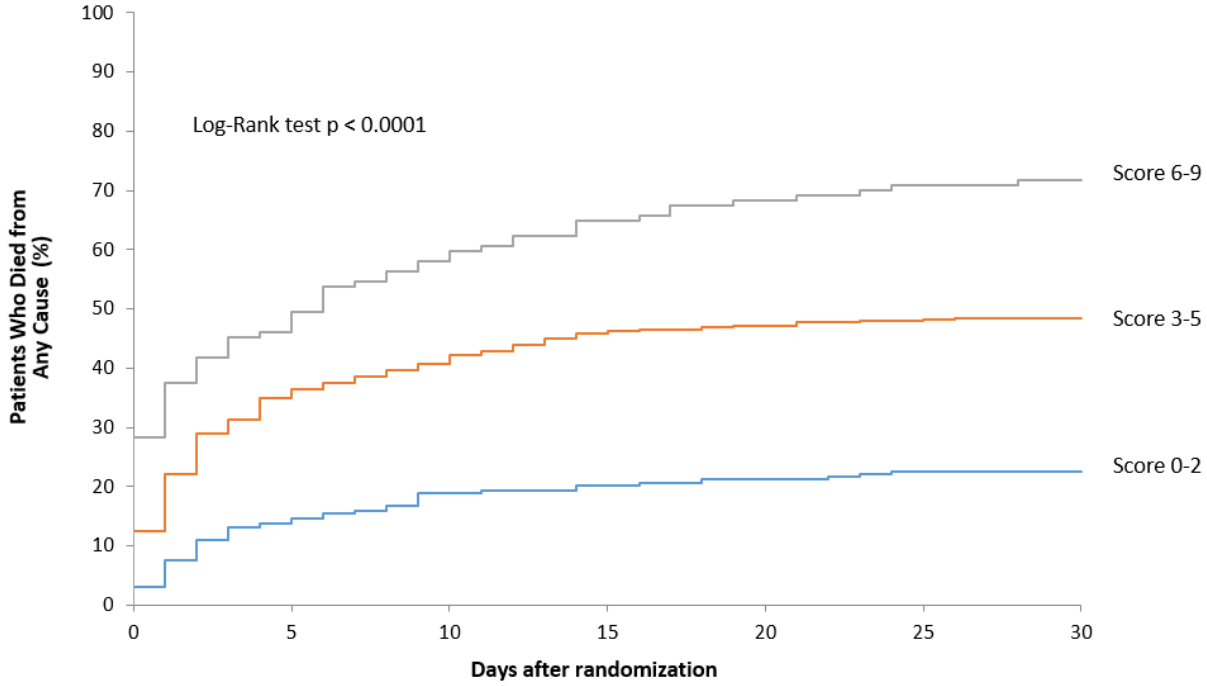
| Score | Points |
|---|---|
| Variables | |
| Age > 73 years | 2 |
| Altered mental status | 2 |
| Heart rate – pre PCI [>100 bpm] | 1 |
| Systolic BP – at admission [<100 mmHg] | 1 |
| Culprit lesion in LAD | 1 |
| TIMI after PCI < 3 | 2 |

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**

| Risk categories | |
|---|---|
| Category | Points |
| Low | 0-2 |
| Intermediate | 3-5 |
| High | 6-9 |

**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.

## 1.4 The 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 clarified 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),[11] whereas the American STEMI guidelines give no specific recommendation.[18] 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.[19]

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,[20] 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).[14]

*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.[21] 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 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


1. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. *Eur Heart J.* 2015;36(20):1223-1230.
2. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med.* 1999;341(9):625-634.
3. Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA.* 2001;285:190-192.
4. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA.* 2006;295:2511-2515.
5. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* 2012;367(14):1287-1296.
6. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock. Final 12-month results of the randomised IntraAortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) Trial. *Lancet.* 2013;382:1638-1645.
7. Sanborn TA, Sleeper LA, Webb JG, et al. Correlates of one-year survival in patients with cardiogenic shock complicating acute myocardial infarction: angiographic findings from the SHOCK trial. *J Am Coll Cardiol.* 2003;42:1373-1379.
8. Webb JG, Sanborn TA, Sleeper LA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK Trial Registry. *Am Heart J.* 2001;141(6):964-970.
9. Wong SC, Sanborn T, Sleeper LA, et al. Angiographic findings and clinical correlates in patients with cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. *J Am Coll Cardiol.* 2000;36(3, Supplement 1):1077-1083.
10. de Waha S, Jobs A, Pöss J, et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: A systematic review and meta-analysis. *Eur Heart J: Acute Card Care.* 2018;7:28-37.
11. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevationThe Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39(2):119-177.
12. Werdan K, Ruß M, Buerke M, Delle-Karth G, Geppert A, Schöndube FA. Cardiogenic shock due to myocardial infarction: diagnosis, monitoring and treatment - A German-Austrian S3 Guideline. *Dtsch Arztebl Int.* 2012;109(18):343-351.
13. Thiele H, Akin I, Sandri M, et al. One-year outcomes after PCI strategies in cardiogenic shock. *N Engl J Med.* 2018;379(18):1699-1710.
14. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med.* 2017;377:2419-2432.
15. Quayyum Z, Briggs A, Robles-Zurita JA, et al. Protocol for an economic evaluation of the randomized controlled trial of culprit lesion only PCI vs. immediate multivessel PCI in acute myocardial infarction complicated by cardiogenic shock: CULPRIT-SHOCK trial. *BMJ Open.* 2017;7(8):e014849.
16. Hochman JS, Katz S. Back to the future in cardiogenic shock - Initial PCI of the culprit lesion only. *N Engl J Med.* 2017;377:2486-2488.
17. Adriaenssens T, van de Werf F. Is culprit-lesion-only PCI in cardiogenic shock still better at 1 year? *N Engl J Med.* 2018;18:1775-1777.
18. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation.* 2016;133(11):1135-1147.
19. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate use criteria for coronary revascularization in patients with acute coronary syndromes. A report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear

Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. *J Am Coll Card.* 2017;69:570-591.

20. Neumann FJ, Sousa Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2018;doi:10.1093/eurheartj/ehy394.
21. Saad M, Fuernau G, Desch S, et al. Prognostic impact of non-culprit chronic total occlusions in infarct-related cardiogenic shock: Results of the randomized IABP-SHOCK II trial. *EuroIntervention.* 2017;epub ahead of print:Jaa-287 2017, doi: 2010.4244/EIJ-D-2017-00451.

# Section 2 – Use and dissemination of foreground

Please see PARTICIPANT PORTAL.

# Section 3 – Report on societal implications

Please see PARTICIPANT PORTAL.

EDITORIALS

# Is Culprit-Lesion-Only PCI in Cardiogenic Shock Still Better at 1 Year?

Tom Adriaenssens, M.D., Ph.D., and Frans Van de Werf, M.D., Ph.D.

Cardiogenic shock occurs in approximately 5% of patients with an acute coronary syndrome — usually, but not always, after ST-segment elevation myocardial infarction. If a large amount of myocardial tissue has become ischemic or injured, pump failure and reduced blood flow to vital organs occur. Urgent percutaneous coronary intervention (PCI) of the culprit lesion is currently the only therapy associated with a significant decrease in mortality.[1] No other intervention with a device or pharmacologic agent has shown a significant benefit, and as a consequence, mortality has plateaued at 50% in recent years. On angiography performed during the acute phase, clinically significant lesions are often found in nonculprit vessels, a finding associated with increased mortality.[2] A logical consideration, therefore, is whether treatment of these lesions during the acute phase could lower mortality. However, in the randomized Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial, the rate of the primary end point of death or renal-replacement therapy at 30 days was significantly lower with culprit-lesion-only PCI than with immediate multivessel PCI.[3] These results led to a downgrading of multivessel PCI to a class III B recommendation in recent European guidelines.[4]

In this issue of the *Journal*, Thiele et al. report the 1-year outcomes of the trial.[5] These data are important, since it could be assumed that multivessel PCI, although harmful in the acute phase, may ultimately result in a long-term benefit. However, no significant difference in mortality or in the rate of recurrent myocardial infarction or renal-replacement therapy was found between the two approaches at 1 year. Not unexpectedly, more repeat revascularization procedures had to be performed in the culprit-lesion-only PCI group than in the multivessel PCI group (in 32.3% of the patients vs. 9.4%). In an exploratory landmark analysis, mortality was lower in the culprit-lesion-only PCI group during the first 30 days and was similar in the two groups between 30 days and 1 year. Thus, the 1-year outcomes show that culprit-lesion-only PCI with the option of staged revascularization afterward did not increase long-term mortality.

A somewhat surprising finding of the trial is the higher rate of rehospitalization for heart failure with the culprit-lesion-only approach than with multivessel PCI (5.2% vs. 1.2%). One explanation is that the higher rate of complete revascularization in the multivessel PCI group could have led to better left ventricular function at long-term follow-up. An alternative explanation, which was also put forward by the authors and supported by their landmark analysis, is that the culprit-lesion-only approach saved patients who would have died during the acute phase if they had received multivessel treatment, but those patients survived with poor left ventricular function and were at high risk for subsequent heart failure. A similar observation has been made in placebo-controlled trials with thrombolytic agents.[6] Taken together, the results of the CULPRIT-SHOCK trial indicate that urgent revascularization of the culprit vessel by immediate PCI, which results in better perfusion of the jeopardized myocardium, is the key beneficial treatment to

offer to patients who are in cardiogenic shock. The 1-year outcomes of the trial do not provide arguments to change (again) the guideline recommendations.

What can be done to further lower mortality in patients with cardiogenic shock? Shortening the time from symptom onset to PCI by streamlining prehospital care is the most important measure that can be taken, since the benefit of immediate revascularization is critically dependent on time. A large registry study showed that every 10 minutes of treatment delay resulted in 3.3 additional deaths per 100 patients who had cardiogenic shock and were treated with early PCI.[7] Since substantial delays may occur before a patient gets to the catheterization laboratory, immediate administration of a thrombolytic agent should be considered in high-risk patients with acute ST-segment elevation myocardial infarction who cannot undergo immediate PCI, in order to reduce the risk of development of cardiogenic shock. The results of a recent meta-analysis that compared pharmacoinvasive treatment with standard primary PCI support this strategy.[8]

Are no further improvements in outcomes possible for patients who present with cardiogenic shock? Since inotropic and vasopressor agents are insufficient to interrupt the downward spiral of organ damage, hopes are set on circulatory-support devices. However, Thiele et al. have already shown that the use of an intraaortic balloon pump did not lower mortality.[9] Other percutaneously inserted or surgically implanted left ventricular assist devices provide more powerful hemodynamic support, but the use of such devices has not been associated with a decrease in mortality thus far.[10] Venoarterial extracorporeal membrane oxygenation is an attractive alternative option that is being used increasingly at tertiary care centers and will be tested for the first time in a large randomized trial of more than 400 patients (EURO-SHOCK). Since all these invasive interventions are expensive and their associated outcomes uncertain, we should not forget the key message of the CULPRIT-SHOCK trial: emergency revascularization in acute myocardial infarction with cardiogenic shock should be kept simple.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium.

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
2. Sanborn TA, Sleeper LA, Webb JG, et al. Correlates of one-year survival in patients with cardiogenic shock complicating acute myocardial infarction: angiographic findings from the SHOCK trial. J Am Coll Cardiol 2003;42:1373-9.
3. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419-32.
4. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2018 August 25 (Epub ahead of print).
5. Thiele H, Akin I, Sandri M, et al. One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med 2018;379:1699-710.
6. Van de Werf F. Discrepancies between the effects of coronary reperfusion on survival and left ventricular function. Lancet 1989;1:1367-9.
7. Scholz KH, Maier SKG, Maier LS, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J 2018;39:1065-74.
8. Vanhaverbeke M, Bogaerts K, Sinnaeve PR, Janssens L, Armstrong P, Van de Werf F. Prevention of cardiogenic shock after acute myocardial infarction. Circulation (in press).
9. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287-96.
10. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. Nat Rev Cardiol 2016;13:481-92.

DOI: 10.1056/NEJMe1810971

EDITORIAL

# Back to the Future in Cardiogenic Shock — Initial PCI of the Culprit Lesion Only

Judith S. Hochman, M.D., and Stuart Katz, M.D.

Approximately 5 to 10% of cases of acute myocardial infarction are complicated by cardiogenic shock, which is associated with early mortality of 40 to 50%.[1] Nearly two decades ago, the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial established that mortality was lower with emergency revascularization than with initial medical stabilization and selective delayed revascularization in patients with ST-segment elevation myocardial infarction (STEMI).[2,3] In the SHOCK trial, percutaneous coronary intervention (PCI) of the culprit lesion only was the most common therapy for initial revascularization. Although more complete revascularization might have been expected to have an increased benefit, the small subgroup that underwent initial multivessel PCI had higher mortality than the subgroup that underwent culprit-lesion-only PCI (adjusted hazard ratio, 2.75; 95% confidence interval [CI], 1.05 to 7.25; P=0.04).[4] A meta-analysis of 10 cohort studies, which included a total of 6051 patients with cardiogenic shock, also showed higher early mortality with multivessel PCI than with culprit-lesion-only PCI (37.5% vs. 28.8%, P=0.001).[5]

Although these results were highly confounded, they led to reevaluation of the recommendation to consider initial multivessel PCI in patients with cardiogenic shock. Thiele and colleagues report the results of the CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial, which was a randomized trial that compared culprit-lesion-only PCI with immediate PCI of all obstructive lesions (i.e., those with >70% stenosis of the diameter) in patients who had STEMI or non–ST-segment elevation myocardial infarction (NSTEMI) with cardiogenic shock.[6] In the multivessel PCI group, recanalization of chronic total occlusions was performed when possible, and complete revascularization was achieved in 81.0% of the patients. Staged revascularization was performed in 17.7% of the patients in the culprit-lesion-only PCI group, and the crossover rate was relatively low (12.5% in the culprit-lesion-only PCI group and 9.4% in the multivessel PCI group). Therefore, there was a large difference between the two groups in the rate of early and overall revascularization.

The major finding was that the risk of the primary end point of death or severe renal failure leading to renal-replacement therapy was higher with immediate multivessel PCI than with culprit-lesion-only PCI. The results were similar for death from any cause (relative risk, 0.84; 95% CI, 0.72 to 0.98; P=0.03) and were consistent across prespecified subgroups, including subgroups defined according to the presence or absence of a chronic total occlusion. The trial was well executed, which is a remarkable accomplishment in this population. Only one participant was lost to follow-up. The consistent risk estimates for the primary end point in the intention-to-treat, per-protocol, and as-treated analyses support the robustness of the findings.

The CULPRIT-SHOCK trial provides compelling evidence that a strategy of culprit-lesion-only PCI is preferred over initial multivessel PCI for patients with cardiogenic shock. These findings are discordant with the results of a meta-analysis of randomized trials that included patients with uncomplicated STEMI, which showed a lower rate of a composite of death or myocardial infarction

with initial multivessel PCI than with culprit-lesion-only PCI.[7] These disparate findings suggest that patients with cardiogenic shock may be at an increased risk for adverse outcomes during complex multivessel PCI procedures. The potential mechanisms of this increased risk remain speculative; in the CULPRIT-SHOCK trial, data on left ventricular function and hemodynamic status were not collected and the large initial increase in markers of cardiac injury may have obscured evidence of PCI-related myocardial infarction. Increased platelet reactivity due to catecholamine therapy and the inflammatory and prothrombotic effects of cardiogenic shock may increase the risk of ischemia or infarction during PCI of nonculprit arteries, with further deterioration of ventricular-pump function.[1] More manipulation of the catheter during multivessel PCI than during culprit-lesion-only PCI may also have contributed to numerically higher risks of renal failure and death due to brain injury. Recent and future advances in PCI technique and periprocedural management might reduce the risk of adverse outcomes associated with multivessel PCI in patients with cardiogenic shock; however, such advances would probably not lead to superiority of multivessel PCI over culprit-lesion-only PCI, even with respect to long-term outcomes, because most deaths due to cardiogenic shock occur within 30 days after myocardial infarction and are caused by pump failure, not recurrent myocardial infarction.

Despite major advances in PCI technique and antithrombotic pharmacology during the approximately 20 years between the SHOCK trial and the CULPRIT-SHOCK trial, 30-day mortality among patients who underwent initial culprit-lesion-only PCI was nearly identical in the two trials (approximately 45%).[2,6] Additional trials are warranted to test strategies that may further reduce mortality. Coronary-artery bypass grafting (CABG) is an alternative method of multivessel revascularization that is used infrequently in the clinical management of cardiogenic shock and among patients in the CULPRIT-SHOCK registry.[6,8] The protocol for the SHOCK trial recommended direct emergency CABG for severe multivessel disease or disease of the left main coronary artery among patients who were assigned to undergo early revascularization. In the SHOCK trial, the method of revascularization was selected on the basis of investigator judgment (initial PCI was performed in 64%, and initial CABG in 36%).[2,4] Although disease of the left main coronary artery and three-vessel disease were more common and the prevalence of diabetes was two times as high among patients who underwent CABG than among those who underwent culprit-lesion-only PCI, survival did not differ significantly between the two groups. These data from a nonrandomized sample support further investigation of outcomes associated with initial revascularization with CABG in patients with cardiogenic shock.

During cardiogenic shock, the onset of systemic hypoperfusion in response to ischemic cardiac injury induces a detrimental cascade of proinflammatory signaling, vasomotor dysregulation, multisystem organ failure, and death.[1] To date, interventions that have been targeted to enhance systemic perfusion in patients with cardiogenic shock have not yielded the anticipated benefits with respect to clinical outcomes. Routine use of an intraaortic balloon pump does not improve outcomes,[9] and small trials of percutaneous mechanical circulatory support have not yielded encouraging findings.[1] Venoarterial extracorporeal membrane oxygenation (ECMO) is a potentially attractive alternative and is increasingly being used to preserve organ perfusion and prevent multisystem organ dysfunction in patients with cardiogenic shock.[10] In the CULPRIT-SHOCK trial, the rates of ECMO use and of death due to brain injury (a known complication of ECMO) were numerically higher in the multivessel PCI group than in the culprit-lesion-only group. ECMO for cardiogenic shock should be subjected to the same rigorous randomized clinical-trial methodology that was used by Thiele et al. in the CULPRIT-SHOCK trial.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Department of Medicine (J.S.H., S.K.), the Cardiovascular Clinical Research Center (J.S.H.), and the Center for Advanced Cardiac Therapeutics (S.K.), New York University Langone Health, New York.

This editorial was published on October 30, 2017, at NEJM.org.

1. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. Nat Rev Cardiol 2016;13:481-92.
2. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
3. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295:2511-5.
4. Webb JG, Lowe AM, Sanborn TA, et al. Percutaneous coro-

nary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol 2003;42:1380-6.
**5.** de Waha S, Jobs A, Eitel I, et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2017 July 1 (Epub ahead of print).
**6.** Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med. DOI: 10.1056/NEJMoa1710261.
**7.** Bainey KR, Welsh RC, Toklu B, Bangalore S. Complete vs culprit-only percutaneous coronary intervention in STEMI with multivessel disease: a meta-analysis and trial sequential analysis of randomized trials. Can J Cardiol 2016;32:1542-51.
**8.** Babaev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 2005;294:448-54.
**9.** Thiele H, Zeymer U, Werdan K. Intraaortic balloon support for cardiogenic shock. N Engl J Med 2013;368:81.
**10.** Agarwal S, Sud K, Martin JM, Menon V. Trends in the use of mechanical circulatory support devices in patients presenting with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2015;8:1772-4.

**DOI: 10.1056/NEJMe1713341**

# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Thiele H, Akin I, Sandri M, et al. One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med. DOI: 10.1056/NEJMoa1808788

**SUPPLEMENTARY APPENDIX**

**TABLE OF CONTENTS**


**1) Table of Contents** **Page 1-2**

**2) Participating Investigators and Trial Committees** **Page 3-8**

**3) Trial Registration** **Page 9**

**4) Informed Consent Process in Participating Countries** **Page 10-11**

**5) Outcome Definitions** **Page 12-16**

**6) List of End Points** **Page 17**

**7) Statistical Analysis – Sample Size Calculation** **Page 18**

**8) Figure S1 – Subgroup analyses of 1-year all-cause death** **Page 19**

The forest plot indicates the relative risk and 95% confidence intervals

PCI=percutaneous coronary intervention

CI=confidence interval

NSTEMI=Non-ST-elevation myocardial infarction

STEMI=ST-elevation myocardial infarction

**9) Figure S2 –** **Page 20**

**Time-to-event curves through 1 year for all-cause death/ recurrent myocardial infarction**

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval

**10) Figure S3 –** **Page 21**

**Time-to-event curves through 1 year for repeat revascularization**

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval

**11) Figure S4 –** **Page 22**

**Time-to-event curves through 1 year for rehospitalization for congestive heart failure**

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval

**12) Figure S5 – Time-to-event curves through 1 year for all-cause death/ recurrent myocardial infarction/rehospitalization for congestive heart failure** **Page 23**

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval

CHF=congestive heart failure

**13) Figure S6 – Time-to-event curves through 1 year for all-cause death or renal replacement therapy** **Page 24**

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval

**14) Figure S7 – Quality of Life at 6 Months and 1 Year** **Page 25**

**15) Figure S8 – Quality of Life at 6 Months and 1 Year** **Page 26**

Visual Analogue Scale

**16) Table S1 – Causes of Death at 1 Year** **Page 27**

**17) Table S2 – Clinical Outcomes and Safety at 1 Year for Survivors** **Page 28**

**18) References** **Page 29**

## 2) Participating Investigators and Trial Committees

The following investigators and institutions participated in the CULPRIT-SHOCK trial:

**Steering Committee**: Holger Thiele (principal investigator and chair), Heart Center Leipzig – University Hospital, Leipzig, Germany; Steffen Desch, Heart Center Leipzig – University Hospital, Leipzig, Germany; Uwe Zeymer, Klinikum Ludwigshafen and Institut für Herzinfarktforschung, Ludwigshafen, Germany; Gilles Montalescot, ACTION group, Paris, France; Jan J. Piek, Academic Medical Center, Amsterdam, The Netherlands; Patrizia Torremante, ARTTIC, Munich, Germany.

**Project Management:** Patrizia Torremante, ARTTIC, Munich, Germany; Roza Meyer-Saraei, University Hospital Schleswig-Holstein, Lübeck, Germany.

**Clinical Endpoints Committee:** Ulrich Tebbe (chair), Detmold, Germany; Jochen Wöhrle, University of Ulm, Germany; Otmar Pachinger, University of Innsbruck, Innsbruck, Austria.

**Data Monitoring:** Institut für Herzinfarktforschung, Ludwigshafen, Germany: Clemens Busch (chair); Nathalie Pfeiffer.

**Data Management:** Institut für Herzinfarktforschung, Ludwigshafen, Germany: Alexander Neumer, Clemens Busch, Nathalie Pfeiffer.

**Data Coordination and Analysis:** Institut für Herzinfarktforschung, Ludwigshafen, Germany: Steffen Schneider (chair statistics); Taoufik Ouarrak (statistics), Thomas Riemer (statistics), Christiane Lober (statistics), Matthias Hochadel (statistics).

**Data Safety Monitoring Board:** Peter Clemmensen, MD (chair), Universitäres Herzzentrum Hamburg, Hamburg, Germany; Ferenc Follath, MD, University of Zurich, Zurich, Switzerland; Karl Wegscheider, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

**Angiographic Core Laboratory Committee (ACLC) at the ACTION Study Group (Paris, France)**: Dr O. Barthélémy (chair), Dr. M. Zeitouni, Dr. P. Overtchouk, Dr P. Guedeney, Dr. G. Hage, Dr. Hauguel-Moreau.

**Study sites and hospitals:**

**Germany; national coordinator: Holger Thiele, Leipzig**

University Heart Center Luebeck, Germany: Georg Fuernau, Ingo Eitel, Roza Meyer-Saraei, Suzanne de Waha: 58 patients and 36 registry patients; Heart Center Leipzig – University of Leipzig, Germany: Holger Thiele, Steffen Desch, Marcus Sandri, Sabrina Weinschenk: 70 patients and 50 registry patients; Universitätsmedizin Mannheim, Mannheim, Germany: Ibrahim Akin, Martin Borggrefe: 75 patients and 5 registry patients; Heart Center Bad Krozingen, Bad Krozingen, Germany: Franz-Josef Neumann, Miroslaw Ferenc: 9 patients and 9 registry patients; Asklepios Klinik Langen, Langen, Germany: Hans-Gerd Olbrich, Hans-Bernd Hopf: 4 patients and 1 registry patient; German Heart Center Munich, Munich, Germany: Adnan Kastrati, Antoinette de Waha, Heribert Schunkert: 1 patient and 0 registry patients; Heart Center - Segeberger Kliniken, Bad Segeberg, Germany: Gert Richardt, Bettina Schwarz, Mohamed Abdel-Wahab, Ralph Toelg, Volker Geist, Monika Bahnsen-Maaß: 6 patients and 2 registry patients; SLK Kliniken Heilbronn, Heilbronn, Germany: Marcus Hennersdorf, Jochen Graf, Urs Riemann, Dominik Scharpf: 3 patients and 0 registry patients; University of Greifswald, Greifswald, Germany: Klaus Empen, Mathias C Busch, Stephan B. Felix: 15 patients and 4 registry patients; Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany: Karl Werdan, Sebastian Nuding: 6 patients and 0 registry patients; Klinikum Links der Weser, Bremen, Germany: Rainer Hambrecht, Andreas Fach, Eduard Fiehn: 25 patients and 11 registry patients; Heart Center Ludwigshafen, Ludwigshafen, Germany: Uwe Zeymer, Anselm K. Gitt, Bernd Mark, Ralph Winkler: 9 patients and 15 registry patients; Zentralklinik Bad Berka, Bad Berka, Germany: Bernward Lauer: 1 patient and 0 registry patients; Friedrich-Schiller University Jena, Jena, Germany: Sven Möbius-Winkler, Christian Schulze: 12 patients and 1 registry patient; Klinik Hennigsdorf, Hennigsdorf, Germany: Hans-Heinrich Minden: 5 patients and 4 registry patients; Otto-von-Guericke-University Magdeburg: Rüdiger C. Braun-Dullaeus, Alexander Schmeißer: 2 patients and 5 registry patients; Heart Center Dresden, Dresden, Germany: Ruth H. Strasser, Bernd Ebner: 3 patients and 0 registry patients; Universitätsklinikum Würzburg, Würzburg, Germany: Georg Ertl, Peter Nordbeck: 51 patients and 11 registry patients; Hospital München – Neuperlach: Harald Mudra, Martin Hug: 4 patients and 0 registry patients; Universitätsklinikum Regensburg, Regensburg, Germany: Dierk

Endemann, Lars Maier: 9 patients and 8 registry patients; Charité Berlin Campus Benjamin Franklin, Berlin, Germany: Ulf Landmesser, Carsten Skurk: 24 patients and 0 registry patients; Kerckhoff Klinik Bad Nauheim, Bad Nauheim, Germany: Christian Hamm, Claudia Walther, Christoph Liebetrau: 7 patients and 0 registry patients; Helios Klinikum Erfurt, Erfurt, Germany: Harald Lapp, Niels Menck: 22 patients and 8 registry patients; Ludwigs-Maximilian University Munich – Hospital Großhadern: Julinda Mehilli, Martin Orban, Jörg Hausleiter, Steffen Massberg: 12 patients and 8 registry patients; Carl-von-Basedow-Klinikum Merseburg, Merseburg, Germany: Roland Prondzinsky: 2 patients and 0 registry patients; Klinikum Lippe-Detmold, Detmold, Germany: Ulrich Tebbe, Stephan Gielen: 1 patient and 10 registry patients; Universitätsklinikum Tübingen, Tübingen, Germany: Meinrad Gawaz, Tobias Geisler: 26 patients and 0 registry patients; Klinikum Nürnberg, Nürnberg, Germany: Matthias Pauschinger, Fadil Ademaj: 12 patients and 0 registry patients; Universitäts-Herzzentrum Freiburg, Freiburg, Germany: Christoph Bode: 11 patients and 2 registry patients; Universitätsklinikum Bonn, Bonn, Germany: Georg Nickenig: 9 patients and 0 registry patients; Universitätsklinikum Frankfurt am Main; Frankfurt am Main, Germany: Stephan Fichtlscherer, Andreas Zeiher: 8 patients and 0 registry patients; Asklepios Klinik Hamburg Barmbek, Hamburg, Germany: Achim Viertel: 7 patients and 8 registry patients; Universitätsklinikum Düsseldorf, Düsseldorf, Germany: Malte Kelm, Christian Jung: 7 patients and 2 registry patients; Universitäres Herzzentrum Hamburg, Hamburg, Germany: Peter Clemmensen, Carsten Sydow, Mahir Karakas: 6 patients and 0 registry patients; Herzzentrum Uniklinik Köln, Cologne, Germany: Volker Rudolph, Stephan Baldus: 6 patients and 0 registry patients; Universitätsmedizin Göttingen; Klinik für Kardiologie und Pneumologie, Göttingen, Germany: Claudius Jacobshagen, Gerd Hasenfuß: 4 patients and 6 registry patients; Universitätsklinikum Leipzig, Leipzig, Germany: Dietrich Pfeiffer: 4 patients and 0 registry patients; Marienhospital Neuwied, Neuwied, Germany: Björn Buchter, Burkhard Hügl: 3 patients and 2 registry patients; Universitätsklinikum Giessen, Giessen, Germany: Holger Nef, Oliver Dörr, Christian Hamm: 2 patients and 0 registry patients; Helios Kreiskrankenhaus Gotha, Gotha, Germany: Karsten Reinig: 2 patients and 0 registry patients; Asklepios Klinik St. Georg, Hamburg, Germany: Karl-

Heinz Kuck, Alexander Ghanem: 1 patient and 0 registry patients; Universitätsklinikum Heidelberg, MED III, Heidelberg, Germany: Hugo Katus: 1 patient and 0 registry patients; Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany: Tommaso Gori, Thomas Münzel: 1 patient and 0 registry patients; Klinikum Coburg, II. Medizinische Klinik, Kardiologie, Coburg, Germany: Steffen Schnupp, Johannes Brachmann: 0 patients and 3 registry patients; HSK Kliniken Wiesbaden, Wiesbaden, Germany: Markus Ferrari: 0 patients and 2 registry patients; Universitätsklinikum Erlangen, Erlangen, Germany: Stephan Achenbach: 0 patients and 2 registry patients.

**France; national coordinator: Gilles Montalescot, Paris**

Institut de Cardiologie - Hôpital Pitié-Salpêtrière, Paris, France: Gilles Montalescot 15 patients and 2 registry patients; Hôpital de Rangueuil-Toulouse, Toulouse, France: Didier Carrié: 9 patients and 3 registry patients; Hôpital Lariboisière- Paris, Paris, France: Patrick Henry, Stephane Manzo-Silberman: 4 patients and 5 registry patients; CHU Caremeau – Nimes, Nimes, France: Bertrand Ledermann, Guillaume Cayla; 2 patients and 0 registry patients; Hospital de la Timone, Marseille, France: Jean-Louis Bonnet: 2 patients and 0 registry patients.

**Switzerland; national coordinator: Stefan Windecker, Bern**

Inselspital Bern - Universitätsklinik für Kardiologie, Bern, Switzerland: André Frenk, Stephan Windecker: 5 patients and 3 registry patients; Universitätsspital Basel, Basel, Switzerland: Raban Jeger: 4 patients and 0 registry patients; CHUV - Service de cardiologie, Lausanne, Switzerland; Eric Eeckhout: 1 patient and 0 registry patients.

**The Netherlands; national coordinator: Jan J. Piek, Amsterdam**

University Hospital of Amsterdam, Amsterdam, The Netherlands: Jan J. Piek, Jose P. Henriques: 16 patients and 16 registry patients; Erasmus MC Rotterdam, Rotterdam, The Netherlands: Robert-Jan Van Geuns; 7 patients and 0 registry patients; University Medical Center Utrecht, Utrecht, The Netherlands: Michiel Voskuil; 1 patient and 7 registry patients; Haga Ziekenhuis Den Haag, Den Haag, The Netherlands: M. Bax; 0 patients and 2 registry patients; University Medical Center Groningen, Groningen, The Netherlands: Pim van der Harst: 0 patients and 2 registry patients.

**Slovenia; national coordinator: Marko Noc, Ljubljana**

University medical centre Ljubljana, Ljubljana, Slovenia: Marko Noc, Tomaž Goslar: 16 patients and 7 registry patients.

**Lithuania; national coordinator: Pranas Serpytis, Vilnius**

Vilnius University Hospital Santaros Klinikos; Vilnius, Lithuania; Faculty of Medicine, Vilnius University: Pranas Serpytis, Rokas Serpytis: 13 patients and 11 registry patients; Klaipeda Seamen Hospital Klaipėda, Lithuania: Dalia Jarasuniene: 1 patient and 0 registry patients.

**Belgium; national coordinator: Christiaan Vrints, Antwerp**

Universitair Ziekenhuis Antwerpen Cardiologie, Edegem, Belgium: Christiaan Vrints: 3 patients and 7 registry patients.

**Austria; national coordinator: Kurt Huber, Vienna**

Wilheminenspital Kardiologie-Wien, Wien, Austria: Kurt Huber: 5 patients and 8 registry patients; Medizinische Universität Wien, Wien, Austria: Irene Marthe Lang, Philipp Pichler: 5 patients and 0 registry patients; Krankenanstalt Rudolfstiftung Wien, Wien, Austria: Franz Weidinger: 0 patients and 2 registry patients; Universitätsklinikum Innsbruck, Innsbruck, Austria: Marc-Michael Zaruba: 2 patients and 0 registry patients.

**Poland; national coordinator: Janina Stepinska; Warsaw**

II Klinika Kardiologii, Uniwersytet Jagielloński, Krakow, Poland: Darius Dudek, Rafal Depukat: 10 patients and 2 registry patients; Instytut Kardiologii – Warszawa, Warszawa, Poland: Janina Stepinska, Adam Witkowski: 3 patients and 1 registry patient; X Oddział Kardiologii Inwazyjnej, Tychy, Poland: Krzysztof Milewski: 2 patients and 1 registry patient; IV Oddział Kardiologii Inwazyjnej, PAKS, Kedzierzyn-Kozle, Poland: Janusz Prokopczuk: 2 patients and 0 registry patients; III Katedra i Oddział Kliniczny Kardiologii ŚAM Zabrze, Zabrze, Poland: Mariusz Gąsior: 1 patient and 2 registry patients; II Oddział Kardiologiczny PAKS, Bielsko-Biala, Poland:: Bogdan Gorycki: 1 patient and 0 registry patients; Zakład Kardiologii Inwazyjne – Katowice, Katowice-Ochojec, Poland: Andrzej Ochała: 0 patient and 1 registry patient.

**Italy; national coordinator: Stefano Savonitto; Lecco**

Manzoni Hospital, Lecco, Italy: Luigi Piatti: 1 patient and 14 registry patients; Ospedale G.B. Morgagni, Forlì, Italy: Marcello Galvani: 1 patient and 5 registry patients; Ospedale Niguarda Ca' Granda, Milano, Italy: Irene Bossi: 0 patients and 3 registry patients; IRCCS Arcispedale S. Maria Nuova, Reggio Emilia, Italy: Gianluca Pignatelli: 0 patients and 2 registry patients.

**United Kingdom; national coordinator: Keith Oldroyd, Glasgow**

Golden Jubilee National Hospital, Glasgow, United Kingdom: Keith Oldroyd; Colin Berry: 10 patients and 6 registry patients; Leeds General Infirmary, Leeds, United Kingdom: John Greenwood: 11 patients and 18 registry patients; Royal Free Hospital London, London, United Kingdom; Tim Lockie: 7 patients and 19 registry patients. Royal Stoke University Hospital, Stafford, United Kingdom; Mamas Mamas: 0 patients and 4 registry patients.

**3) Trial Registration**

This trial is registered with www.ClinicalTrials.gov: NCT01927549. The time of final approved trial registration was August 14th 2013. First patient inclusion was April 15th 2013 at the Heart Center Leipzig – University Hospital, Leipzig, Germany.

Thus, there was a delay between first patient inclusion and trial registration which was due to a misunderstanding between the project coordination for the EU grant (at this time gabo:mi, later on ARTTIC) and the clinical project coordination at the investigator's site at the Heart Center Leipzig - University of Leipzig. According to initial communication registration should have been performed by gabo:mi. When the study coordinator recognized that it had not been performed we immediately registered it at clinicaltrials.gov. At this time only 13 patients at the Heart Center Leipzig – University Hospital (and no other study site) had been included into the trial.

**4) Informed Consent Process in Participating Countries**

Informed consent in cardiogenic shock is generally difficult because the majority of patients is intubated and mechanically ventilated or show altered mental status. Therefore, a dedicated informed consent process was applied and approved by the ethical committees (slightly differing between the participating countries).

The informed consent process in the participating countries is shown below:

| Country | Informed consent procedure |
|---|---|
| **Germany** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent<br>This process was only different for centers of the ethical committee of the Landesärztekammer Rheinland-Pfalz where only version 1. was allowed. |
| **Austria** | 2 different informed consent forms:<br>1. Patient is able to consent<br>2. Patient is not able to consent |
| **Switzerland** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent |
| **Italy** | 2 different informed consent forms:<br>1. Short version<br>2. Extended version<br>Italy by law was not allowed to enter patients into the randomized clinical trial if the patient was unable to consent. In this case, patients entered the registry. |
| **Belgium** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent |
| **Poland** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent |
| **Slovenia** | The informed consent procedure in Slovenia requires no consent prior to randomization. Patients need to sign consent only after they have regained the ability to consent after the procedure and in case of survival. Thus, there is only one patient informed consent version. |

| | |
|---|---|
| **Lithuania** | The informed consent procedure in Lithuania requires the consent of two physicians and an independent third person in case the patient is not able to consent. |
| **United Kingdom** | The informed consent procedure in Scotland differs from the process applicable e.g. in Germany. A relative must be informed and provide consent for patients not capable of providing own consent. If a patient survives, further consent is not mandatory, but desirable. Thus, a short form with the consent of a relative is sufficient.<br><br>The informed consent procedure in the UK without Scotland requires two physicians to consent in representation of the patient, in case he or she lacks the capacity to consent. In this case, the patient has to be consented retrospectively. Capable patients are first consented using a short form prior to randomization and a long form after recovery to full consent. |
| **France** | The informed consent procedure in France requires a third person to consent in addition to the treating physician in case of a patient's inability to consent. In this case, patients need to sign consent after they have regained the ability to consent after the procedure and in case of survival. |
| **The Netherlands** | The informed consent procedure in the Netherlands requires no consent prior to randomization. Patients need to sign consent only after they have regained the ability to consent after the procedure and in case of survival. Thus, there is only one patient informed consent version. |

## 5) Outcome Definitions

*Death*
Death of all cause.

*Death cardiovascular*
Death due to cardiovascular causes, such as heart failure, cardiac arrhythmias, myocardial infarction, sudden cardiac death or all deaths of unknown cause.

*Severe renal failure requiring renal replacement therapy*
Any indication for renal replacement therapy such as dialysis, hemofiltration or hemodiafiltration such as renal failure with one of the following criteria:

- Otherwise untreatable volume overload
- hyperpotassemia (>6.0 mmol/L)
- severe uremia (BUN >50 mg/dL or >8.4 mmol/L)
- persistent severe metabolic acidosis (pH <7.2)

*Myocardial reinfarction*
The definition of myocardial reinfarction in the CULPRIT-SHOCK trial is based on the universal definition of myocardial infarction.[1] Thus, myocardial reinfarction is defined according to the specific situation (see **Table 4**).

| **Re-MI**<br>***<24 h*** | **Re-MI**<br>***24 h – 7 days*** | **Re-MI**<br>***>7 days*** |
|---|---|---|
| Symptoms, such as angina pectoris for ≥20 minutes, most likely due to myocardial ischemia<br>***and or***<br>new ST-elevation ≥1 mm in ≥2 contiguous leads or new left bundle branch block<br>***or***<br>angiographic evidence of re-occlusion of a previously open coronary artery or graft | Symptoms, such as angina pectoris for ≥20 minutes, most likely due to myocardial ischemia<br>***and or***<br>if cardiac markers are still elevated, new increase ≥20% from the last non-normalized measurement<br>***or***<br>if cardiac markers are normalized, application of the "universal definition" for myocardial infarction (see next column) | "Universal definition" for myocardial infarction<br><br>**1.** Rise and/or fall of cardiac biomarkers above the 99$^{th}$ percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following:<br>• Symptoms of ischemia<br>• ECG changes indicative of new ischemia<br>• Development of pathological Q waves in ECG<br>• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality<br>**2.** Sudden, unexpected cardiac death with ST-elevation and presumably new LBBB or evidence of fresh thrombus by coronary angiography, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.<br>**3.** Peri-PCI myocardial infarction: increases of biomarkers > 3 of the upper reference level<br>**4.** Peri-CABG myocardial infarction: increases of biomarkers > 5 of the upper reference level plus new pathological Q waves or new LBBB or angiographically documented new graft or native coronary artery occlusion<br>**5.** Pathological findings of acute myocardial infarction |

*Repeat revascularization*
Any revascularization procedure (PCI or CABG) after the initial intervention including planned staged and urgent revascularization.

*Chronic total occlusion (CTO)*
Complete obstruction of a coronary artery, described as ≥99% stenosis of >3 months duration with poor or no antegrade blood flow (TIMI 0-1).

*Stent thrombosis*
Stent thrombosis is classified in definite, probable and possible stent thrombosis according to the Academic Research Consortium (ARC) definition:[2]

| Definite | Probable | Possible |
|---|---|---|
| Acute coronary syndrome and angiographic OR pathological confirmation of stent thrombosis | Unexplained death within the first 30 days OR acute ischemia in the territory of an implanted stent without angiographic confirmation of stent thrombosis in the absence of another culprit lesion | Unexplained death >30 days |

*Bleeding complications*
Bleeding complications will be classified according to 3 different definitions (for further evaluation which one best predicts outcome in cardiogenic shock patients).
BARC bleeding definition:[3]

| Type | Bleeding definition |
|---|---|
| Type 0 | no bleeding |
| Type 1 | bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional |
| Type 2 | any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:<br>(1) requiring nonsurgical, medical intervention by a healthcare professional<br>(2) leading to hospitalization or increased level of care, or<br>(3) prompting evaluation |
| Type 3 | |
| Type 3a | Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)<br>Any transfusion with overt bleeding |
| Type 3b | Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)<br>Cardiac tamponade<br>Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)<br>Bleeding requiring intravenous vasoactive agents |
| Type 3c | Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)<br>Subcategories confirmed by autopsy or imaging or lumbar puncture<br>Intraocular bleed compromising vision |
| Type 4 | CABG-related bleeding |

| | |
|---|---|
| | Perioperative intracranial bleeding within 48 h<br>Reoperation after closure of sternotomy for the purpose of controlling bleeding<br>Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†<br>Chest tube output ≥2L within a 24-h period |
| Type 5 | Fatal bleeding |
| Type 5a | Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious |
| Type 5b | Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation |

GUSTO-definition:[4]

| Severe/life-threatening bleeding complications | Moderate bleeding | Mild bleeding |
|---|---|---|
| *Intracranial* hemorrhage or bleeding that causes hemodynamic compromise requiring intervention | Bleeding that requires blood transfusion but does not result in hemodynamic compromise | Bleeding that does not meet criteria for either severe or moderate bleeding. |

TIMI definition:[5]

| Classification | Description |
|---|---|
| TIMI major | Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)<br>Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL<br>Fatal bleeding (bleeding that directly results in death within 7 d) |
| TIMI minor | Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL |

*Stroke*

Stroke will be classified in hemorrhagic (cranial CT, MRI, or autopsy) or non-hemorrhagic. Stroke is defined as an acute new neurological deficit ending in death or lasting longer than 24 hours, and classified by a physician as a stroke.

1. Primary hemorrhagic - defined as an intracerebral hemorrhage or subdural hematoma
    a. Intracerebral hemorrhage - Stroke with focal collections of intracerebral blood seen on brain imaging (CT or MRI) or a post-mortem examination, not felt to represent hemorrhagic conversion. Subarachnoid hemorrhage should be included in this category.
    b. Subdural hematoma - High density fluid collection in subdural space on brain images or blood in the subdural space on autopsy.
2. Non-hemorrhagic cerebral infarction - Stroke without focal collections of intracerebral blood on brain imaging.
3. Non-hemorrhagic infarction with hemorrhagic conversion - Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage.
4. Uncertain - Any stroke without brain imaging (CT or MRI) or autopsy documentation of type, or if tests are inconclusive.

*New congestive heart failure*

Occurrence of congestive heart failure after hospital discharge:
Defined as:

- Re-hospitalization due to new or worsening heart failure >24 h after hospital discharge.

*Infarct artery/culprit vessel*
Artery responsible for acute myocardial infarction.
In general its identification is based on

1) ECG
2) Wall motion abnormalities
3) Angiographic morphology of the lesion (e.g. ulceration and/or thrombus consistent with plaque rupture).

*Patency of culprit vessel and additional major vessels before and after PCI (TIMI-Flow)*
The TIMI-flow is visually assessed according to the following grading system:[6]

| Grade | Perfusion | Characterization |
|---|---|---|
| 0 | No Perfusion | No antegrade flow beyond the point of occlusion |
| 1 | Penetration without perfusion | Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary distal bed |
| 2 | Partial reperfusion | Contrast material passes across the obstruction with delayed entry and clearance from the distal bed |
| 3 | Complete reperfusion | Normal flow |

*Hemodynamic stability criterion*
Sustained (> 60 min) systolic blood pressure >90 mmHg
WITHOUT requirement for catecholamines
AND
WITHOUT signs of peripheral endorgan hypoperfusion

*Quality of life*
Quality of life will be assessed using the Euroqol 5D-questionnaire (www.euroqol.org):

| **Euroqol 5D: Quality of life** | |
|---|---|
| **Mobility** | ○ Pat. has no problems in walking about<br>○ Pat. has some problems in walking about<br>○ Pat. is confined to bed |
| **Self-Care** | ○ Pat. has no problems with self-care<br>○ Pat. has some problems washing or dressing himself<br>○ Pat. is unable to wash or dress himself |
| **Usual Activities (e.g. work, study, housework, family or leisure activities)** | ○ Pat. has no problems with performing his usual activities<br>○ Pat. has some problems with performing his usual activities<br>○ Pat. is unable to perform his usual activities |
| **Pain/Discomfort** | ○ Pat. has no pain or discomfort<br>○ Pat. has moderate pain or discomfort<br>○ Pat. has extreme pain or discomfort |
| **Anxiety/Depression** | ○ Pat. is not anxious or depressed<br>○ Pat. is moderately anxious or depressed<br>○ Pat. is extremely anxious or depressed |
| **In comparison to the general health state (GHS) in the past 12 months, today's GHS of the patient is** | ○ better<br>○ overall similar<br>○ worse |
| **How does the patient scales his GHS today?** | % |

Best imaginable GHS: 100%
Worst imaginable GHS: 0%

**6) List of End Points**

| **End Points** | |
|---|---|
| 12-month all-cause death | Table 3, Figure 2a |
| 12-month severe renal failure with renal replacement therapy | Table 3 |
| 12-month recurrent myocardial infarction | Table 3 |
| 12-month all-cause death/recurrent myocardial infarction | Table 3, Figure S2 |
| 12-month rehospitalization for congestive heart failure | Table 3, Figure S4 |
| 12-month all-cause death/recurrent infarction/rehospitalization for congestive heart failure | Table 3, Figure S5 |
| 12-month repeat revascularization | Table 3, Figure S3 |
| Quality of life | Figure S7 and S8 |
| | |
| *Post hoc* | |
| 12-month all-cause death or severe renal failure with renal replacement therapy | Table 3, Figure S6 |
| | |
| **Safety** | |
| Bleeding (BARC) grade 2-3 and 5 | Table 3 |
| Stroke | Table 3 |

## 7) Statistical Analysis – Sample Size Calculation

We estimated event rates of the primary composite end point of death or renal replacement therapy of 38% in the culprit-lesion-only PCI group versus 50% in the multivessel PCI group for sample size calculation.[7,8] A group sequential statistical design was chosen, with 1 interim analysis performed after 50% of all analyzable patients had completed 30-day follow-up. The global type I error level was set at 0.05. A total of 684 patients was needed to reject the null hypothesis of no difference between groups (2-sided chi-square test; power: 80%; alpha=0.048 for final analysis). Allowing for a 3% drop-out rate, 706 patients were recruited. The software used for sample size calculation was nQuery Advisor 7.0, Statistical Solutions, Cork, Ireland.

## 8) Figure S1 – Forest plot subgroup analyses of 1-year all-cause death

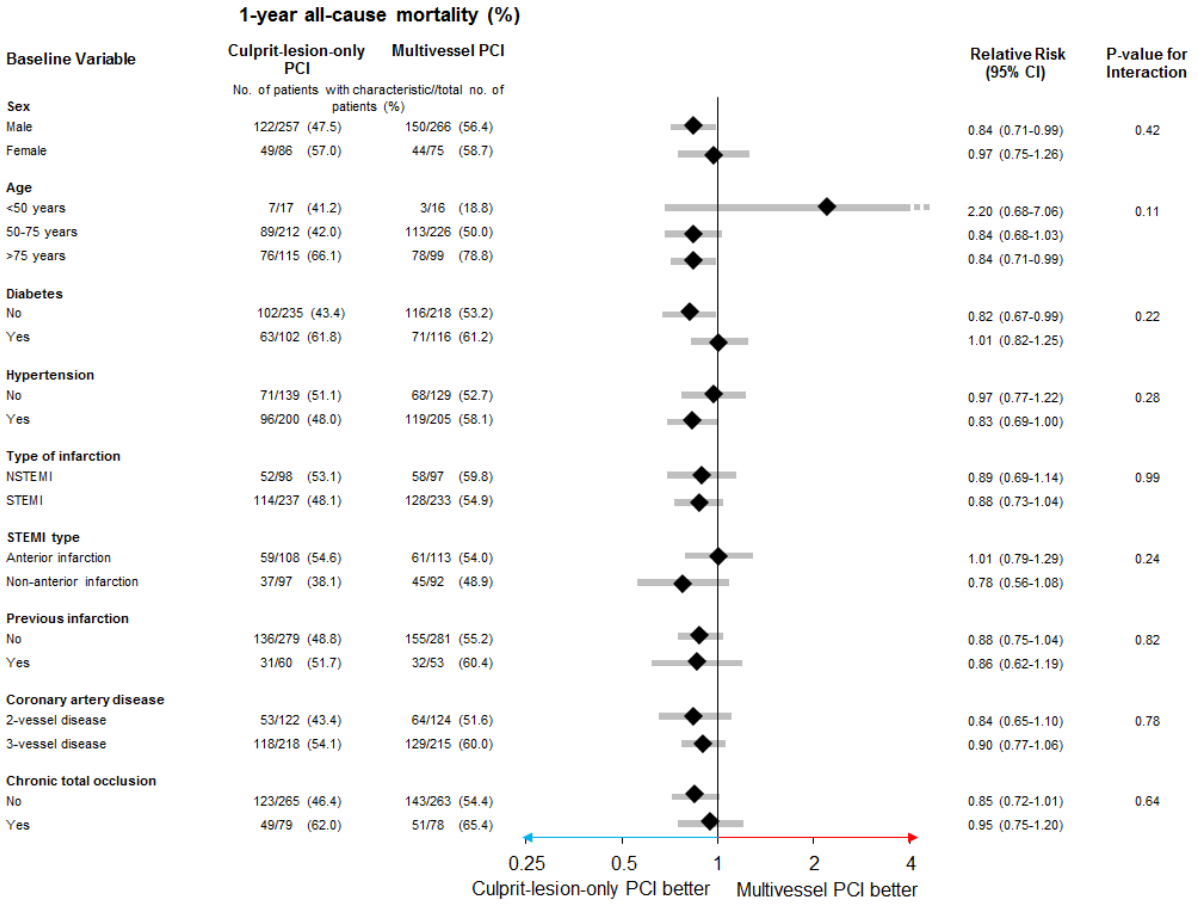
The forest plot indicates the relative risk and 95% confidence intervals

PCI=percutaneous coronary intervention

CI=confidence interval

NSTEMI=Non-ST-elevation myocardial infarction

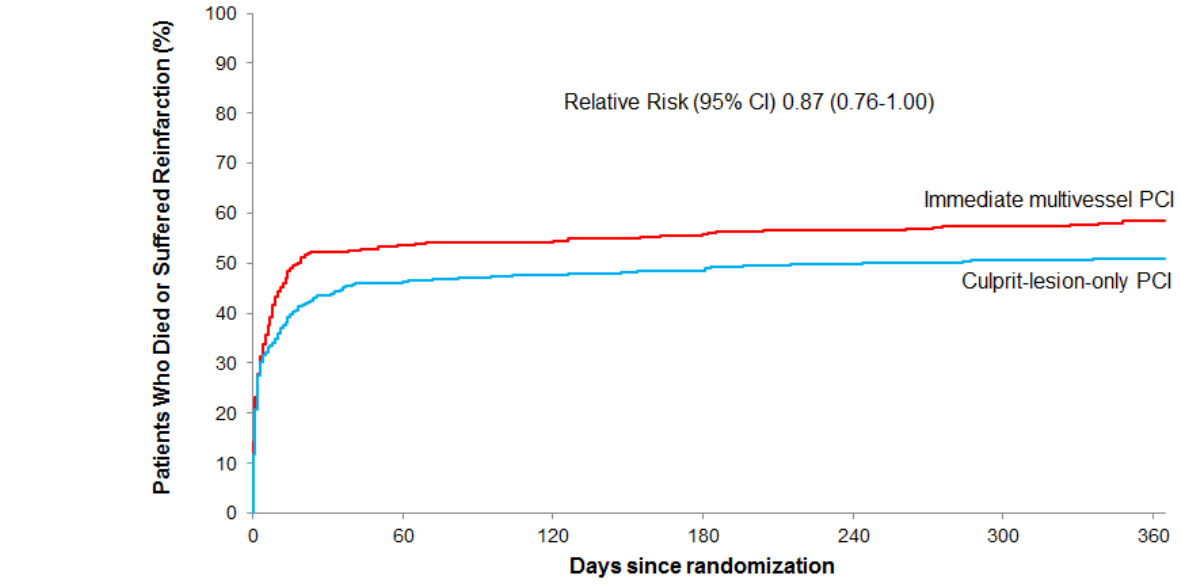
STEMI=ST-elevation myocardial infarction



## 9) Figure S2 – Time-to-event curves through 1 year for all-cause death/ recurrent myocardial infarction

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval



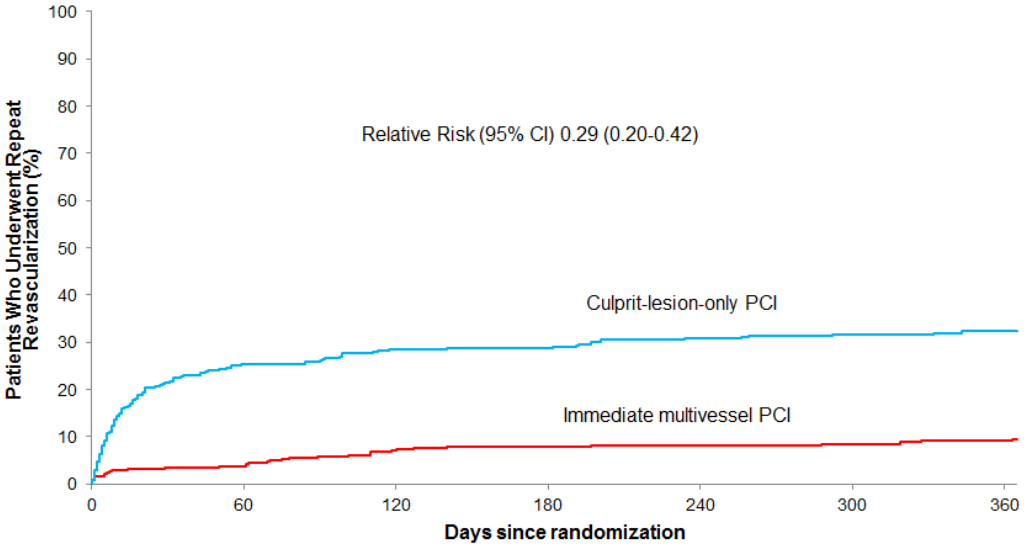

**Number at risk:**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multivessel PCI | 341 | 158 | 156 | 152 | 148 | 145 | 126 |
| Culprit-lesion-only PCI | 344 | 185 | 179 | 176 | 172 | 169 | 145 |

## 10) Figure S3 – Time-to-event curves through 1 year for repeat revascularization

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval




**Number at risk:**

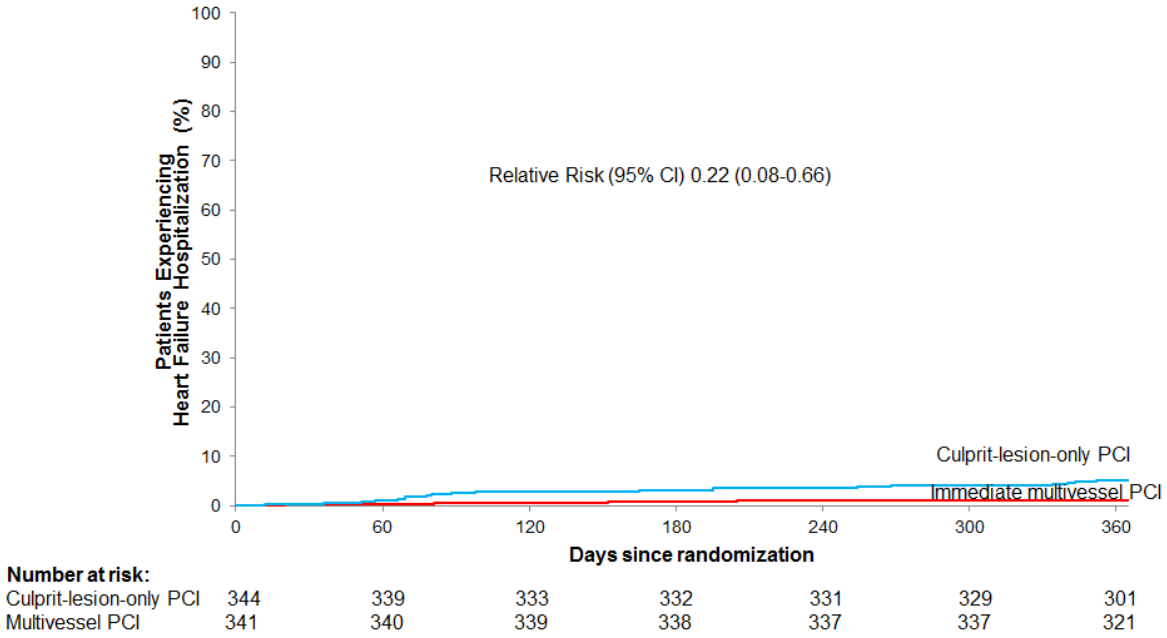
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Culprit-lesion only PCI | 344 | 256 | 245 | 244 | 237 | 234 | 223 |
| Multivessel PCI | 341 | 327 | 316 | 313 | 312 | 311 | 293 |

**11) Figure S4 – Time-to-event curves through 1 year for rehospitalization for congestive heart failure**

Event rates represent Kaplan-Meier estimates.

PCI=percutaneous coronary intervention; CI=confidence interval

CHF=congestive heart failure

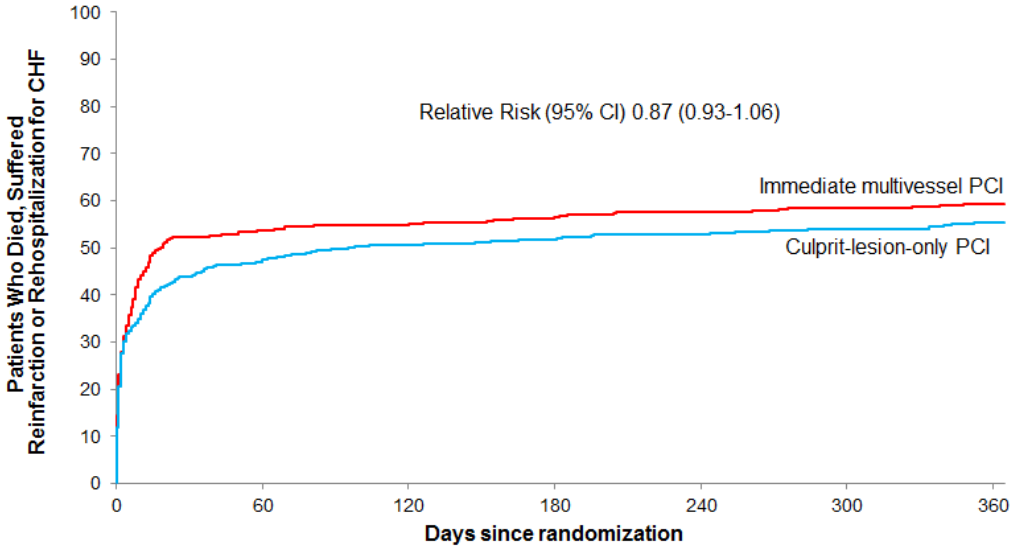


**12) Figure S5 – Time-to-event curves through 1 year for all-cause death/ recurrent myocardial infarction/rehospitalization for congestive heart failure**

Event rates represent Kaplan-Meier estimates.

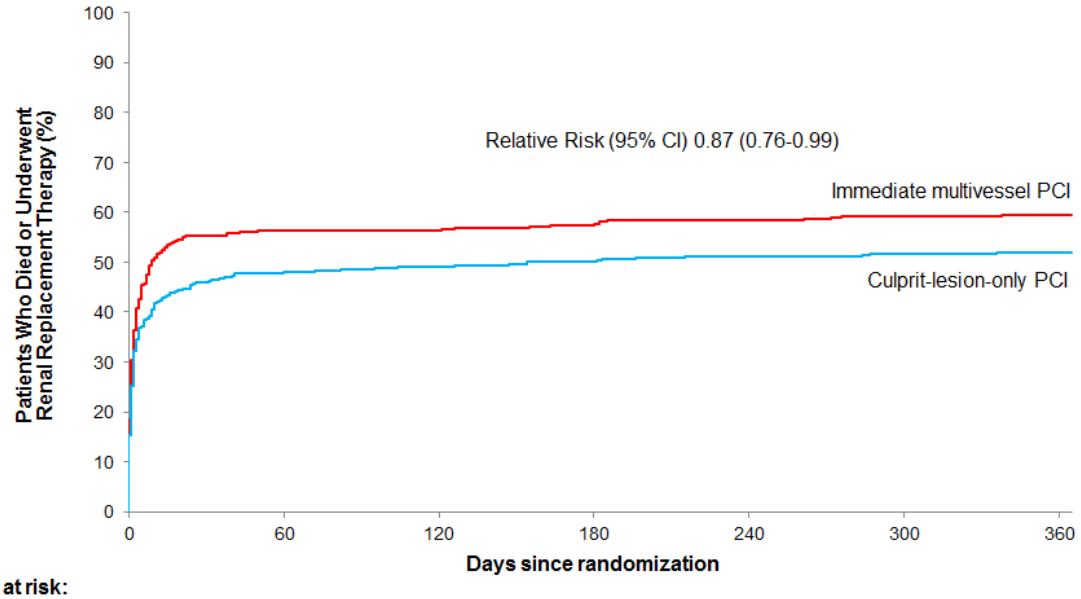
PCI=percutaneous coronary intervention; CI=confidence interval

CHF=congestive heart failure




| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multivessel PCI | 341 | 157 | 154 | 149 | 144 | 141 | 122 |
| Culprit-lesion-only PCI | 344 | 181 | 169 | 165 | 161 | 157 | 130 |

## 13) Figure S6 – Time-to-event curves through 1 year for all-cause death or renal replacement therapy




**Number at risk:**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Culprit-lesion-only PCI | 344 | 179 | 174 | 171 | 167 | 165 | 142 |
| Immediate multivessel PCI | 341 | 149 | 149 | 145 | 142 | 139 | 122 |

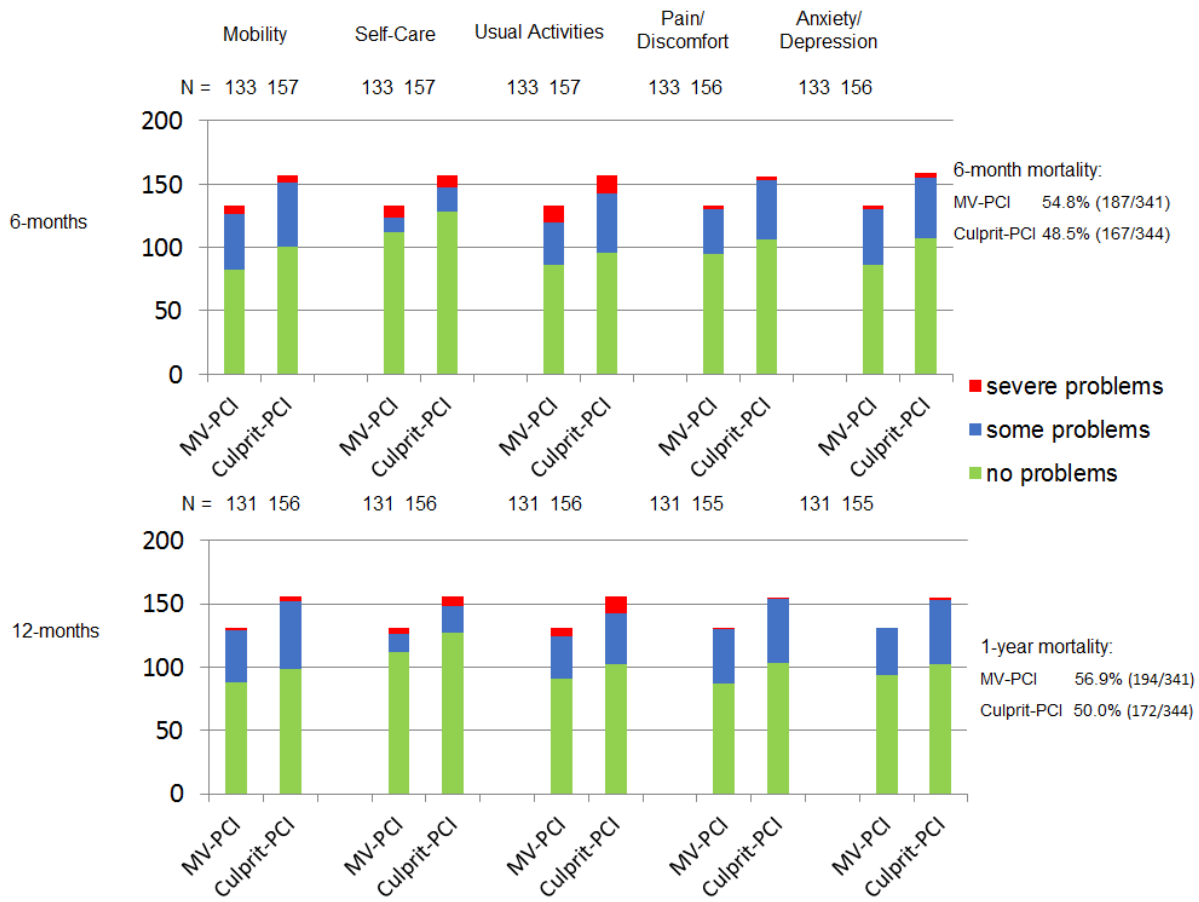
## 14) Figure S7 – Quality of Life at 6 Months and 1 Year

Quality of life was assessed by the Euroqol 5D (EQ-5D) questionnaire.

This questionnaire is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses (no problems/some or moderate problems/extreme problems). In addition, the EQ visual analogue scale (EQ VAS) was obtained. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state".[9] Results are displayed as EQ-5D-3L index value with 1 indicating best quality of life and the EQ VAS with 100 indicating the best subjective health status.[10]

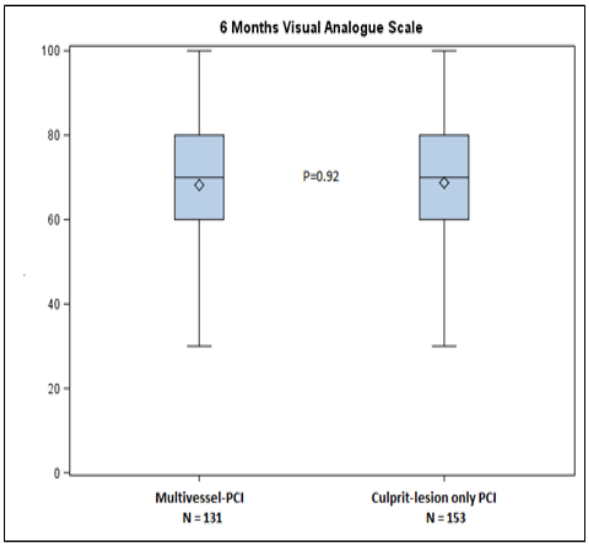
PCI=percutaneous coronary intervention

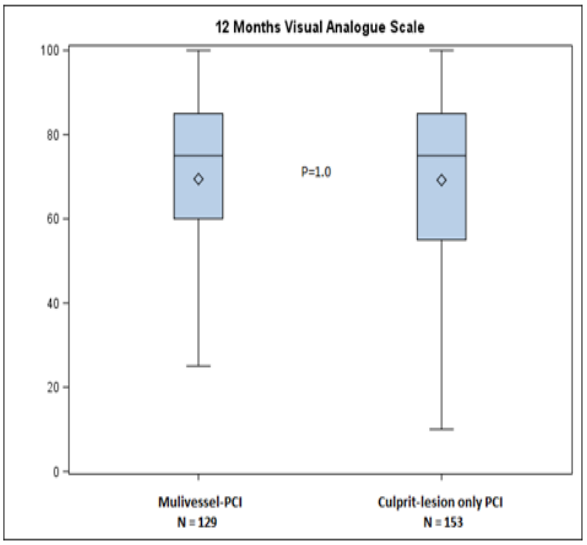
There was no adjustment for multiple testing.



## 15) Figure S8 – Quality of Life at 6 Months and 1 Year

Visual analogue scale




| | | | | |
|---|---|---|---|---|
| Median | 70 | 70 | 75 | 75 |
| IQR | 60-80 | 60-80 | 60-85 | 55-85 |
| Min, max | 0-100 | 10-100 | 1-100 | 10-100 |

**16) Table S1 – Causes of Death at 1 Year**

| | Culprit-lesion-only PCI (n=344) | Multivessel PCI (n=341) |
|---|---|---|
| All-cause mortality; n/total (%) | 172/344 (50.0) | 194/341 (56.9) |
| Death cause | | |
| Sudden cardiac death; n/total (%) | 16/172 (9.3) | 16/194 (8.2) |
| Refractory cardiogenic shock¸ n/total (%) | 114/172 (66.3) | 118/194 (60.8) |
| Recurrent myocardial infarction; n/total (%) | 2/172 (1.2) | 4/194 (2.1) |
| Brain injury; n/total (%) | 14/172 (8.1) | 25/194 (12.9) |
| Sepsis; n/total (%) | 12/172 (7.0) | 10/194 (5.2) |
| Unknown cause; n/total (%) | 13/172 (7.6) | 17/194 (8.8) |
| Other cause; n/total (%) | 1/172 (0.6) | 4/194 (2.1) |

**17) Table S2 Clinical Outcomes and Safety at 1 Year for Survivors**

| | Culprit-lesion-only PCI (n=172) | Multivessel PCI (n=147) | Relative Risk | 95% CI |
|---|---|---|---|---|
| Renal replacement therapy; n/total (%) | 7/172 (4.1) | 9/147 (6.1) | 0.66 | 0.25–1.74 |
| Reinfarction; n/total (%) | 3/172 (1.7) | 5/147 (3.4) | 0.51 | 0.12–2.11 |
| Rehospitalization for congestive heart failure; n/total (%) | 15/172 (8.7) | 4/147 (2.7) | 3.20 | 1.09–9.44 |
| Repeat revascularization; n/total (%) | 98/172 (57.0) | 26/147 (17.7) | 3.22 | 2.22-4.67 |
| Repeat PCI; n/total (%) | 94/172 (54.7) | 23/147 (15.7) | 3.49 | 2.34-5.21 |
| Repeat CABG; n/total (%) | 4/172 (2.3) | 3/147 (2.0) | 1.14 | 0.26-5.01 |
| Stroke; n/total (%) | 6/172 (3.5) | 8/147 (5.4) | 0.64 | 0.23–1.81 |
| Bleeding (BARC 2, 3 or 5); n/total (%) | 33/172 (19.2) | 34/147 (23.1) | 0.83 | 0.54–1.27 |
| Any bleeding event; n/total (%) | 39/172 (22.7) | 40/147 (27.2) | 0.83 | 0.57–1.22 |

BARC=Bleeding Academic Research Consortium**;** PCI=percutaneous coronary intervention; CABG = coronary artery bypass grafting

Renal replacement therapy was defined as any treatment including dialysis, hemofiltration, or hemodiafiltration.

## 18) References


1. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.
2. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials. Circulation 2007;115:2344-51.
3. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011;123:2736-47.
4. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
5. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. Ann Intern Med 1991;115:256-65.
6. The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI II A results. JAMA 1988;260:2849-58.
7. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419-32.
8. Thiele H, Desch S, Piek JJ, et al. Multivessel versus culprit lesion only percutaneous revascularization plus potential staged revascularization in patients with acute myocardial infarction complicated by cardiogenic shock: Design and rationale of CULPRIT-SHOCK trial. Am Heart J 2016;172:160-9.
9. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
10. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 1, 2018 VOL. 379 NO. 18

# One-Year Outcomes after PCI Strategies in Cardiogenic Shock

H. Thiele, I. Akin, M. Sandri, S. de Waha-Thiele, R. Meyer-Saraei, G. Fuernau, I. Eitel, P. Nordbeck, T. Geisler, U. Landmesser, C. Skurk, A. Fach, A. Jobs, H. Lapp, J.J. Piek, M. Noc, T. Goslar, S.B. Felix, L.S. Maier, J. Stepinska, K. Oldroyd, P. Serpytis, G. Montalescot, O. Barthelemy, K. Huber, S. Windecker, L. Hunziker, S. Savonitto, P. Torremante, C. Vrints, S. Schneider, U. Zeymer, and S. Desch, for the CULPRIT-SHOCK Investigators*

## ABSTRACT

### BACKGROUND

Among patients with acute myocardial infarction, cardiogenic shock, and multivessel coronary artery disease, the risk of a composite of death from any cause or severe renal failure leading to renal-replacement therapy at 30 days was found to be lower with percutaneous coronary intervention (PCI) of the culprit lesion only than with immediate multivessel PCI. We evaluated clinical outcomes at 1 year.

### METHODS

We randomly assigned 706 patients to either culprit-lesion-only PCI or immediate multivessel PCI. The results for the primary end point of death or renal-replacement therapy at 30 days have been reported previously. Prespecified secondary end points at 1 year included death from any cause, recurrent myocardial infarction, repeat revascularization, rehospitalization for congestive heart failure, the composite of death or recurrent infarction, and the composite of death, recurrent infarction, or rehospitalization for heart failure.

### RESULTS

As reported previously, at 30 days, the primary end point had occurred in 45.9% of the patients in the culprit-lesion-only PCI group and in 55.4% in the multivessel PCI group (P=0.01). At 1 year, death had occurred in 172 of 344 patients (50.0%) in the culprit-lesion-only PCI group and in 194 of 341 patients (56.9%) in the multivessel PCI group (relative risk, 0.88; 95% confidence interval [CI], 0.76 to 1.01). The rate of recurrent infarction was 1.7% with culprit-lesion-only PCI and 2.1% with multivessel PCI (relative risk, 0.85; 95% CI, 0.29 to 2.50), and the rate of a composite of death or recurrent infarction was 50.9% and 58.4%, respectively (relative risk, 0.87; 95% CI, 0.76 to 1.00). Repeat revascularization occurred more frequently with culprit-lesion-only PCI than with multivessel PCI (in 32.3% of the patients vs. 9.4%; relative risk, 3.44; 95% CI, 2.39 to 4.95), as did rehospitalization for heart failure (5.2% vs. 1.2%; relative risk, 4.46; 95% CI, 1.53 to 13.04).

### CONCLUSIONS

Among patients with acute myocardial infarction and cardiogenic shock, the risk of death or renal-replacement therapy at 30 days was lower with culprit-lesion-only PCI than with immediate multivessel PCI, and mortality did not differ significantly between the two groups at 1 year of follow-up. (Funded by the European Union Seventh Framework Program and others; CULPRIT-SHOCK ClinicalTrials.gov number, NCT01927549.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Thiele at Heart Center Leipzig at University of Leipzig, Department of Internal Medicine–Cardiology, Strümpellstr. 39, 04289 Leipzig, Germany, or at holger.thiele@medizin.uni-leipzig.de.

*A complete list of the investigators in the CULPRIT-SHOCK trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Zeymer and Desch contributed equally to this article.

This article was published on August 25, 2018, at NEJM.org.

N Engl J Med 2018;379:1699-710.
DOI: 10.1056/NEJMoa1808788

Early revascularization has been shown to reduce mortality among patients with acute myocardial infarction that is complicated by cardiogenic shock.[1-3] Most patients with cardiogenic shock present with multivessel coronary artery disease,[4] which is associated with higher mortality than single-vessel disease.[5-7] For the treatment of patients with multivessel disease, current European guidelines for the management of acute ST-segment elevation myocardial infarction recommend immediate percutaneous coronary intervention (PCI) of both culprit and nonculprit lesions,[8] and U.S. appropriate-use criteria consider immediate revascularization of both culprit and nonculprit arteries during the same procedure to be highly appropriate.[9] However, the 30-day results of the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial[10] showed that the risk of a composite of death from any cause or severe renal failure leading to renal-replacement therapy was lower with culprit-lesion-only PCI than with immediate multivessel PCI, thus challenging the guideline recommendations. On the basis of these results, the European revascularization guidelines have now downgraded immediate multivessel PCI in cardiogenic shock to a class III B recommendation (i.e., a recommendation that the procedure is not useful and may be harmful, according to evidence from a single randomized trial).[11]

In light of the short-term results of the CULPRIT-SHOCK trial, the use of multivessel PCI in patients with cardiogenic shock is now controversial.[12,13] Although immediate multivessel PCI is associated with initial harm, the resulting complete revascularization could lead to a benefit over the long term. This possibility is supported by pooled evidence from nonrandomized trials showing that the higher short-term mortality with multivessel PCI than with culprit-lesion-only PCI was not sustained after longer-term follow-up.[14,15] Furthermore, a recent registry study suggested that there was lower mortality at 1 year with multivessel PCI than with culprit-lesion-only PCI.[16] Further data obtained during longer observation periods in randomized trials have been limited. Here, we report the 1-year results of the CULPRIT-SHOCK trial.

## Methods

### Trial Design and Oversight

The trial design and the short-term results have been published previously.[4,10] In summary, the CULPRIT-SHOCK trial was an investigator-initiated, multicenter, randomized, open-label, multicenter trial that compared culprit-lesion-only PCI (with optional staged revascularization) with immediate multivessel PCI in patients who had acute myocardial infarction that was complicated by cardiogenic shock. The protocol (available with the full text of this article at NEJM.org) was designed by the principal investigator and was modified and approved by the steering committee[4]; it was also approved by regional and national ethics review boards. The trial was registered at ClinicalTrials.gov 4 months after the enrollment of the first patient, as discussed in the Supplementary Appendix (available at NEJM.org).

Trial funding was provided by the European Union Seventh Framework Program, the German Heart Research Foundation, and the German Cardiac Society. Additional support was provided by the German Center for Cardiovascular Research. These institutions had no involvement in the conduct of the trial, as reported previously. Data were maintained and independent statistical analysis was performed by a coordinating research organization, Institut für Herzinfarktforschung (Institute for Myocardial Infarction Research). The steering committee vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The statistician vouches for the accuracy of the data analysis. The patient-level data, analytic methods, and trial materials cannot be made available to other researchers, because the European Union contract and the consortium agreement of the trial do not allow data sharing.

### Patients

Patients who had acute myocardial infarction that was complicated by cardiogenic shock, as described previously,[10] were eligible for the trial if they met the following criteria: planned early revascularization by means of PCI, multivessel coronary artery disease (defined as at least two major vessels [≥2 mm diameter] with >70% stenosis of the diameter), and an identifiable culprit lesion. Exclusion criteria were resuscitation for longer than 30 minutes, no intrinsic heart action, an assumed severe deficit in cerebral function with fixed dilated pupils, an indication for primary coronary-artery bypass grafting, single-vessel coronary artery disease, a mechanical cause of cardiogenic shock, the onset of shock more than 12 hours before randomization, an age of more than

90 years, shock with a noncardiogenic cause, massive pulmonary embolism, known severe renal insufficiency (creatinine clearance, <30 ml per minute), and other severe concomitant disease associated with a life expectancy of less than 6 months. Written informed consent was obtained with the use of a prespecified process (see the Supplementary Appendix).[4]

### RANDOMIZATION, TREATMENT, AND FOLLOW-UP

Patients underwent randomization immediately after diagnostic angiography. Randomization was performed centrally with the use of an Internet-based program with randomly changing blocks of 4 or 6 and stratification according to center.

Patients were randomly assigned, in a 1:1 ratio, to undergo either culprit-lesion-only PCI or immediate multivessel PCI. In all patients, the culprit lesion was treated first, with the use of standard PCI techniques and with the recommended use of drug-eluting stents. In patients in the culprit-lesion-only PCI group, all other lesions were to be left untreated at the time of the initial procedure. Staged revascularization was recommended on the basis of the patient's clinical status and the presence of residual ischemia on objective testing. In patients in the multivessel PCI group, all additional lesions (major coronary arteries with >70% stenosis of the diameter), including chronic total occlusions, were recommended to be treated with PCI immediately after treatment of the culprit lesion. In each group, the advised maximum dose of contrast material was 300 ml.

The use of mechanical circulatory support was left to the discretion of the operator. If renal-replacement therapy was deemed to be necessary, the method, duration, and reason for initiation were documented.

Trial-specific follow-up assessments were performed at 6 months and at 1 year by means of a structured telephone interview. Any potential end-point event was verified in a review of original records. In addition, death registries were searched to identify or confirm all deaths.

### END POINTS

The primary end point was a composite of death from any cause or severe renal failure leading to renal-replacement therapy within 30 days after randomization; results for this outcome have been reported previously.[10] For the 1-year analysis, results are reported for the following prespecified secondary end points: death from any cause, renal-replacement therapy, recurrent myocardial infarction, repeat revascularization, and rehospitalization for congestive heart failure. In addition, results are reported for the composite of death or recurrent infarction and for the composite of death, recurrent infarction, or rehospitalization for heart failure.

Safety end points included stroke and bleeding, which was defined as bleeding of type 2, 3, or 5 on the Bleeding Academic Research Consortium (BARC) scale (with type 2 indicating any overt, actionable sign of bleeding; type 3, bleeding with a decrease in the hemoglobin level of >3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; and type 5, fatal bleeding).[4,17] Quality of life was assessed with the European Quality of Life–5 Dimensions (EQ-5D) questionnaire (www.euroqol.org), including a visual-analogue scale, at 6 months and at 1 year. As a post hoc exploratory analysis, the primary end point of a composite of death or renal-replacement therapy was assessed at 1 year. Definitions of all end points are provided in the Supplementary Appendix. All end-point events were adjudicated by a clinical end-points committee whose members were unaware of the group assignments.

### STATISTICAL ANALYSIS

The sample-size calculation and the design for the 30-day analysis have been described previously and are summarized in the Supplementary Appendix.[4,10] For the 1-year analysis, data were included for all the patients who had at least 30 days of follow-up. All analyses were performed according to the intention-to-treat principle. The 1-year event rates were the percentages of patients who had an event within 365 days after randomization. Event rates were compared by chi-square tests. Robustness of results was evaluated in sensitivity analyses performed in the per-protocol and as-treated populations. End points that did not include death from any cause as a component were analyzed in all patients as well as in patients who survived. Kaplan–Meier curves are used to show event rates over time with classification according to group assignment. We also performed a post hoc landmark analysis using a cutoff point of 30 days after randomization, with hazard ratios calculated separately for events that occurred within 30 days and those that occurred between 30 days and 1 year.

Data from the quality-of-life assessment were analyzed, with chi-square tests, in patients who survived. Values on the visual-analogue scale were compared with Mann–Whitney U tests. Predefined subgroup analyses for 1-year mortality were performed, as described previously.[10] The resulting relative risks and 95% confidence intervals are presented in a forest plot. The Breslow–Day test was used to analyze the interaction between group assignment and subgroup.

No adjustment for multiple comparisons was performed for any of the analyses. P values are not reported, since all analyses presented here are for secondary end points. All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### PATIENTS

In total, 1075 patients with cardiogenic shock were screened at 83 centers, and 706 patients (65.7%) were randomly assigned to undergo culprit-lesion-only PCI (351 patients) or immediate multivessel PCI (355 patients) (Fig. 1). Full informed consent was obtained for 344 and 342 patients, respectively. One patient was lost to follow-up within 30 days, and one additional patient was lost to follow-up between 30 days and 1 year. Data on vital status were available at 1 year for 343 patients in the culprit-lesion-only PCI group and for 341 patients in the multivessel PCI group, exactly meeting the prespecified sample-size requirement of 684 patients after withdrawals.

The characteristics of the patients at baseline and procedural characteristics, including medications at discharge, are shown in Table 1 and Table 2, respectively. Immediate crossover occurred in 43 patients (12.5%) in the culprit-lesion-only PCI group and in 32 patients (9.4%) in the multivessel PCI group. Among patients who received stents, drug-eluting stents were used in 93.6% of the patients in the culprit-lesion-only PCI group and in 95.1% in the multivessel PCI group. There was no significant difference between the two groups in the Thrombolysis in Myocardial Infarction grade for epicardial perfusion before or after PCI of the culprit artery. The overall dose of contrast material was significantly greater and the duration of fluoroscopy was significantly longer in the multivessel PCI group than the culprit-lesion-only PCI group.

### CLINICAL END POINTS

As reported previously, at 30 days, the primary end point of a composite of death or renal-replacement therapy had occurred in 158 of 344 patients (45.9%) in the culprit-lesion-only PCI group and in 189 of 341 patients (55.4%) in the multivessel PCI group (relative risk, 0.83; 95% confidence interval [CI], 0.71 to 0.96; P=0.01). At 1 year, mortality did not differ significantly between the culprit-lesion-only PCI group and the multivessel PCI group; death from any cause had occurred in 172 of 344 patients (50.0%) and 194 of 341 patients (56.9%), respectively (relative risk, 0.88; 95% CI, 0.76 to 1.01) (Table 3 and Fig. 2A). Death from cardiovascular causes had occurred in 159 patients (46.2%) in the culprit-lesion-only PCI group and in 180 patients (52.8%) in the multivessel PCI group (relative risk, 0.88; 95% CI, 0.75 to 1.02). (For details on causes of death at 1 year, see Table S1 in the Supplementary Appendix.)

A post hoc landmark analysis revealed a difference between the two groups in mortality within the first 30 days (relative risk, 0.84; 95% CI, 0.72 to 0.98), but mortality was similar in the two groups thereafter (relative risk, 1.08; 95% CI, 0.60 to 1.93) (Fig. 2B). Between 30 days and 1 year, 23 patients (6.7%) died in the culprit-lesion-only PCI group and 18 patients (5.3%) died in the multivessel PCI group. Results for mortality between baseline and 1 year in the intention-to-treat population were similar to results in the per-protocol population (relative risk, 0.87; 95% CI, 0.75 to 1.02) and the as-treated population (relative risk, 0.90; 95% CI, 0.78 to 1.03). Predefined subgroup analyses revealed consistency of the results across all subgroups (Fig. S1 in the Supplementary Appendix).

Events leading to renal-replacement therapy occurred only within the first 30 days, with no further events recorded between 30 days and 1 year of follow-up. Such an event occurred in 11.6% of the patients in the culprit-lesion-only PCI group and in 16.4% in the multivessel PCI group (relative risk, 0.71; 95% CI, 0.49 to 1.03) (Table 3). Recurrent myocardial infarction occurred in 1.7% of the patients in the culprit-lesion-only PCI group and in 2.1% in the multivessel PCI group (relative risk, 0.85; 95% CI, 0.29 to 2.50), and the composite of death or recurrent infarction was observed in 50.9% and 58.4%, respectively (relative risk, 0.87; 95% CI, 0.76 to 1.00)

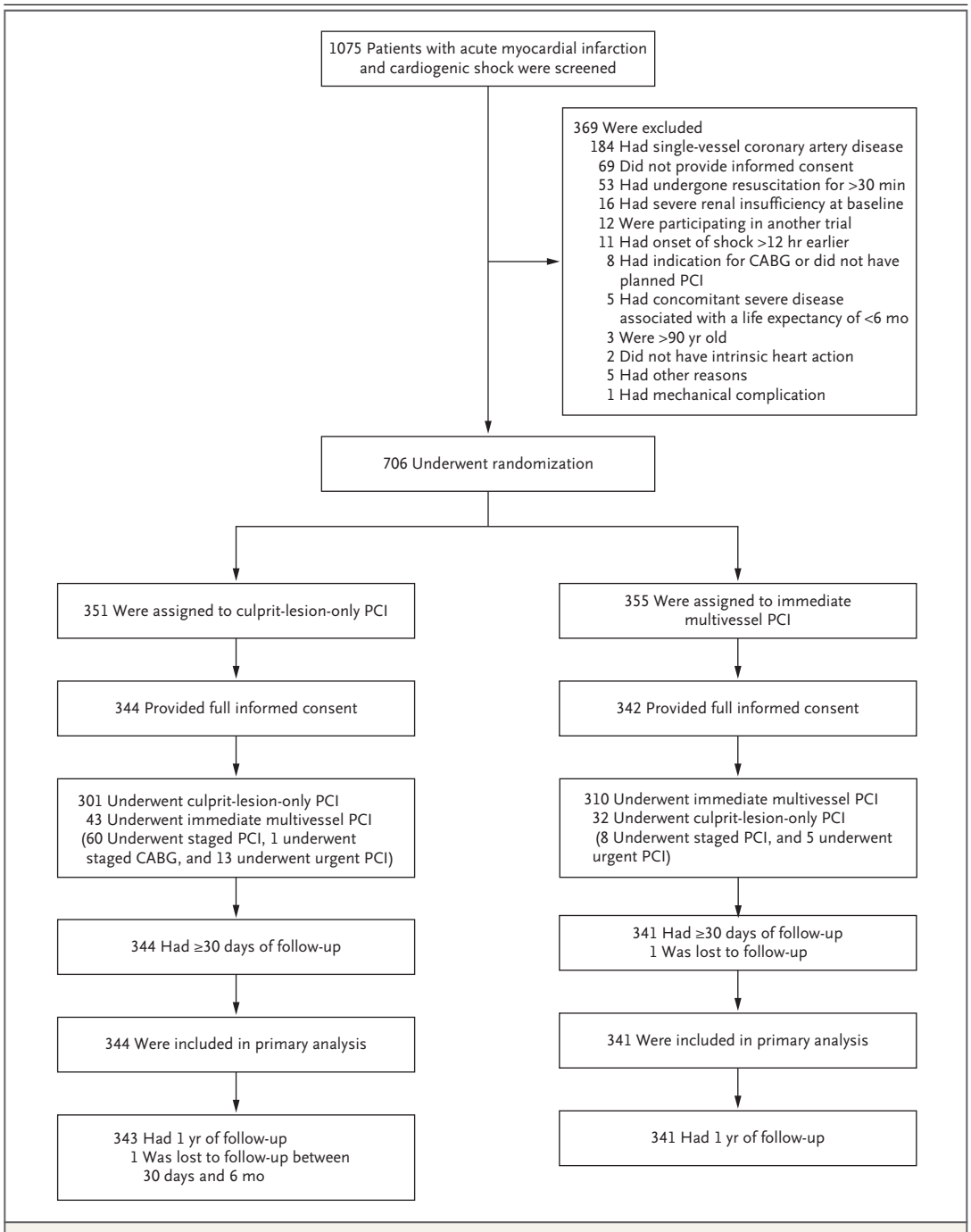



**Figure 1. Screening, Randomization, Treatment, and Follow-up at 30 Days and at 1 Year in the Intention-to-Treat Population.**

CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

(Table 3, and Fig. S2 in the Supplementary Appendix).

Repeat revascularization was performed more often with the culprit-lesion-only PCI strategy than with the multivessel PCI strategy (in 32.3% of the patients vs. 9.4%; relative risk, 3.44; 95% CI, 2.39 to 4.95) (Table 3, and Fig. S3 in the Supplementary Appendix). Although there were

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=342) |
|---|---|---|
| Age — yr | | |
| Median | 70 | 70 |
| Interquartile range | 60–78 | 60–77 |
| Male sex — no./total no. (%) | 257/343 (74.9) | 267/342 (78.1) |
| Body-mass index† | | |
| Median | 26.6 | 26.7 |
| Interquartile range | 24.2–29.4 | 24.7–29.4 |
| Cardiovascular risk factors — no./total no. (%) | | |
| Current smoking | 85/334 (25.4) | 89/325 (27.4) |
| Hypertension | 200/339 (59.0) | 206/335 (61.5) |
| Hypercholesterolemia | 112/338 (33.1) | 116/333 (34.8) |
| Diabetes mellitus | 102/337 (30.3) | 116/335 (34.6) |
| Previous myocardial infarction — no./total no. (%) | 60/339 (17.7) | 53/335 (15.8) |
| Previous stroke — no./total no. (%) | 29/341 (8.5) | 20/336 (6.0) |
| Known peripheral artery disease — no./total no. (%) | 43/341 (12.6) | 37/337 (11.0) |
| Previous PCI — no./total no. (%) | 64/339 (18.9) | 63/335 (18.8) |
| Previous coronary-artery bypass grafting — no./total no. (%) | 20/341 (5.9) | 13/337 (3.9) |
| Resuscitation before randomization — no./total no. (%) | 177/341 (51.9) | 189/342 (55.3) |
| ST-segment elevation myocardial infarction — no./total no. (%) | 206/335 (61.5) | 209/330 (63.3) |
| Systolic blood pressure — mm Hg | | |
| Median | 100 | 100 |
| Interquartile range | 83–120 | 85–130 |
| Diastolic blood pressure — mm Hg | | |
| Median | 60 | 61 |
| Interquartile range | 50–80 | 50–80 |
| Mean blood pressure — mm Hg | | |
| Median | 76 | 76 |
| Interquartile range | 63–92 | 63–93 |
| Use of catecholamine — no./total no. (%) | 304/344 (88.4) | 309/339 (91.2) |
| Creatinine — mg/dl‡ | | |
| Median | 1.17 | 1.20 |
| Interquartile range | 0.90–1.66 | 0.90–1.68 |
| Creatinine clearance — ml/min | | |
| Median | 64 | 66 |
| Interquartile range | 42–95 | 43–93 |
| No. of affected vessels — no./total no. (%) | | |
| 1 | 3/343 (0.9) | 2/342 (0.6) |
| 2 | 122/343 (35.6) | 124/342 (36.3) |
| 3 | 218/343 (63.6) | 216/342 (63.2) |

**Table 1. (Continued.)**

| Characteristic | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=342) |
|---|---|---|
| Vessel related to the infarction — no./total no. (%) | | |
| Left anterior descending artery | 132/343 (38.5) | 156/342 (45.6) |
| Left circumflex artery | 76/343 (22.2) | 70/342 (20.5) |
| Right coronary artery | 102/343 (29.7) | 89/342 (26.0) |
| Left main artery | 31/343 (9.0) | 22/342 (6.4) |
| Bypass graft | 2/343 (0.6) | 5/342 (1.5) |
| ≥1 Chronic total occlusion — no./total no. (%) | 77/344 (22.4) | 82/342 (24.0) |
| Left ventricular ejection fraction — % | | |
| Median | 33 | 30 |
| Interquartile range | 25–40 | 21–40 |

* There were no significant differences between the two groups in baseline characteristics. PCI denotes percutaneous coronary intervention.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

few cases of rehospitalization for congestive heart failure, the rate was higher in the culprit-lesion-only PCI group than in the multivessel PCI group (5.2% vs. 1.2%; relative risk, 4.46; 95% CI, 1.53 to 13.04) (Table 3, and Fig. S4 in the Supplementary Appendix).

The rate of the composite of death, recurrent infarction, or rehospitalization for heart failure did not differ significantly between the two groups (Table 3, and Fig. S5 in the Supplementary Appendix). In addition, the rates for safety end points did not differ significantly between the two groups (Table 3). The original primary end point of a composite of death or renal-replacement therapy was evaluated in a post hoc analysis at 1 year; an end-point event occurred in 52.0% of the patients in the culprit-lesion-only PCI group and in 59.5% in the multivessel PCI group (relative risk, 0.87; 95% CI, 0.76 to 0.99) (Table 3, and Fig. S6 in the Supplementary Appendix).

EQ-5D values were obtained for 286 of the 317 patients who survived. Results on the quality-of-life assessment, including the visual-analogue scale, at 6 months and at 1 year did not differ significantly between the two groups (Figs. S7 and S8 in the Supplementary Appendix).

## DISCUSSION

This multicenter, randomized trial compared culprit-lesion-only PCI (with the option of staged revascularization) with immediate multivessel PCI in patients with acute myocardial infarction, cardiogenic shock, and multivessel coronary artery disease. We previously reported that the risk of a composite of death from any cause or renal-replacement therapy was lower with culprit-lesion-only PCI than with multivessel PCI in the 30-day analysis of this trial. In the analysis reported here, we found that mortality did not differ significantly between the two groups at 1 year. However, the rates of rehospitalization for heart failure and repeat revascularization were higher in the culprit-lesion-only PCI group than the multivessel PCI group at 1 year.

The major randomized trials for cardiogenic shock showed that death in patients with cardiogenic shock was mainly confined to the first 30 days, with mortality during that period ranging from 39.7 to 46.7%, depending on the cohorts of patients included in the trial, the revascularization strategy, and the standard method for revascularization during that time.[2,18,19] Mortality between 30 days and 1 year was 6.6% in the Should We Emergently Revascularize Occluded

**Table 2. Procedural Characteristics.**

| Variable | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=342) | P Value |
|---|---|---|---|
| Arterial access — no./total no. (%) | | | |
| Femoral | 287/343 (83.7) | 277/342 (81.0) | 0.36 |
| Radial | 61/343 (17.8) | 66/342 (19.3) | 0.61 |
| Brachial | 2/343 (0.6) | 1/342 (0.3) | >0.99 |
| Stent in culprit lesion — no./total no. (%) | | | |
| Any | 326/343 (95.0) | 324/342 (94.7) | 0.86 |
| Bare metal | 20/326 (6.1) | 17/324 (5.2) | 0.63 |
| Drug eluting | 305/326 (93.6) | 308/324 (95.1) | 0.41 |
| Bioresorbable scaffold in culprit lesion — no./total no. (%) | 2/326 (0.6) | 3/324 (0.9) | 0.69 |
| TIMI grade for blood flow — no./total no. (%)* | | | |
| Before PCI of culprit lesion | | | 0.49 |
| 0 | 189/339 (55.8) | 178/337 (52.8) | |
| I | 37/339 (10.9) | 45/337 (13.4) | |
| II | 56/339 (16.5) | 50/337 (14.8) | |
| III | 57/339 (16.8) | 64/337 (19.0) | |
| After PCI of culprit lesion | | | 0.46 |
| 0 | 13/342 (3.8) | 16/338 (4.7) | |
| I | 12/342 (3.5) | 8/338 (2.4) | |
| II | 28/342 (8.2) | 21/338 (6.2) | |
| III | 289/342 (84.5) | 293/338 (86.7) | |
| Immediate PCI of nonculprit lesions — no./total no. (%) | 43/344 (12.5) | 310/342 (90.6) | <0.001 |
| Immediate complete revascularization achieved — no./total no. (%) | 26/344 (7.6) | 277/342 (81.0) | <0.001 |
| Total dose of contrast material — ml | | | <0.001 |
| Median | 190 | 250 | |
| Interquartile range | 140–25 | 200–350 | |
| Total duration of fluoroscopy — min | | | <0.001 |
| Median | 13 | 19 | |
| Interquartile range | 7–20 | 12–29 | |
| Staged PCI of nonculprit lesions within 30 days — no./total no. (%) | 60/344 (17.4) | 8/341 (2.3) | <0.001 |
| Staged coronary-artery bypass grafting within 30 days — no./total no. (%) | 1/344 (0.3) | 0/341 (0) | >0.99 |
| Mechanical circulatory support — no./total no. (%) | 99/344 (28.8) | 95/342 (27.8) | 0.77 |
| Mechanical ventilation — no./total no. (%) | 273/344 (79.4) | 282/339 (83.2) | 0.20 |
| Subsequent medications in patients who survived until hospital discharge — no./total no. (%) | | | |
| Statin | 184/195 (94.4) | 152/165 (92.1) | 0.40 |
| Beta-blocker | 181/195 (92.8) | 148/165 (89.7) | 0.29 |
| Angiotensin-converting–enzyme inhibitor or angiotensin II type 1 receptor antagonist | 176/195 (90.3) | 140/165 (84.8) | 0.12 |
| Aspirin | 191/195 (97.9) | 163/165 (98.8) | 0.54 |
| Clopidogrel | 89/195 (45.6) | 73/165 (44.2) | 0.79 |
| Prasugrel | 67/195 (34.4) | 56/165 (33.9) | 0.93 |
| Ticagrelor | 78/195 (40.0) | 65/165 (39.4) | 0.91 |

* Thrombolysis in Myocardial Infarction (TIMI) grades for blood flow range from 0 to III, with higher grades indicating better flow. TIMI grades were reported by the investigator.

**Table 3. Clinical and Safety Outcomes at 1 Year.***

| Outcome | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=341) | Relative Risk (95% CI) |
|---|---|---|---|
| | *no. (%)* | | |
| Death from any cause† | 172 (50.0) | 194 (56.9) | 0.88 (0.76–1.01) |
| Renal-replacement therapy‡ | 40 (11.6) | 56 (16.4) | 0.71 (0.49–1.03) |
| Recurrent myocardial infarction | 6 (1.7) | 7 (2.1) | 0.85 (0.29–2.50) |
| Death or recurrent infarction | 175 (50.9) | 199 (58.4) | 0.87 (0.76–1.00) |
| Rehospitalization for congestive heart failure | 18 (5.2) | 4 (1.2) | 4.46 (1.53–13.04) |
| Death, recurrent infarction, or rehospitalization for heart failure | 190 (55.2) | 203 (59.5) | 0.87 (0.93–1.06) |
| Repeat revascularization | | | |
| Any | 111 (32.3) | 32 (9.4) | 3.44 (2.39–4.95) |
| PCI | 107 (31.1) | 29 (8.5) | 3.66 (2.50–5.36) |
| Coronary-artery bypass grafting | 4 (1.2) | 3 (0.9) | 1.32 (0.30–5.86) |
| Death or renal-replacement therapy | 179 (52.0) | 203 (59.5) | 0.87 (0.76–0.99) |
| Stroke | 15 (4.4) | 14 (4.1) | 1.06 (0.52–2.17) |
| Bleeding | | | |
| Any | 75 (21.8) | 86 (25.2) | 0.86 (0.66–1.13) |
| BARC type 2, 3, or 5§ | 65 (18.9) | 79 (23.2) | 0.82 (0.61–1.09) |

* Confidence intervals were not adjusted for multiple comparisons, and clinical inferences may not be reproducible. Results for clinical end points that were analyzed only for patients who survived are shown in Table S2 in the Supplementary Appendix.
† Causes of death are shown in Table S1 in the Supplementary Appendix.
‡ Renal-replacement therapy was defined as any treatment that included dialysis, hemofiltration, or hemodiafiltration.
§ On the Bleeding Academic Research Consortium (BARC) scale, type 2 indicates any overt, actionable sign of bleeding; type 3, bleeding with a decrease in the hemoglobin level of more than 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; and type 5, fatal bleeding.

Coronaries for Cardiogenic Shock (SHOCK) trial and 12.3% in the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial.[20,21] These rates are similar to the 6.6% mortality between 30 days and 1 year that was reported in this trial. The results of the landmark analysis showed a benefit of culprit-lesion-only PCI over multivessel PCI with respect to short-term mortality, and there was no statistical difference between the two groups in mortality thereafter. These findings do not support the hypothesis that immediate multivessel PCI is associated with a higher short-term risk of death than culprit-lesion-only PCI but with a diminished risk during the longer-term course.[22]

The rate of rehospitalization for heart failure was higher in the culprit-lesion-only PCI group than in the multivessel PCI group, although the rates were low in both groups and the absolute difference in risk between the two groups was small. It is possible that this finding could be related to the higher rate of complete revascularization in the multivessel PCI group than in the culprit-lesion-only PCI group, with complete revascularization leading to subsequent improved ventricular function and a lower subsequent incidence of heart failure. However, this interpretation is only speculative, since, to our knowledge, no randomized trials have addressed this issue and data on ventricular function were not obtained in this trial. The higher rate of rehospitalization for heart failure in the culprit-lesion-only PCI group could also be a consequence of competing risks. Patients with cardiogenic shock are at an extreme risk for death, and if they die early, they therefore do not survive long enough for heart failure to develop in the longer-term course. Accordingly, because culprit-lesion-only PCI has shown a benefit over multivessel PCI with respect to short-term survival, the risk of

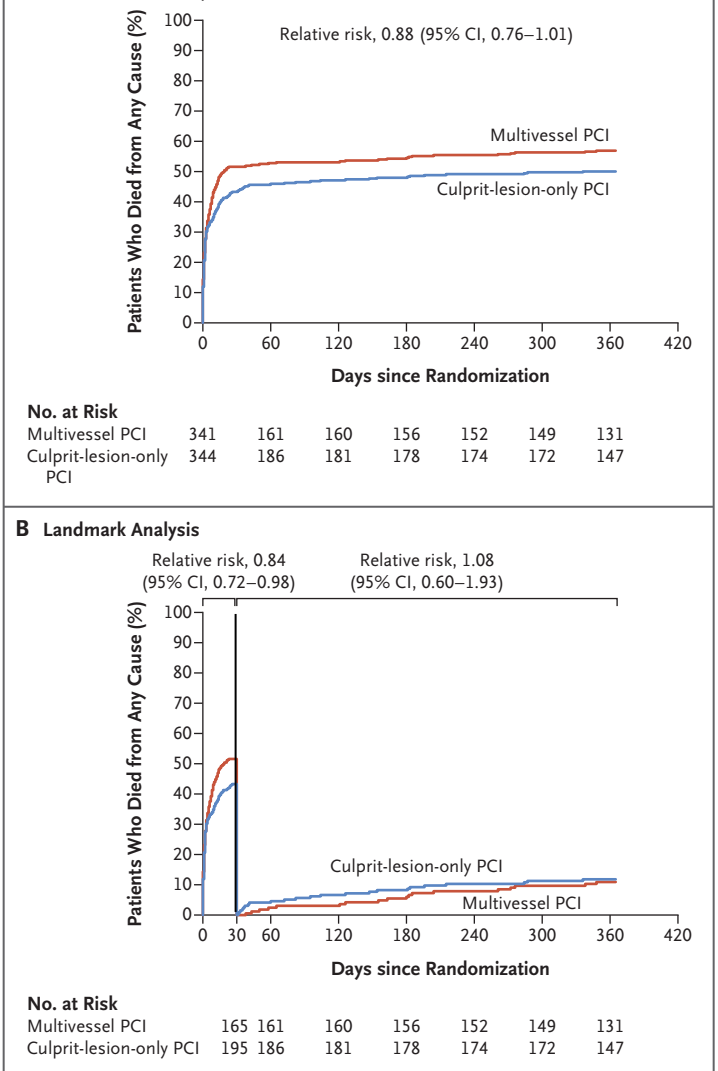



**Figure 2. Time-to-Event and Landmark Analyses for Death from Any Cause through 1 Year.**

Panel A shows Kaplan–Meier estimates of the rate of death from any cause through 1 year. Panel B shows the results of a landmark analysis of the rate of death from any cause through 30 days, as well as the rate between 30 days and 1 year.

heart failure within the first year may be higher with culprit-lesion-only PCI than with multivessel PCI.

In previous studies involving patients with acute myocardial infarction who did not have cardiogenic shock, the differences in outcomes between those who underwent culprit-lesion-only PCI and those who underwent immediate multivessel or early staged PCI were driven mainly by a difference in the rate of repeat revascularization and not by differences in rates of hard end points, such as death or recurrent infarction. Among patients who have cardiogenic shock, the short-term risks that are associated with longer procedure times, more complex initial interventions, and higher doses of contrast material seem to outweigh any potential benefits associated with reducing the subsequent risk of repeat revascularization. In this trial, after 1 year, 32.3% of the patients in the culprit-lesion-only PCI group had undergone staged or urgent repeat revascularization. This rate is higher than rates seen in trials of revascularization strategies in patients who did not have cardiogenic shock, which range from 8.2 to 17.4% at 1 year of follow-up.[23-26] The higher rate of repeat revascularization in the culprit-lesion-only PCI group in this trial may be related to the extent of coronary artery disease, the presence of impaired left ventricular function, and the severity of illness in patients with cardiogenic shock, as well as to the trial design. It is unclear whether an even higher rate of revascularization of nonculprit lesions could have prevented rehospitalizations for heart failure.

This trial has several limitations. First, all the end points in the 1-year analysis are exploratory because the trial was powered for the 30-day analysis of the primary composite end point. Second, blinding was not possible owing to the nature of the intervention performed. Management of cardiogenic shock involves a complex series of clinical decisions, and residual bias in the course of such management cannot be ruled out. Third, the results of serial echocardiography to assess cardiac function were not available, and such results would have allowed us to explore potential underlying causes of the initial higher mortality with multivessel PCI and the subsequent higher rate of rehospitalization for heart failure with culprit-lesion-only PCI.

In conclusion, this multicenter, randomized trial compared culprit-lesion-only PCI (with the option of staged revascularization) with immediate multivessel PCI in patients with acute myocardial infarction, cardiogenic shock, and multivessel coronary artery disease. At 30 days, the risk of a composite of death from any cause or renal-replacement therapy was significantly lower with culprit-lesion-only PCI than with multivessel PCI. At 1 year, mortality did not differ significantly between the two groups. However,

the incidence of rehospitalization for heart failure was higher and repeat revascularization was more frequent with culprit-lesion-only PCI than with multivessel PCI at 1 year.

Supported by a grant agreement (602202) from the European Union Seventh Framework Program and by the German Heart Research Foundation and the German Cardiac Society. Also supported by the German Center for Cardiovascular Research.

Dr. Landmesser reports receiving lecture fees and advisory-board fees from Abbott and Biotronik; Dr. Piek, serving on an advisory board and receiving travel support from Abbott Vascular, and receiving consulting fees, advisory-board fees, and travel support from Philips (Volcano); Dr. Noc, receiving consulting fees from Zoll Circulation, lecture fees from Maquet (Getinge), and grant support from AstraZeneca; Dr. Goslar, receiving lecture fees from AstraZeneca; Dr. Montalescot, receiving grant support and lecture fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Sanofi-Aventis, and Servier, grant support from Bristol-Myers Squibb, Ican, Medtronic, and INSERM (Institut National de la Santé et de la Recherche Médicale), grant support and advisory-board fees from MSD, consulting fees from Menarini, the TIMI (Thrombolysis in Myocardial Infarction) Study Group, and Actelion, lecture fees from CME Resources, Europa, Lead-Up, and WebMD, and fees for review from Elsevier; Dr. Windecker, receiving grant support from Biotronik, Boston Scientific, Bracco, Edwards Lifesciences, Medtronic, Terumo, and St. Jude Medical; Dr. Savonitto, receiving grant support from Novartis, Daiichi Sankyo, and Eli Lilly, and lecture fees from Pfizer, Bristol-Myers Squibb, AstraZeneca, and Bayer; and Dr. Zeymer, receiving lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Sanofi, MSD, The Medicines Company, Pfizer, Daiichi Sankyo, Eli Lilly, and Abiomed. No other potential conflict of interest relevant to this article was reported.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who agreed to participate in this trial and their relatives, the trial contributors, and the investigators who recruited the patients.

## APPENDIX

The authors' full names and academic degrees are as follows: Holger Thiele, M.D., Ibrahim Akin, M.D., Marcus Sandri, M.D., Suzanne de Waha-Thiele, M.D., Roza Meyer-Saraei, Ph.D., Georg Fuernau, M.D., Ingo Eitel, M.D., Peter Nordbeck, M.D., Tobias Geisler, M.D., Ulf Landmesser, M.D., Carsten Skurk, M.D., Andreas Fach, M.D., Alexander Jobs, M.D., Harald Lapp, M.D., Ph.D., Jan J. Piek, M.D., Ph.D., Marko Noc, M.D., Tomaž Goslar, M.D., Stephan B. Felix, M.D., Lars S. Maier, M.D., Janina Stepinska, M.D., Keith Oldroyd, M.D., Pranas Serpytis, M.D., Gilles Montalescot, M.D., Olivier Barthelemy, M.D., Kurt Huber, M.D., Stephan Windecker, M.D., Lukas Hunziker, M.D., Stefano Savonitto, M.D., Patrizia Torremante, B.A., Christiaan Vrints, M.D., Steffen Schneider, Ph.D., Uwe Zeymer, M.D., and Steffen Desch, M.D.

The authors' affiliations are as follows: Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig (H.T., M.S., A.J., S.D.), Universitätsmedizin Mannheim, Mannheim (I.A.), University Heart Center Lübeck, Lübeck (S.W.-T., R.M.-S., G.F., I.E.), German Center for Cardiovascular Research (I.A., S.W.-T., R.M.-S., G.F., I.E., U.L., C.S., A.J., S.B.F., S.D.) and Universitätsklinikum Charité, Campus Benjamin Franklin (U.L., C.S.), Berlin, Universitätsklinikum Würzburg, Würzburg (P.N.), Klinikum der Eberhard-Karls-Universität Tübingen, Tübingen (T. Geisler), Klinikum Links der Weser, Bremen (A.F.), Helios Klinik Erfurt, Erfurt (H.L.), Ernst-Moritz-Arndt-Universität, Greifswald (S.B.F.), Universitäres Herzzentrum Regensburg, Regensburg (L.S.M.), and Institut für Herzinfarktforschung (S. Schneider, U.Z.) and Klinikum Ludwigshafen (U.Z.), Ludwigshafen — all in Germany; Academic Medical Center, Amsterdam (J.J.P.); University Medical Center Ljubljana, Ljubljana, Slovenia (M.N., T. Goslar); Institute of Cardiology, Warsaw, Poland (J.S.); Golden Jubilee National Hospital, Glasgow, United Kingdom (K.O.); Vilnius University Hospital Santaros Klinikos and Faculty of Medicine, Vilnius University, Vilnius, Lithuania (P.S.); Sorbonne Université Paris 6, ACTION Study Group, Centre Hospitalier Universitaire Pitié–Salpêtrière (G.M., O.B.), and Applied Research, Technology Transfer, Industrial Collaboration, Société par Actions Simplifiée (P.T.), Paris; Wilhelminenpital, Department of Cardiology, and Sigmund Freud University, Medical School, Vienna (K.H.); the Department of Cardiology, Inselspital Bern, University of Bern, Bern, Switzerland (S.W., L.H.); Manzoni Hospital, Lecco, Italy (S. Savonitto); and Universitair Ziekenhuis Antwerp, Antwerp, Belgium (C.V.).

## REFERENCES

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295:2511-5.
2. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
3. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. Eur Heart J 2015;36:1223-30.
4. Thiele H, Desch S, Piek JJ, et al. Multivessel versus culprit lesion only percutaneous revascularization plus potential staged revascularization in patients with acute myocardial infarction complicated by cardiogenic shock: design and rationale of CULPRIT-SHOCK trial. Am Heart J 2016;172:160-9.
5. Sanborn TA, Sleeper LA, Webb JG, et al. Correlates of one-year survival inpatients with cardiogenic shock complicating acute myocardial infarction: angiographic findings from the SHOCK trial. J Am Coll Cardiol 2003;42:1373-9.
6. Webb JG, Lowe AM, Sanborn TA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol 2003;42:1380-6.
7. Wong SC, Sanborn T, Sleeper LA, et al. Angiographic findings and clinical correlates in patients with cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. J Am Coll Cardiol 2000;36:Suppl A:1077-83.
8. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation: the Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
9. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:570-91.

**10.** Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419-32.
**11.** Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2018 August 25 (Epub ahead of print).
**12.** Ibanez B, Halvorsen S, Roffi M, et al. Integrating the results of the CULPRIT-SHOCK trial in the 2017 ESC ST-elevation myocardial infarction guidelines: viewpoint of the task force. Eur Heart J 2018 May 29 (Epub ahead of print).
**13.** Thiele H, Desch S. CULPRIT-SHOCK (culprit lesion only PCI versus multivessel percutaneous coronary intervention in cardiogenic shock): implications on guideline recommendations. Circulation 2018;137:1314-6.
**14.** de Waha S, Jobs A, Eitel I, et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2018;7:28-37.
**15.** Kolte D, Sardar P, Khera S, et al. Culprit vessel-only versus multivessel percutaneous coronary intervention in patients with cardiogenic shock complicating ST-segment-elevation myocardial infarction: a collaborative meta-analysis. Circ Cardiovasc Interv 2017;10(11):e005582.
**16.** Lee JM, Rhee T-M, Hahn J-Y, et al. Multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction with cardiogenic shock. J Am Coll Cardiol 2018;71:844-56.
**17.** Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
**18.** Alexander JH, Reynolds HR, Stebbins AL, et al. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. JAMA 2007;297:1657-66.
**19.** Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287-96.
**20.** Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. JAMA 2001;285:190-2.
**21.** Thiele H, Zeymer U, Neumann F-J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet 2013;382:1638-45.
**22.** Gershlick AH, Banning AS. What can we do about cardiogenic shock? Circ Cardiovasc Interv 2017;10(11):e006020.
**23.** Smits PC, Abdel-Wahab M, Neumann F-J, et al. Fractional flow reserve–guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017;376:1234-44.
**24.** Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115-23.
**25.** Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963-72.
**26.** Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3–PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665-71.

# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med. DOI: 10.1056/NEJMoa1710261

**SUPPLEMENTARY APPENDIX**

**TABLE OF CONTENTS**


| | | |
|---|---|---|
| 1) | Table of Contents | Page 1 |
| 2) | Participating Investigators and Trial Committees | Page 2-7 |
| 3) | Trial Registration | Page 8 |
| 4) | Informed Consent Process in Participating Countries | Page 9-10 |
| 5) | Outcome Definitions | Page 11-15 |
| 6) | List of End Points | Page 16 |
| 7) | Figure S1 – Trial Flow | Page 17 |
| 8) | Figure S2 – Simplified Acute Physiology Score – II | Page 18 |
| 9) | Figure S3 – Arterial Lactate | Page 19 |
| 10) | Figure S4 – Renal Function | Page 20 |
| 11) | Figure S5 – High-Sensitive Troponin T | Page 21 |
| 12) | Figure S6 – Creatine Kinase | Page 22 |
| 13) | Table S1 – Individual Case Reports of Cross-overs from Culprit-Only PCI to Immediate Multivessel PCI | Page 23 |
| 14) | Table S2 – Individual Case Reports of Cross-overs from Immediate Multivessel PCI to Culprit-Only PCI | Page 25 |
| 15) | Table S3 – Causes of Death at 30 Days | Page 27 |
| 16) | Table S4 – Clinical Outcomes at 30 Days for Registry Patients | Page 28 |
| 17) | References | Page 29-30 |

## 2) Participating Investigators and Trial Committees

The following investigators and institutions participated in the CULPRIT-SHOCK trial:

**Steering Committee**: Holger Thiele (principal investigator and chair), Heart Center Leipzig – University Hospital, Leipzig, Germany; Steffen Desch, Heart Center Leipzig – University Hospital, Leipzig, Germany; Uwe Zeymer, Klinikum Ludwigshafen and Institut für Herzinfarktforschung, Ludwigshafen, Germany; Gilles Montalescot, ACTION group, Paris, France; Jan J. Piek, Academic Medical Center, Amsterdam, The Netherlands; Patrizia Torremante, ARTTIC, Munich, Germany.

**Project Management:** Patrizia Torremante, ARTTIC, Munich, Germany; Roza Meyer-Saraei, University Hospital Schleswig-Holstein, Lübeck, Germany.

**Clinical Endpoints Committee:** Ulrich Tebbe (chair), Detmold, Germany; Jochen Wöhrle, University of Ulm, Germany; Otmar Pachinger, University of Innsbruck, Innsbruck, Austria.

**Data Monitoring:** Institut für Herzinfarktforschung, Ludwigshafen, Germany: Clemens Busch (chair); Nathalie Pfeiffer.

**Data Management:** Institut für Herzinfarktforschung, Ludwigshafen, Germany: Alexander Neumer, Clemens Busch, Nathalie Pfeiffer.

**Data Coordination and Analysis:** Institut für Herzinfarktforschung, Ludwigshafen, Germany: Steffen Schneider (chair statistics); Taoufik Ouarrak (statistics), Thomas Reimer (statistics), Christiane Lober (statistics).

**Data Safety Monitoring Board:** Peter Clemmensen, MD (chair), Universitäres Herzzentrum Hamburg, Hamburg, Germany; Ferenc Follath, MD, University of Zurich, Zurich, Switzerland; Karl Wegscheider, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

**Angiographic Core Laboratory Committee (ACLC) at the ACTION Study Group**: Dr O. Barthélémy (chair), Dr. M. Zeitouni, Dr. P. Overtchouk, Dr P. Guedeney, Dr. G. Hage, Dr. Hauguel-Moreau.

**Study sites and hospitals:**

**Germany; national coordinator: Holger Thiele, Leipzig**

University Heart Center Luebeck, Germany: Georg Fuernau, Ingo Eitel, Roza Meyer-Saraei, Suzanne de Waha: 58 patients and 36 registry patients; Heart Center Leipzig – University of Leipzig, Germany: Holger Thiele, Steffen Desch, Marcus Sandri, Sabrina Weinschenk: 70 patients and 50 registry patients; Universitätsmedizin Mannheim, Mannheim, Germany: Ibrahim Akin, Martin Borggrefe: 75 patients and 5 registry patients; Heart Center Bad Krozingen, Bad Krozingen, Germany: Franz-Josef Neumann, Miroslaw Ferenc: 9 patients and 9 registry patients; Asklepios Klinik Langen, Langen, Germany: Hans-Gerd Olbrich, Hans-Bernd Hopf: 4 patients and 1 registry patient; German Heart Center Munich, Munich, Germany: Adnan Kastrati, Antoinette de Waha, Heribert Schunkert: 1 patient and 0 registry patients; Heart Center - Segeberger Kliniken, Bad Segeberg, Germany: Gert Richardt, Bettina Schwarz, Mohamed Abdel-Wahab, Ralph Toelg, Volker Geist, Monika Bahnsen-Maaß: 6 patients and 2 registry patients; SLK Kliniken Heilbronn, Heilbronn, Germany: Marcus Hennersdorf, Jochen Graf, Urs Riemann, Dominik Scharpf: 3 patients and 0 registry patients; University of Greifswald, Greifswald, Germany: Klaus Empen, Mathias C Busch, Stephan B. Felix: 15 patients and 4 registry patients; Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany: Karl Werdan, Sebastian Nuding: 6 patients and 0 registry patients; Klinikum Links der Weser, Bremen, Germany: Rainer Hambrecht, Andreas Fach, Eduard Fiehn: 25 patients and 11 registry patients; Heart Center Ludwigshafen, Ludwigshafen, Germany: Uwe Zeymer, Anselm K. Gitt, Bernd Mark, Ralph Winkler: 9 patients and 15 registry patients; Zentralklinik Bad Berka, Bad Berka, Germany: Bernward Lauer: 1 patient and 0 registry patients; Friedrich-Schiller University Jena, Jena, Germany: Sven Möbius-Winkler, Christian Schulze: 12 patients and 1 registry patient; Klinik Hennigsdorf, Hennigsdorf, Germany: Hans-Heinrich Minden: 5 patients and 4 registry patients; Otto-von-Guericke-University Magdeburg: Rüdiger C. Braun-Dullaeus, Alexander Schmeißer: 2 patients and 5 registry patients; Heart Center Dresden, Dresden, Germany: Ruth H. Strasser, Bernd Ebner: 3 patients and 0 registry patients; Universitätsklinikum Würzburg, Würzburg, Germany: Georg Ertl, Peter Nordbeck: 51 patients and 11 registry patients; Hospital München – Neuperlach: Harald Mudra, Martin Hug: 4 patients and 0 registry patients; Universitätsklinikum Regensburg, Regensburg, Germany: Dierk

Endemann, Lars Maier: 9 patients and 8 registry patients; Charité Berlin Campus Benjamin Franklin, Berlin, Germany: Ulf Landmesser, Carsten Skurk: 24 patients and 0 registry patients; Kerckhoff Klinik Bad Nauheim, Bad Nauheim, Germany: Christian Hamm, Claudia Walther, Christoph Liebetrau: 7 patients and 0 registry patients; Helios Klinikum Erfurt, Erfurt, Germany: Harald Lapp, Niels Menck: 22 patients and 8 registry patients; Ludwigs-Maximilian University Munich – Hospital Großhadern: Julinda Mehilli, Martin Orban, Jörg Hausleiter, Steffen Massberg: 12 patients and 8 registry patients; Carl-von-Basedow-Klinikum Merseburg, Merseburg, Germany: Roland Prondzinsky: 2 patients and 0 registry patients; Klinikum Lippe-Detmold, Detmold, Germany: Ulrich Tebbe, Stephan Gielen: 1 patient and 10 registry patients; Universitätsklinikum Tübingen, Tübingen, Germany: Meinrad Gawaz, Tobias Geisler: 26 patients and 0 registry patients; Klinikum Nürnberg, Nürnberg, Germany: Matthias Pauschinger, Fadil Ademaj: 12 patients and 0 registry patients; Universitäts-Herzzentrum Freiburg, Freiburg, Germany: Christoph Bode: 11 patients and 2 registry patients; Universitätsklinikum Bonn, Bonn, Germany: Georg Nickenig: 9 patients and 0 registry patients; Universitätsklinikum Frankfurt am Main; Frankfurt am Main, Germany: Stephan Fichtlscherer, Andreas Zeiher: 8 patients and 0 registry patients; Asklepios Klinik Hamburg Barmbek, Hamburg, Germany: Achim Viertel: 7 patients and 8 registry patients; Universitätsklinikum Düsseldorf, Düsseldorf, Germany: Malte Kelm, Christian Jung: 7 patients and 2 registry patients; Universitäres Herzzentrum Hamburg, Hamburg, Germany: Peter Clemmensen, Carsten Sydow, Mahir Karakas: 6 patients and 0 registry patients; Herzzentrum Uniklinik Köln, Cologne, Germany: Volker Rudolph, Stephan Baldus: 6 patients and 0 registry patients; Universitätsmedizin Göttingen; Klinik für Kardiologie und Pneumologie, Göttingen, Germany: Claudius Jacobshagen, Gerd Hasenfuß: 4 patients and 6 registry patients; Universitätsklinikum Leipzig, Leipzig, Germany: Dietrich Pfeiffer: 4 patients and 0 registry patients; Marienhospital Neuwied, Neuwied, Germany: Björn Buchter, Burkhard Hügl: 3 patients and 2 registry patients; Universitätsklinikum Giessen, Giessen, Germany: Holger Nef, Oliver Dörr, Christian Hamm: 2 patients and 0 registry patients; Helios Kreiskrankenhaus Gotha, Gotha, Germany: Karsten Reinig: 2 patients and 0 registry patients; Asklepios Klinik St. Georg, Hamburg, Germany: Karl-

Heinz Kuck, Alexander Ghanem: 1 patient and 0 registry patients; Universitätsklinikum Heidelberg, MED III, Heidelberg, Germany: Hugo Katus: 1 patient and 0 registry patients; Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany: Tommaso Gori, Thomas Münzel: 1 patient and 0 registry patients; Klinikum Coburg, II. Medizinische Klinik, Kardiologie, Coburg, Germany: Steffen Schnupp, Johannes Brachmann: 0 patients and 3 registry patients; HSK Kliniken Wiesbaden, Wiesbaden, Germany: Markus Ferrari: 0 patients and 2 registry patients; Universitätsklinikum Erlangen, Erlangen, Germany: Stephan Achenbach: 0 patients and 2 registry patients.

**France; national coordinator: Gilles Montalescot, Paris**

Institut de Cardiologie - Hôpital Pitié-Salpêtrière, Paris, France: Gilles Montalescot 15 patients and 2 registry patients; Hôpital de Rangueuil-Toulouse, Toulouse, France: Didier Carrié: 9 patients and 3 registry patients; Hôpital Lariboisière- Paris, Paris, France: Patrick Henry, Stephane Manzo-Silberman: 4 patients and 5 registry patients; CHU Caremeau – Nimes, Nimes, France: Bertrand Ledermann, Guillaume Cayla; 2 patients and 0 registry patients; Hospital de la Timone, Marseille, France: Jean-Louis Bonnet: 2 patients and 0 registry patients.

**Switzerland; national coordinator: Stefan Windecker, Bern**

Inselspital Bern - Universitätsklinik für Kardiologie, Bern, Switzerland: André Frenk, Stephan Windecker: 5 patients and 3 registry patients; Universitätsspital Basel, Basel, Switzerland: Raban Jeger: 4 patients and 0 registry patients; CHUV - Service de cardiologie, Lausanne, Switzerland; Eric Eeckhout: 1 patient and 0 registry patients.

**The Netherlands; national coordinator: Jan J. Piek, Amsterdam**

University Hospital of Amsterdam, Amsterdam, The Netherlands: Jan J. Piek, Jose P. Henriques: 16 patients and 16 registry patients; Erasmus MC Rotterdam, Rotterdam, The Netherlands: Robert-Jan Van Geuns; 7 patients and 0 registry patients; University Medical Center Utrecht, Utrecht, The Netherlands: Michiel Voskuil; 1 patient and 7 registry patients; Haga Ziekenhuis Den Haag, Den Haag, The Netherlands: M. Bax; 0 patients and 2 registry patients; University Medical Center Groningen, Groningen, The Netherlands: Pim van der Harst: 0 patients and 2 registry patients.

**Slovenia; national coordinator: Marko Noc, Ljubljana**

University medical centre Ljubljana, Ljubljana, Slovenia: Marko Noc, Tomaž Goslar: 16 patients and 7 registry patients.

**Lithuania; national coordinator: Pranas Serpytis, Vilnius**

Vilnius University Hospital Santaros Klinikos; Vilnius, Lithuania; Faculty of Medicine, Vilnius University: Pranas Serpytis, Rokas Serpytis: 13 patients and 11 registry patients; Klaipeda Seamen Hospital Klaipėda, Lithuania: Dalia Jarasuniene: 1 patient and 0 registry patients.

**Belgium; national coordinator: Christiaan Vrints, Antwerp**

Universitair Ziekenhuis Antwerpen Cardiologie, Edegem, Belgium: Christiaan Vrints: 3 patients and 7 registry patients.

**Austria; national coordinator: Kurt Huber, Vienna**

Wilheminenspital Kardiologie-Wien, Wien, Austria: Kurt Huber: 5 patients and 8 registry patients; Medizinische Universität Wien, Wien, Austria: Irene Marthe Lang, Philipp Pichler: 5 patients and 0 registry patients; Krankenanstalt Rudolfstiftung Wien, Wien, Austria: Franz Weidinger: 0 patients and 2 registry patients; Universitätsklinikum Innsbruck, Innsbruck, Austria: Marc-Michael Zaruba: 2 patients and 0 registry patients.

**Poland; national coordinator: Janina Stepinska; Warsaw**

II Klinika Kardiologii, Uniwersytet Jagielloński, Krakow, Poland: Darius Dudek, Rafal Depukat: 10 patients and 2 registry patients; Instytut Kardiologii – Warszawa, Warszawa, Poland: Janina Stepinska, Adam Witkowski: 3 patients and 1 registry patient; X Oddział Kardiologii Inwazyjnej, Tychy, Poland: Krzysztof Milewski: 2 patients and 1 registry patient; IV Oddział Kardiologii Inwazyjnej, PAKS, Kedzierzyn-Kozle, Poland: Janusz Prokopczuk: 2 patients and 0 registry patients; III Katedra i Oddział Kliniczny Kardiologii ŚAM Zabrze, Zabrze, Poland: Mariusz Gąsior: 1 patient and 2 registry patients; II Oddział Kardiologiczny PAKS, Bielsko-Biala, Poland:: Bogdan Gorycki: 1 patient and 0 registry patients; Zakład Kardiologii Inwazyjne – Katowice, Katowice-Ochojec, Poland: Andrzej Ochała: 0 patient and 1 registry patient.

**Italy; national coordinator: Stefano Savonitto; Lecco**

Manzoni Hospital, Lecco, Italy: Luigi Piatti: 1 patient and 14 registry patients; Ospedale G.B. Morgagni, Forlì, Italy: Marcello Galvani: 1 patient and 5 registry patients; Ospedale Niguarda Ca' Granda, Milano, Italy: Irene Bossi: 0 patients and 3 registry patients; IRCCS Arcispedale S. Maria Nuova, Reggio Emilia, Italy: Gianluca Pignatelli: 0 patients and 2 registry patients.

**United Kingdom; national coordinator: Keith Oldroyd, Glasgow**

Golden Jubilee National Hospital, Glasgow, United Kingdom: Keith Oldroyd: 10 patients and 6 registry patients; Leeds General Infirmary, Leeds, United Kingdom: John Greenwood: 11 patients and 18 registry patients; Royal Free Hospital London, London, United Kingdom; Tim Lockie: 7 patients and 19 registry patients. Royal Stoke University Hospital, Stafford, United Kingdom; Mamas Mamas: 0 patients and 4 registry patients.

**3) Trial Registration**

This trial is registered with www.ClinicalTrials.gov: NCT01927549. The time of final approved trial registration was August 14th 2013. First patient inclusion was April 15th 2013 at the Heart Center Leipzig – University Hospital, Leipzig, Germany.

Thus, there was a delay of trial registration before first patient inclusion which was induced by a misunderstanding between the project coordination for the EU grant (at this time gabo:mi, later on ARTTIC) and the clinical project coordination at the investigator's site at the Heart Center Leipzig - University of Leipzig. According to initial communication registration should be performed by gabo:mi. When the study coordinator recognized that it has not been performed we immediately registered it at clinicaltrials.gov. At this time only 13 patients at the Heart Center Leipzig – University Hospital (and no other study site) have been included into the trial.

**4) Informed Consent Process in Participating Countries**

"Informed consent in cardiogenic shock is generally difficult because the majority of patients is intubated and mechanically ventilated or show altered mental status. Therefore, a dedicated informed consent process was applied and approved by the ethical committees (slightly differing between the participating countries).

The informed consent process in the participating countries is shown below:"

| Country | Informed consent procedure |
|---|---|
| **Germany** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent<br>This process was only different for centers of the ethical committee of the Landesärztekammer Rheinland-Pfalz where only version 1. was allowed. |
| **Austria** | 2 different informed consent forms:<br>1. Patient is able to consent<br>2. Patient is not able to consent |
| **Switzerland** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent |
| **Italy** | 2 different informed consent forms:<br>1. Short version<br>2. Extended version<br>Italy by law was not allowed to enter patients into the randomized clinical trial if the patient was unable to consent. In this case, patients entered the registry. |
| **Belgium** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent |
| **Poland** | 4 different informed consent forms:<br>1. Patient is unable to consent: 2 independent physicians assess patient's will (if possible by contact with relatives)<br>2. Patient is only partly able to consent: short version of informed consent<br>3. Patient is able to consent: long version of informed consent<br>4. Patient stabilizes: retrospective long version of informed consent |
| **Slovenia** | The informed consent procedure in Slovenia requires no consent prior to randomization. Patients need to sign consent only after they have regained the ability to consent after the procedure and in case of survival. Thus, there is only one patient informed consent version. |

| | |
|---|---|
| **Lithuania** | The informed consent procedure in Lithuania requires the consent of two physicians and an independent third person in case the patient is not able to consent. |
| **United Kingdom** | The informed consent procedure in Scotland differs from the process applicable e.g. in Germany. A relative must be informed and provide consent for patients not capable of providing own consent. If a patient survives, further consent is not mandatory, but desirable. Thus, a short form with the consent of a relative is sufficient.<br><br>The informed consent procedure in the UK without Scotland requires two physicians to consent in representation of the patient, in case he or she lacks the capacity to consent. In this case, the patient has to be consented retrospectively. Capable patients are first consented using a short form prior to randomization and a long form after recovery to full consent. |
| **France** | The informed consent procedure in France requires a third person to consent in addition to the treating physician in case of a patient's inability to consent. In this case, patients need to sign consent after they have regained the ability to consent after the procedure and in case of survival. |
| **The Netherlands** | The informed consent procedure in the Netherlands requires no consent prior to randomization. Patients need to sign consent only after they have regained the ability to consent after the procedure and in case of survival. Thus, there is only one patient informed consent version. |

## 5) Outcome Definitions

*Death*
Death of all cause.

*Death cardiovascular*
Death due to cardiovascular causes, such as heart failure, cardiac arrhythmias, myocardial infarction, sudden cardiac death or all deaths of unknown cause.

*Severe renal failure requiring renal replacement therapy*
Any indication for renal replacement therapy such as dialysis, hemofiltration or hemodiafiltration such as renal failure with one of the following criteria:

- Otherwise untreatable volume overload
- hyperpotassemia (>6.0 mmol/L)
- severe uremia (BUN >50 mg/dL or >8.4 mmol/L)
- persistent severe metabolic acidosis (pH <7.2)

*Myocardial reinfarction*
The definition of myocardial reinfarction in the CULPRIT-SHOCK trial is based on the universal definition of myocardial infarction.[1] Thus, myocardial reinfarction is defined according to the specific situation (see **Table 4**).

| **Re-MI**<br>***<24 h*** | **Re-MI**<br>***24 h – 7 days*** | **Re-MI**<br>***>7 days*** |
|---|---|---|
| Symptoms, such as angina pectoris for ≥20 minutes, most likely due to myocardial ischemia<br>***and or***<br>new ST-elevation ≥1 mm in ≥2 contiguous leads or new left bundle branch block<br>***or***<br>angiographic evidence of re-occlusion of a previously open coronary artery or graft | Symptoms, such as angina pectoris for ≥20 minutes, most likely due to myocardial ischemia<br>***and or***<br>if cardiac markers are still elevated, new increase ≥20% from the last non-normalized measurement<br>***or***<br>if cardiac markers are normalized, application of the "universal definition" for myocardial infarction (see next column) | "Universal definition" for myocardial infarction<br><br>**1.** Rise and/or fall of cardiac biomarkers above the 99$^{th}$ percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following:<br>• Symptoms of ischemia<br>• ECG changes indicative of new ischemia<br>• Development of pathological Q waves in ECG<br>• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality<br>**2.** Sudden, unexpected cardiac death with ST-elevation and presumably new LBBB or evidence of fresh thrombus by coronary angiography, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.<br>**3.** Peri-PCI myocardial infarction: increases of biomarkers > 3 of the upper reference level<br>**4.** Peri-CABG myocardial infarction: increases of biomarkers > 5 of the upper reference level plus new pathological Q waves or new LBBB or angiographically documented new graft or native coronary artery occlusion<br>**5.** Pathological findings of acute myocardial infarction |

*Repeat revascularization*
Any revascularization procedure (PCI or CABG) after the initial intervention including planned staged and urgent revascularization.

*Chronic total occlusion (CTO)*
Complete obstruction of a coronary artery, described as ≥99% stenosis of >3 months duration with poor or no antegrade blood flow (TIMI 0-1).

*Stent thrombosis*
Stent thrombosis is classified in definite, probable and possible stent thrombosis according to the Academic Research Consortium (ARC) definition:[2]

| Definite | Probable | Possible |
|---|---|---|
| Acute coronary syndrome and angiographic OR pathological confirmation of stent thrombosis | Unexplained death within the first 30 days OR acute ischemia in the territory of an implanted stent without angiographic confirmation of stent thrombosis in the absence of another culprit lesion | Unexplained death >30 days |

*Bleeding complications*
Bleeding complications will be classified according to 3 different definitions (for further evaluation which one best predicts outcome in cardiogenic shock patients).
BARC bleeding definition:[3]

| Type | Bleeding definition |
|---|---|
| Type 0 | no bleeding |
| Type 1 | bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional |
| Type 2 | any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:<br>(1) requiring nonsurgical, medical intervention by a healthcare professional<br>(2) leading to hospitalization or increased level of care, or<br>(3) prompting evaluation |
| Type 3 | |
| Type 3a | Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)<br>Any transfusion with overt bleeding |
| Type 3b | Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)<br>Cardiac tamponade<br>Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)<br>Bleeding requiring intravenous vasoactive agents |
| Type 3c | Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)<br>Subcategories confirmed by autopsy or imaging or lumbar puncture<br>Intraocular bleed compromising vision |
| Type 4 | CABG-related bleeding |

| | |
|---|---|
| | Perioperative intracranial bleeding within 48 h<br>Reoperation after closure of sternotomy for the purpose of controlling bleeding<br>Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†<br>Chest tube output ≥2L within a 24-h period |
| Type 5 | Fatal bleeding |
| Type 5a | Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious |
| Type 5b | Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation |

GUSTO-definition:[4]

| Severe/life-threatening bleeding complications | Moderate bleeding | Mild bleeding |
|---|---|---|
| *Intracranial* hemorrhage or bleeding that causes hemodynamic compromise requiring intervention | Bleeding that requires blood transfusion but does not result in hemodynamic compromise | Bleeding that does not meet criteria for either severe or moderate bleeding. |

TIMI definition:[5]

| Classification | Description |
|---|---|
| TIMI major | Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)<br>Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL<br>Fatal bleeding (bleeding that directly results in death within 7 d) |
| TIMI minor | Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL |

*Stroke*

Stroke will be classified in hemorrhagic (cranial CT, MRI, or autopsy) or non-hemorrhagic. Stroke is defined as an acute new neurological deficit ending in death or lasting longer than 24 hours, and classified by a physician as a stroke.

1. Primary hemorrhagic - defined as an intracerebral hemorrhage or subdural hematoma
    a. Intracerebral hemorrhage - Stroke with focal collections of intracerebral blood seen on brain imaging (CT or MRI) or a post-mortem examination, not felt to represent hemorrhagic conversion. Subarachnoid hemorrhage should be included in this category.
    b. Subdural hematoma - High density fluid collection in subdural space on brain images or blood in the subdural space on autopsy.
2. Non-hemorrhagic cerebral infarction - Stroke without focal collections of intracerebral blood on brain imaging.
3. Non-hemorrhagic infarction with hemorrhagic conversion - Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage.
4. Uncertain - Any stroke without brain imaging (CT or MRI) or autopsy documentation of type, or if tests are inconclusive.

*New congestive heart failure*

Occurrence of congestive heart failure after hospital discharge:
Defined as;

- Re-hospitalization due to new or worsening heart failure >24 h after hospital discharge.

*Infarct artery/culprit vessel*
Artery responsible for acute myocardial infarction.
In general its identification is based on

1) ECG
2) Wall motion abnormalities
3) Angiographic morphology of the lesion (e.g. ulceration and/or thrombus consistent with plaque rupture).

*Patency of culprit vessel and additional major vessels before and after PCI (TIMI-Flow)*
The TIMI-flow is visually assessed according to the following grading system:[6]

| Grade | Perfusion | Characterization |
|---|---|---|
| 0 | No Perfusion | No antegrade flow beyond the point of occlusion |
| 1 | Penetration without perfusion | Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary distal bed |
| 2 | Partial reperfusion | Contrast material passes across the obstruction with delayed entry and clearance from the distal bed |
| 3 | Complete reperfusion | Normal flow |

*Hemodynamic stability criterion*
Sustained (> 60 min) systolic blood pressure >90 mmHg
WITHOUT requirement for catecholamines
AND
WITHOUT signs of peripheral endorgan hypoperfusion

*Sepsis*
Sepsis is defined according to the ACCP/SCCM Consensus-conference plus additional elevated pro-calcitonin (≥ 2 pg/ml).[7,8]

| **I) Signs of infection** |
|---|
| Diagnosis of infection via microbiological evaluation or by clinical criteria |
| **II) Systemic Inflammatory Response Syndrome (SIRS) (≥2 criteria required)** |
| • Body temperature >38°C or <36°C<br>• Tachycardia: Heart rate >90/min<br>• Tachypnoe: ventilation rate >20/min or hyperventilation ($PaCO_2$ <4,3 kPa or 33 mmHg)<br>• White blood cell count (>12.000/$mm^3$) or (<4.000/$mm^3$) or >10 % premature neutrophil granulocytes |

*SAPS II-Score*
The severity of cardiogenic shock and concomitant organ dysfunction will be assessed by the SAPS II-Score.[9] This score is evaluated on a routine basis in all hospitals in Germany. The calculation of the SAPS II-Score can be done using the following link: http://www.sfar.org/scores2/saps2.html. The individual parameters of the SAPS-II-score can be found in Figure 5.

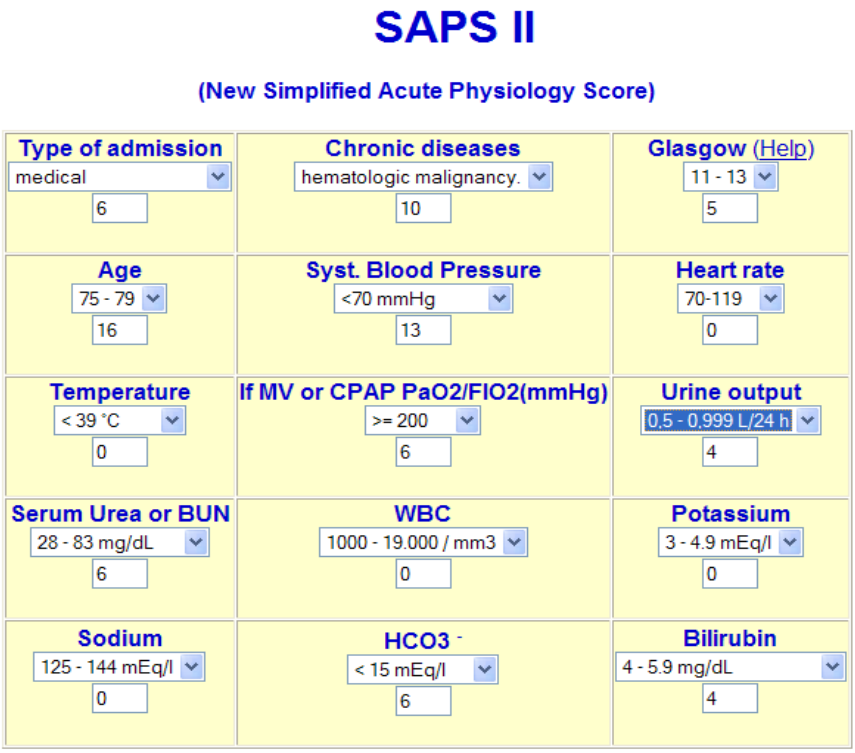



**Figure: Parameters of the SAPS-II Score[9]**

*Quality of life*

Quality of life will be assessed using the Euroqol 5D-questionnaire (www.euroqol.org):

| **Euroqol 5D: Quality of life** | |
|---|---|
| **Mobility** | ○ Pat. has no problems in walking about<br>○ Pat. has some problems in walking about<br>○ Pat. is confined to bed |
| **Self-Care** | ○ Pat. has no problems with self-care<br>○ Pat. has some problems washing or dressing himself<br>○ Pat. is unable to wash or dress himself |
| **Usual Activities (e.g. work, study, housework, family or leisure activities)** | ○ Pat. has no problems with performing his usual activities<br>○ Pat. has some problems with performing his usual activities<br>○ Pat. is unable to perform his usual activities |
| **Pain/Discomfort** | ○ Pat. has no pain or discomfort<br>○ Pat. has moderate pain or discomfort<br>○ Pat. has extreme pain or discomfort |
| **Anxiety/Depression** | ○ Pat. is not anxious or depressed<br>○ Pat. is moderately anxious or depressed<br>○ Pat. is extremely anxious or depressed |
| **In comparison to the general health state (GHS) in the past 12 months, today's GHS of the patient is** | ○ better<br>○ overall similar<br>○ worse |
| **How does the patient scales his GHS today?**<br>Best imaginable GHS: 100%<br>Worst imaginable GHS: 0% | % |

**6) List of End Points**

| **End Points** | |
|---|---|
| 30-day all-cause mortality and/or severe renal failure | Table 3, Figure 1a |
| 30-day all-cause mortality | Table 3, Figure 1b |
| 30-day severe renal failure | Table 3, Figure 1c |
| 30-day recurrent myocardial infarction | Table 3 |
| 30-day rehospitalization for congestive heart failure | Table 3 |
| 30-day death/recurrent infarction/rehospitalization for congestive heart failure | Table 3 |
| 30-day repeat revascularization | Table 3 |
| Time to hemodynamic stabilization | Table 2 |
| Requirement of catecholamine therapy | Table 2 |
| Duration of catecholamine therapy | Table 2 |
| Length of mechanical ventilation | Table 2 |
| Length of intensive care unit stay | Table 2 |
| Procedural success | not assessable |
| Serial SAPS-II score | Figure S2 |
| Serial estimated creatinine clearance | Figure S4 |
| Serial high-sensitive troponin | Figure S5 |
| Serial creatine kinase | Figure S6 |
| Serial creatine kinase myocardial band fraction | not assessable |

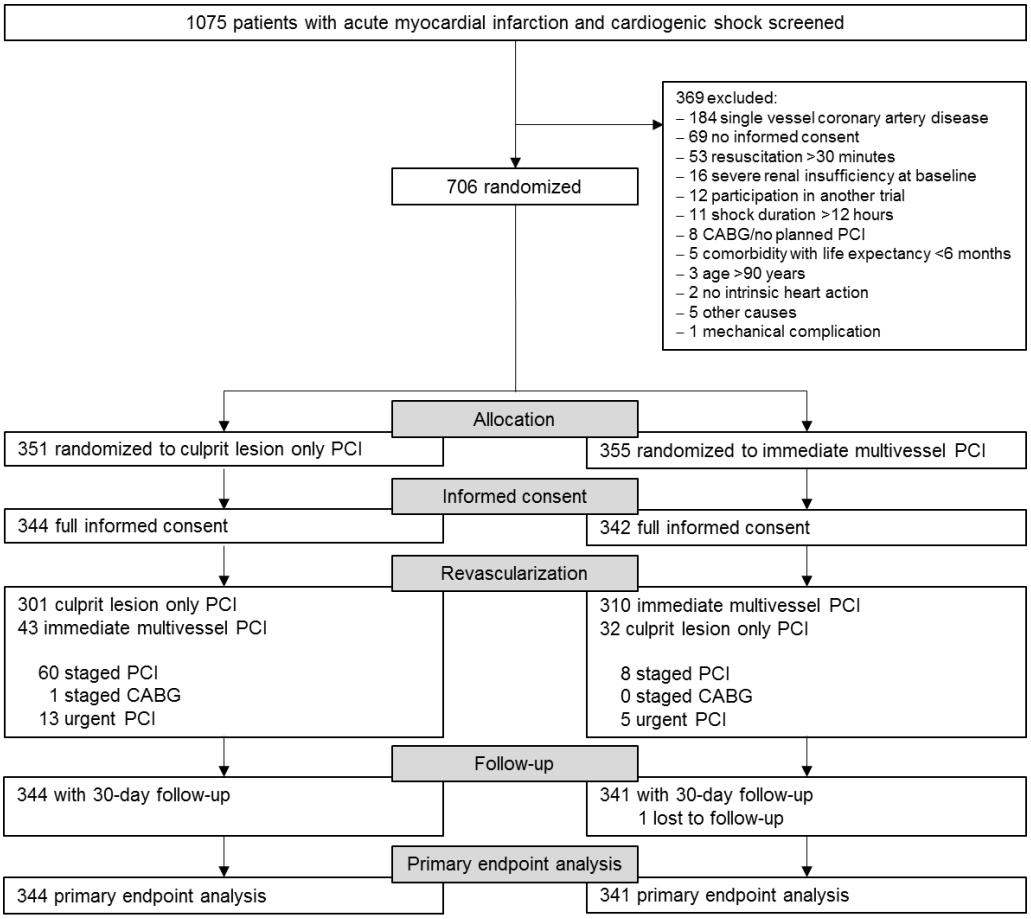
| **Safety** | |
|---|---|
| Bleeding (BARC) grade 2-3 and 5 | Table 3 |
| Stroke | Table 3 |

## 7) Figure S1 – Trial Flow

Screening, randomization, management strategy, and follow-up at 30 days for the intention-to-treat analysis

PCI=percutaneous coronary intervention

CABG=coronary artery bypass grafting




**Definition of per–protocol population:**

The per-protocol population was defined by patients fulfilling the in- and exclusion criteria and non-cross-over patients undergoing successful or unsuccessful revascularization. Cross-over patients were any intention-to-treat subjects undergoing a different treatment than the treatment indicated by the result of randomization.

Patients who died before start of revascularization or who did not undergo any revascularization attempt for other reasons were not included in the per-protocol analysis.

In addition, patients with significant deviations from the study protocol were excluded from the per-protocol population. The decision of a significant deviation from the study protocol was made by the steering committee.

The per-protocol population of the culprit lesion only arm excluded 43 patients undergoing immediate multivessel PCI, but did not exclude the 56 undergoing staged PCI. The patients with single vessel disease were also excluded. Thus, the per-protocol population in the culprit lesion only arm included 299 patients.

The per-protocol population included 310 patients undergoing multivessel PCI and excluded those undergoing culprit-lesion only PCI even if they underwent staged PCI. The patients with single vessel disease and the one lost to follow-up were also not included. Accordingly, the per-protocol in the immediate multivessel PCI arm consisted of 307 patients.

## 8) Figure S2 – Simplified Acute Physiology Score – II

SAPS-II score during daily follow-up until hemodynamic stabilization.

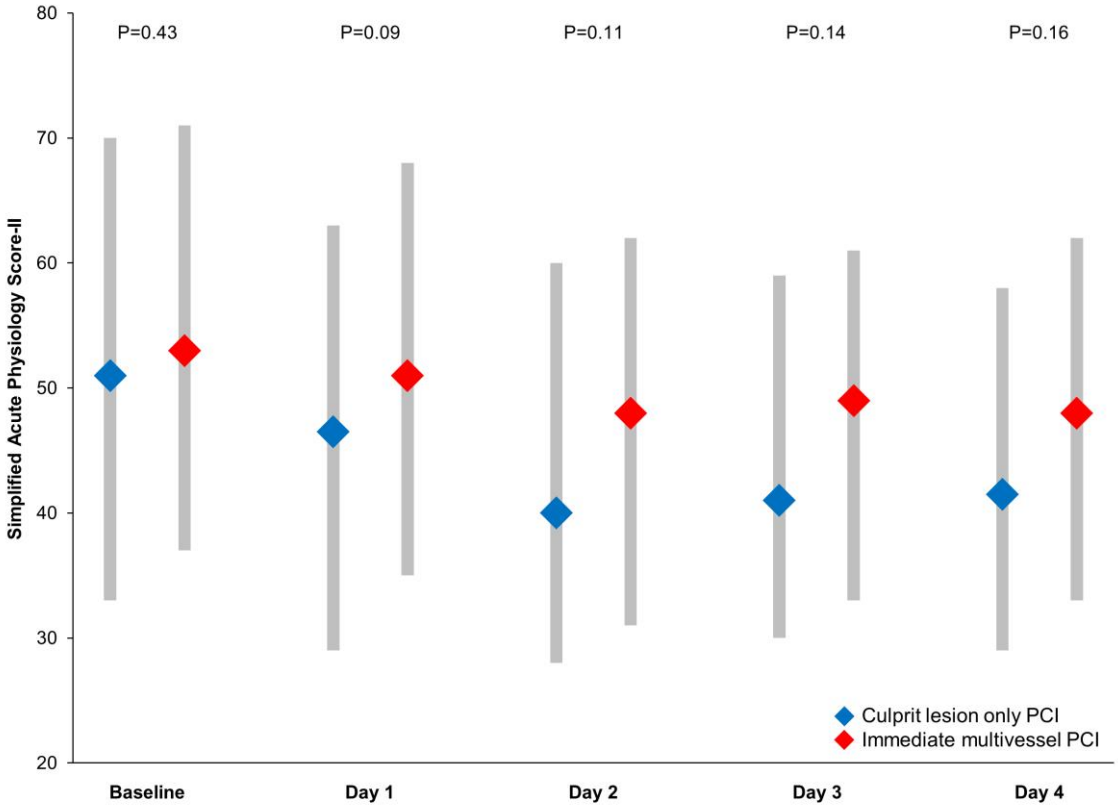
SAPS-II is calculated from 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease.[10]

The variables included into the SAPS-II score are: 1) age; 2) heart rate; 3) systolic blood pressure; 4) body temperature; 5) mechanical ventilation; 6) $PaO_2$ (partial pressure of $O_2$ in the blood); 7) $FiO_2$ (fraction of inspired $O_2$); 8) urine output; 9) blood-urea-nitrogen; 10) white blood cell count; 11) potassium; 12) sodium; 13) bicarbonate; 14) bilirubin; 15) Glasgow coma scale; 16) history of chronic diseases; 17) type of admission.

Plots showing the median and interquartile range.

PCI=percutaneous coronary intervention

There was no adjustment for multiple testing.



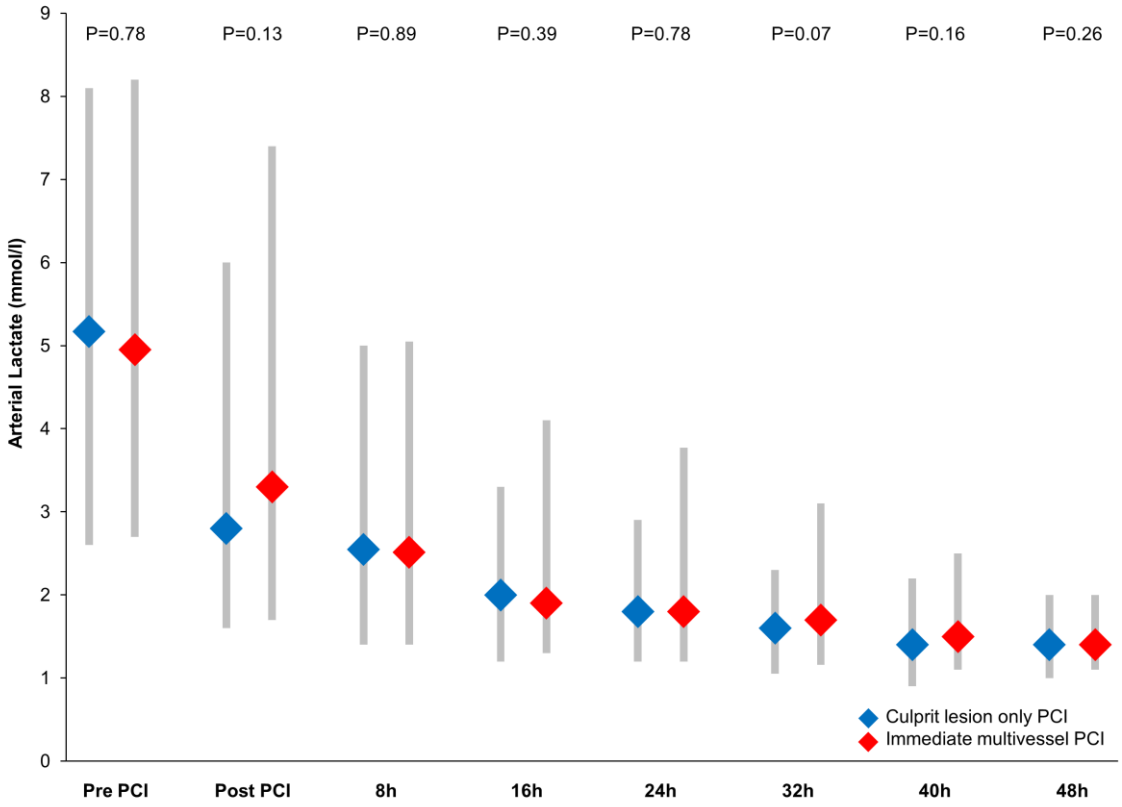
## 9) Figure S3 – Arterial Lactate

Arterial lactate during measurements every 8 h for 48 h.

Plots showing the median and interquartile range.

PCI=percutaneous coronary intervention

There was no adjustment for multiple testing.



## 10) Figure S4 – Renal Function

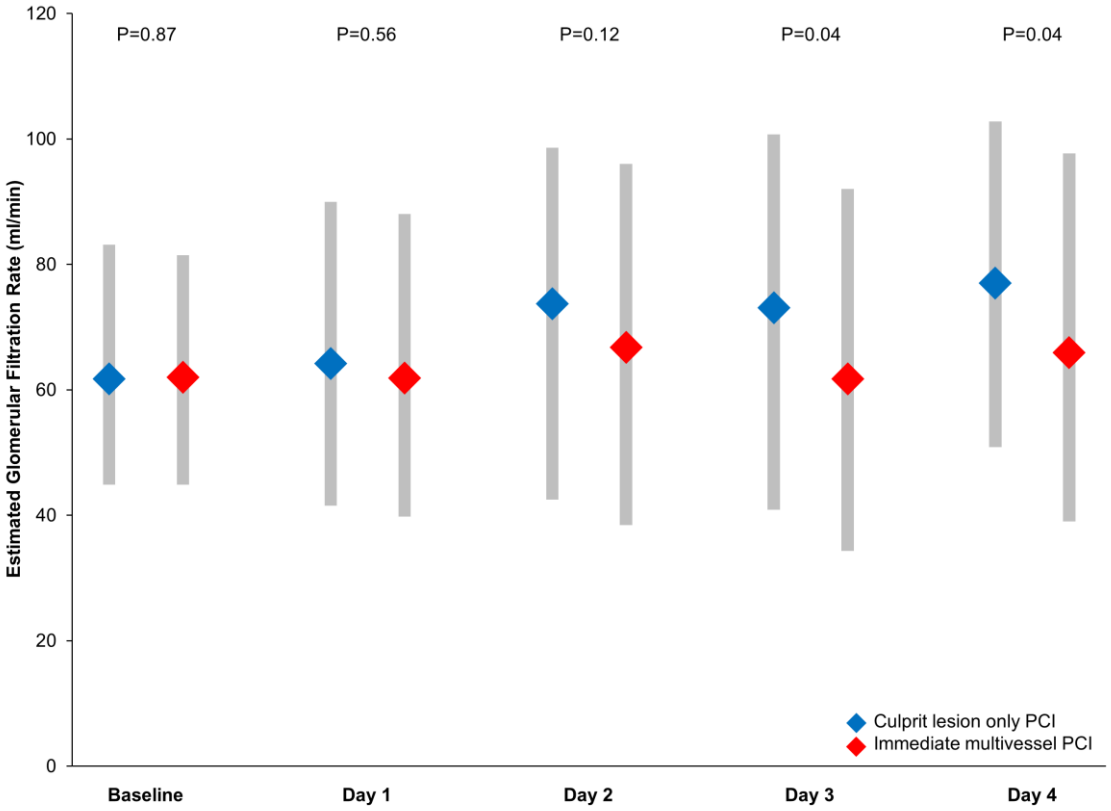
Estimated glomerular filtration rate during daily follow-up until hemodynamic stabilization.

Estimated glomerular filtration rate was calculated using the Cockcroft-Gault-formula.[11]

Plots showing the median and interquartile.

PCI=percutaneous coronary intervention

There was no adjustment for multiple testing.



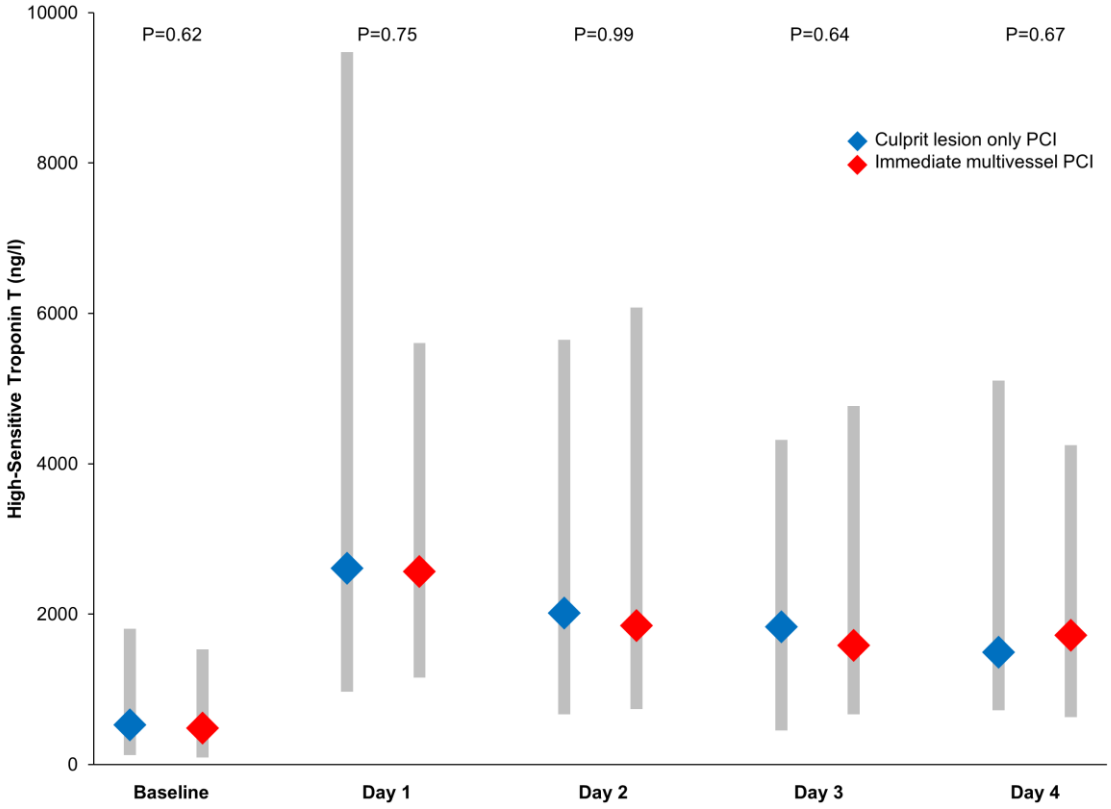
## 11) Figure S5 – High-Sensitive Troponin T

High-sensitive (hs) Troponin T during daily follow-up.

Plots showing the median and interquartile range.

PCI=percutaneous coronary intervention

There was no adjustment for multiple testing.



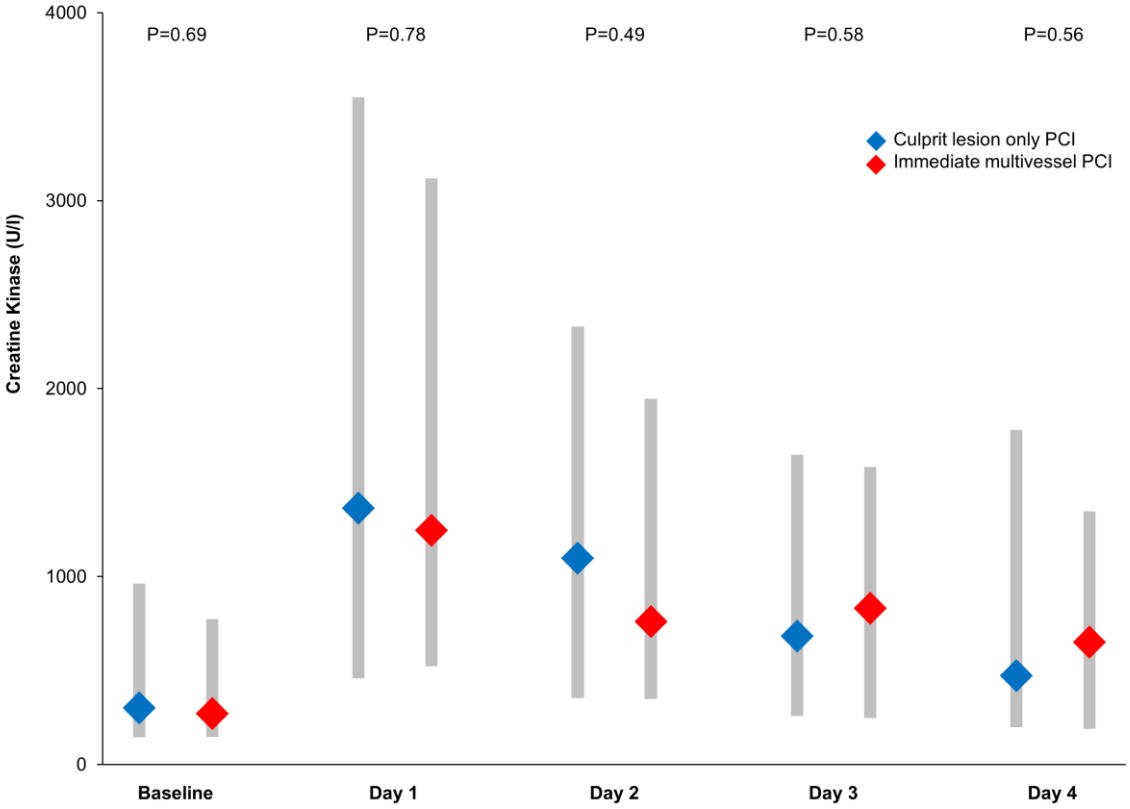
**12) Figure S6 – Creatine Kinase**

Creatine kinase during daily follow-up.

Plots showing the median and interquartile range.

PCI=percutaneous coronary intervention

There was no adjustment for multiple testing.



## 13) Table S1 – Individual Case Reports of Cross-overs from Culprit-Only PCI to Immediate Multivessel PCI

| Center No. | Case No. | Value |
|---|---|---|
| 4830 | 10 | initially thrombotic occlusion ostial LAD, after PCI thrombus in LCX and occlusion of LCX, patient with progression of hemodynamic deterioration |
| 4113 | 2 | PCI LAD (culprit lesion) failed, so PCI RCA instead to improve the condition. |
| 4830 | 95 | Physician decision, not based on hemodynamic situation |
| 9843 | 1 | massive cardiogenic shock significant stenosis also in proximal LAD and mid LCX => possibly no benefit of staged revascularization |
| 7792 | 7 | After stenting of ostial LAD plaque shift to LCX, after that PCI with DEB in LCX |
| 9640 | 3 | bifurcation lesion |
| 2311 | 11 | Initially operator believed the segment 12 belongs to the LAD and performed additional stenting. Finally the segment 12 should be classified as a part of LCX. The stenosis of the main branch of LCX and the RCA were not treated. |
| 3920 | 6 | Initially, despite multiple attempts the culprit lesion (RCA) could not be recanalized by multiple guide wires. The acute thrombotic occlusion was located directly proximal to a high-grade calcified stenosis. Therefore, as ultima ratio the additional LCX stenosis was intervened because based on ECG this stenosis may also have contributed to acute ischemia. In second attempt RCA was successfully recanalized and stented. |
| 3920 | 8 | After PCI of culprit lesion in LCX there is a new significant lesion in left main which requires PCI to LAD. After left main PCI no-reflow in LAD with subsequent PCI of LAD. Additional stenoses remain in RCA, distal LAD und obtuse marginal. |
| 6912 | 5 | Otherwise stent-placement (culprit lesion) in non-diseased vessel would not have been feasible |
| 5603 | 2 | There was a stenosis extending from left main to LCX after PCI, that's why both stenoses were stented. |
| 3873 | 8 | A second presumably also acute occlusion was noticed after PCI of culprit lesion: RDP. This lesion was therefore threated in the same PCI setting. Other lesions were left untreated. |
| 7553 | 2 | By implantation stent in LAD there was a plaque shift in LCX -> Culotte stenting in main stem and LCX was absolute necessary |
| 7553 | 5 | Persistent hemodynamic instability despite high catecholamine doses with indication for Impella implantation |
| 4145 | 13 | diffuse coronary atherosclerosis, the proximal culprit lesion continues to segment 2 |
| 7553 | 17 | severe left main stem stenosis |
| 6912 | 7 | Progressive stenosis of ostial LCX after PCI of culprit lesion |
| 5603 | 7 | The PCI was done on the extension of culprit lesion. |
| 2311 | 15 | Live saving step to achieve better perfusion under ECLS therapy |
| 7553 | 23 | hemodynamically relevant main stem stenosis |
| 5233 | 6 | Bifurcation of the circumflex artery and the left descending artery |
| 6767 | 10 | operator preference |

| | | |
|---|---|---|
| 6907 | 25 | operator preference |
| 6767 | 11 | operator preference |
| 6907 | 34 | Decision to complete revascularization due to increasing hypotension and loss of pressure |
| 6907 | 43 | Decision to complete revascularization due to increasing hypotension and loss of blood pressure |
| 7553 | 43 | Because of subtotal LAD stenosis decision to immediate PCI of additional lesions |
| 8483 | 21 | Consultant felt patient had multiple culprit lesions involving proximal LAD, LCX and OM which all required primary intervention. Not based on hemodynamic situation. |
| 6392 | 3 | operator preference |
| 2311 | 18 | still hemodynamic instability |
| 9237 | 1 | Culprit lesion was from proximal to mid LAD. |
| 6907 | 75 | operator preference |
| 6907 | 76 | hemodynamic instability and clinical deterioration cross-over in multivessel PCI arm |
| 1679 | 34 | Culprit lesion despite initial clear assessment was not 100% determinable after PCI -> additional PCI of presumably other culprit lesion performed. |
| 7553 | 60 | left-dominant coronary circulation |
| 6907 | 79 | operator preference |
| 6907 | 80 | critical condition and resuscitation during PCI |
| 9829 | 14 | Dissection post PCI in LCX with thrombus |

## 14) Table S2 – Individual Case Reports of Crossovers from Immediate Multivessel PCI to Culprit-Only PCI

| Center No. | Case No. | Value |
|---|---|---|
| 4830 | 56 | Patient died before PCI of additional lesions |
| 6657 | 1 | PCI of native diagonal branch and LCX technically not possible, stenosis of RCA probably chronic total occlusion -> could not be recanalized; PCI of LAD not done because of long Intervention-time and high use of contrast medium |
| 7792 | 3 | Patient had one lesion in RCA segment 2 which was not intervened for technical reasons |
| 4145 | 5 | After culprit PCI, the patient went into refractory cardiac arrest requiring VA ECMO implantation. It was decision of attending interventional cardiologist not to proceed with PCI of non-culprit after ECMO because of the priorities of other interventions. |
| 3870 | 4 | Died before PCI of additional lesions |
| 8095 | 1 | Initial intubation of RCA with Judgkins left 4 catheter, later on with Amplatzer left 1. Multiple guide wires (BMW, Sion blue, Fielder XT) and Finecross catheter no success of CTO recanalization (old stents in RCA?). Therefore, PCI of LAD only. |
| 6037 | 33 | Death in cath lab after PCI of culprit lesion. |
| 8401 | 3 | death of patient |
| 8483 | 3 | Patient died during intervention to culprit lesion. |
| 3873 | 12 | Practical limitations due to contrast dye |
| 7313 | 13 | Resuscitation was initiated. Because of persistent pump failure resuscitation was stopped after 30 minutes. The patient died subsequently |
| 1313 | 1 | Bystander LCX disease would have needed rotablation, LAD known CTO since 2010 |
| 7403 | 12 | no safe catheter and wire placement possible due to abnormal take-off of the RCA |
| 3464 | 2 | huge volume of contrast injected, probably stroke on the cath lab table |
| 7553 | 22 | stenosis presumably hemodynamically not relevant and unclear neurological outcome due to hypoxemia |
| 1005 | 10 | Peri-interventional refractory ventricular fibrillation, treatment with Impella and LUCAS system |
| 2767 | 5 | due to presence of full TIMI 3 flow in the LCX artery and need to quickly proceed to implement hypothermia therapy as soon as possible due to presumed long period of ventricular fibrillation before emergency team intervention |
| 1679 | 21 | prolonged resuscitation with need for veno-arterial ECMO |
| 4795 | 2 | Death before PCI of other lesions |
| 6037 | 70 | High contrast volume and perforation of mid LAD (culprit lesion) |
| 8483 | 13 | PCI to LAD disease attempted but lesion appeared to be a CTO which could not be crossed with a guidewire. The operator decided to end the procedure as PCI could not be completed and the patient developed more severe acute pulmonary edema. |
| 4944 | 8 | New cardiorespiratory arrest after LAD intervention. Unfavorable evolution with major vasoplegia |
| 7778 | 9 | long procedure duration, high contrast agent consumption |

| | | |
|---|---|---|
| 6907 | 65 | Additional LCA stenoses due to high-grade ostial LCX stenosis not accessible for PCI. Therefore, restriction to left main PCI only |
| 9237 | 4 | Initial estimation of the LCX stenosis was non-significant (<50%), and therefore no PCI of the CX lesion was performed. However, the analysis of angiography on the next day confirmed that the proximal CX indeed had a significant >70% stenosis. |
| 5603 | 26 | During the PCI ventricular fibrillation was observed. The patient was defibrillated. After defibrillation pulseless electrical activity was observed. Patient was resuscitated without effect and the patient died. |
| 9237 | 5 | The RCA was occluded. However, due to the total occlusion of the vessel, the PCI was not possible. |

**15) Table S3 – Causes of Death at 30 Days**

| | Culprit only PCI (n=344) | Multivessel PCI (n=341) | P-Value |
|---|---|---|---|
| All-cause mortality; n/total (%) | 149/344 (43.3) | 176/341 (51.5) | 0.03 |
| Death cause | | | 0.12 |
| Sudden cardiac death; n/total (%) | 11/149 (7.4) | 12/176 (6.8) | |
| Refractory cardiogenic shock¸ n/total (%) | 104/149 (69.8) | 108/176 (61.4) | |
| Recurrent myocardial infarction; n/total (%) | 2/149 (1.3) | 2/176 (1.1) | |
| Brain injury; n/total (%) | 11/149 (7.4) | 25/176 (14.2) | |
| Sepsis; n/total (%) | 10/149 (6.7) | 8/176 (4.5) | |
| Unknown cause; n/total (%) | 2/149 (1.3) | 9/176 (5.1) | |
| Other cause; n/total (%) | 9/149 (6.0) | 12/176 (6.8) | |

**16) Clinical Outcomes at 30 Days for Registry Patients**

| | n/total (%) |
|---|---|
| All-cause mortality and renal replacement therapy; n/total (%) | 169/369 (45.8) |
| All-cause mortality; n/total (%) | 160/369 (43.4) |
| Renal replacement therapy; n/total (%) | 29/369 (7.9) |
| Indication for renal replacement therapy | |
| Hyperkalemia (>6 mmol/L); n/total (%) | 5/29 (17.2) |
| Metabolic acidosis (pH <7.2); n/total (%)) | 13/29 (44.8) |
| Uremia (blood urea >50 mg/dL); n/total (%) | 13/29 (44.8) |
| Volume overload; n/total (%) | 9/29 (31.0) |
| Other cause; n/total (%) | 7/29 (24.1) |

**17) References**


1. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.
2. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials. Circulation 2007;115:2344-51.
3. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011;123:2736-47.
4. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
5. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. Ann Intern Med 1991;115:256-65.
6. The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI II A results. JAMA 1988;260:2849-58.
7. Remmelink M, Sjauw KD, Henriques JP, et al. Effects of mechanical left ventricular unloading by impella on left ventricular dynamics in high-risk and primary percutaneous coronary intervention patients. Catheter Cardiovasc Interv 2010;75:187-94.
8. Remmelink M, Sjauw KD, Henriques JP, et al. Effects of left ventricular unloading by Impella recover LP2.5 on coronary hemodynamics. Catheter Cardiovasc Interv 2007;70:532-7.
9. Metra M, Eichhorn E, Abraham WT, et al. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced

heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. Eur Heart J 2009;30:3015-26.

10. Le Gall JR, Lemeshow S, F. S. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-63.

11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 21, 2017 VOL. 377 NO. 25

# PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock

H. Thiele, I. Akin, M. Sandri, G. Fuernau, S. de Waha, R. Meyer-Saraei, P. Nordbeck, T. Geisler, U. Landmesser, C. Skurk, A. Fach, H. Lapp, J.J. Piek, M. Noc, T. Goslar, S.B. Felix, L.S. Maier, J. Stepinska, K. Oldroyd, P. Serpytis, G. Montalescot, O. Barthelemy, K. Huber, S. Windecker, S. Savonitto, P. Torremante, C. Vrints, S. Schneider, S. Desch, and U. Zeymer, for the CULPRIT-SHOCK Investigators*

## ABSTRACT

### BACKGROUND

In patients who have acute myocardial infarction with cardiogenic shock, early revascularization of the culprit artery by means of percutaneous coronary intervention (PCI) improves outcomes. However, the majority of patients with cardiogenic shock have multivessel disease, and whether PCI should be performed immediately for stenoses in nonculprit arteries is controversial.

### METHODS

In this multicenter trial, we randomly assigned 706 patients who had multivessel disease, acute myocardial infarction, and cardiogenic shock to one of two initial revascularization strategies: either PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, or immediate multivessel PCI. The primary end point was a composite of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization. Safety end points included bleeding and stroke.

### RESULTS

At 30 days, the composite primary end point of death or renal-replacement therapy had occurred in 158 of the 344 patients (45.9%) in the culprit-lesion-only PCI group and in 189 of the 341 patients (55.4%) in the multivessel PCI group (relative risk, 0.83; 95% confidence interval [CI], 0.71 to 0.96; P=0.01). The relative risk of death in the culprit-lesion-only PCI group as compared with the multivessel PCI group was 0.84 (95% CI, 0.72 to 0.98; P=0.03), and the relative risk of renal-replacement therapy was 0.71 (95% CI, 0.49 to 1.03; P=0.07). The time to hemodynamic stabilization, the risk of catecholamine therapy and the duration of such therapy, the levels of troponin T and creatine kinase, and the rates of bleeding and stroke did not differ significantly between the two groups.

### CONCLUSIONS

Among patients who had multivessel coronary artery disease and acute myocardial infarction with cardiogenic shock, the 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy was lower among those who initially underwent PCI of the culprit lesion only than among those who underwent immediate multivessel PCI. (Funded by the European Union 7th Framework Program and others; CULPRIT-SHOCK ClinicalTrials.gov number, NCT01927549.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Thiele at Heart Center Leipzig–University Hospital, Department of Internal Medicine–Cardiology, Strümpellstr. 39, 04289 Leipzig, Germany, or at holger.thiele@medizin.uni-leipzig.de.

*A complete list of investigators in the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Desch and Zeymer contributed equally to this article.

This article was published on October 30, 2017, at NEJM.org.

N Engl J Med 2017;377:2419-32.
DOI: 10.1056/NEJMoa1710261

The mortality associated with cardiogenic shock in acute myocardial infarction can be reduced with the use of early revascularization, predominantly percutaneous coronary intervention (PCI), to restore blood flow to the culprit coronary artery.[1-3] Up to 80% of patients who have cardiogenic shock present with multivessel coronary artery disease,[4] and mortality is higher with multivessel disease than with single-vessel disease.[5-7] The value of performing immediate PCI for clinically important stenoses of major nonculprit coronary arteries is controversial, and to our knowledge, randomized trials that have addressed this issue have not included patients with cardiogenic shock.[8-11]

Several theoretical arguments support immediate revascularization of all coronary arteries with clinically important stenoses or chronic total occlusions in addition to the culprit lesion, particularly in patients with cardiogenic shock. The most notable argument is the potential to improve overall myocardial perfusion and function. However, immediate multivessel PCI might pose additional risks, such as induction of further ischemia, volume overload, and renal impairment due to the use of an increased dose of contrast material. Current evidence from nonrandomized studies involving patients with cardiogenic shock suggests that mortality at short-term follow-up is higher after immediate multivessel PCI than after PCI of the culprit lesion only.[12] Guideline recommendations differentiate between stable and unstable hemodynamic status.[13,14] European guidelines recommend the consideration of immediate PCI of nonculprit lesions in patients with cardiogenic shock. U.S. guidelines give no specific recommendation. However, recent U.S. appropriate-use criteria indicate that it is appropriate to perform immediate revascularization of a nonculprit artery if cardiogenic shock persists after revascularization of the culprit artery.[13-15] The Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial was designed to test the hypothesis that PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, would result in better clinical outcomes than immediate multivessel PCI among patients who have multivessel coronary artery disease and acute myocardial infarction with cardiogenic shock.

## Methods

### Trial Design and Oversight

The trial design has been published previously.[4] This investigator-initiated, randomized, open-label, European multicenter trial involved patients who had acute ST-segment elevation or non–ST-segment elevation myocardial infarction that was complicated by cardiogenic shock, with planned early revascularization by means of PCI and an identifiable culprit lesion. The protocol (available with the full text of this article at NEJM.org) was designed by the principal investigator and was modified and approved by the steering committee[4]; it was also approved by all relevant ethics committees. The trial was registered at ClinicalTrials.gov 4 months after enrollment of the first patient, as discussed in the Supplementary Appendix (available at NEJM.org).

The institutions that funded the trial had no involvement in the conduct of the trial. A coordinating research organization, Institut für Herzinfarktforschung (Institute for Myocardial Infarction Research), maintained the data and performed independent statistical analysis. The steering committee vouches for the integrity and completeness of the data, and the statistician vouches for the accuracy of the data analysis and the fidelity of the trial to the protocol.

### Patients

Patients were eligible for the trial if they had acute myocardial infarction with cardiogenic shock. Additional eligibility criteria were planned early revascularization by means of PCI, multivessel coronary artery disease (defined as at least two major vessels [≥2 mm in diameter] with >70% stenosis of the diameter), and an identifiable culprit lesion. Criteria for cardiogenic shock included a systolic blood pressure of less than 90 mm Hg for longer than 30 minutes or the use of catecholamine therapy to maintain a systolic pressure of at least 90 mm Hg, clinical signs of pulmonary congestion, and signs of impaired organ perfusion with at least one of the following manifestations: altered mental status, cold and clammy skin and limbs, oliguria with a urine output of less than 30 ml per hour, or an arterial lactate level of more than 2.0 mmol per liter.

Exclusion criteria were resuscitation for longer

than 30 minutes, no intrinsic heart action, an assumed severe deficit in cerebral function with fixed dilated pupils, an indication for primary urgent coronary-artery bypass grafting, single-vessel coronary artery disease, a mechanical cause of cardiogenic shock, the onset of shock more than 12 hours before randomization, an age of more than 90 years, shock with a noncardiogenic cause, massive pulmonary embolism, known severe renal insufficiency (creatinine clearance, <30 ml per minute), and other severe concomitant disease associated with a life expectancy of less than 6 months. For all eligible patients, written informed consent was obtained with the use of a prespecified process that varied slightly according to country (see the Supplementary Appendix).[4] Patients with cardiogenic shock who were not eligible for randomization were entered into the prospective CULPRIT-SHOCK registry.

### RANDOMIZATION AND TREATMENT

Patients underwent randomization immediately after diagnostic angiography. Randomization was performed centrally with the use of an Internet-based program with randomly changing blocks of four or six and stratification according to center.

Patients were randomly assigned, in a 1:1 ratio, to one of two initial revascularization strategies: either PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, or immediate multivessel PCI. In all the patients, PCI of the culprit lesion was performed first, with the use of standard interventional techniques. In patients in the culprit-lesion-only PCI group, all other lesions were to be left untreated at the time of the initial procedure. Staged revascularization procedures were encouraged on the basis of the presence of residual ischemic lesions (evaluated by means of noninvasive testing or with the use of fractional flow reserve [FFR]), symptoms, and clinical and neurologic status. In patients in the multivessel PCI group, PCI of all major coronary arteries with more than 70% stenosis of the diameter was to be performed. This included efforts to recanalize chronic total occlusions during the acute phase; the recommended maximum dose of contrast material was 300 ml.

All other interventional therapeutic measures were allowed, independent of the assigned treatment strategy. In particular, the use of mechanical circulatory support was left to the discretion of the operator. Further therapy was provided in the intensive care unit (ICU) in accordance with generally accepted intensive care guidelines. If renal-replacement therapy was deemed to be necessary, the method, duration, and reason for initiation (in accordance with predefined criteria) were documented.

### PRIMARY AND SECONDARY END POINTS

The primary end point was a composite of death from any cause or severe renal failure leading to renal-replacement therapy within 30 days after randomization. Renal-replacement therapy (dialysis, hemofiltration, or hemodiafiltration) was considered for otherwise untreatable volume overload, hyperkalemia (potassium level, >6.0 mmol per liter), severe uremia (blood urea level, >50 mg per deciliter), or persistent severe metabolic acidosis (pH, <7.2).[4]

Clinical secondary end points included the individual components of the primary end point, recurrent myocardial infarction, rehospitalization for congestive heart failure, and repeat revascularization. Other secondary end points included time to hemodynamic stabilization, the use of catecholamine therapy and the duration of such therapy, the duration of the ICU stay, the Simplified Acute Physiology Score II (SAPS-II), and the use of mechanical ventilation and the duration of such therapy. For the assessment of renal and myocardial injury, serial measurements of estimated creatinine clearance and creatine kinase and troponin levels were obtained. Procedural success was included as a secondary end point but was not clearly prespecified, and therefore the results are not reported.

Safety end points included bleeding, which was defined as type 2, 3, or 5 on the Bleeding Academic Research Consortium (BARC) scale (with type 2 indicating any overt, actionable sign of bleeding; type 3 bleeding with a decrease in the hemoglobin level of >3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; and type 5 fatal bleeding), as well as occurrence of stroke.[4,16] Detailed definitions of the outcome measures and specific information regarding the reporting of individual prespecified end points are provided in the Supplementary Appendix.

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=342) |
|---|---|---|
| Age — yr | | |
| Median | 70 | 70 |
| Interquartile range | 60–78 | 60–77 |
| Male sex — no./total no. (%) | 257/343 (74.9) | 267/342 (78.1) |
| Weight — kg | | |
| Median | 80 | 80 |
| Interquartile range | 70–90 | 75–90 |
| Height — cm | | |
| Median | 174 | 175 |
| Interquartile range | 168–180 | 170–180 |
| Body-mass index† | | |
| Median | 26.6 | 26.7 |
| Interquartile range | 24.2–29.4 | 24.7–29.4 |
| Cardiovascular risk factors — no./total no. (%) | | |
| Current smoking | 85/334 (25.4) | 89/325 (27.4) |
| Hypertension | 200/339 (59.0) | 206/335 (61.5) |
| Hypercholesterolemia | 112/338 (33.1) | 116/333 (34.8) |
| Diabetes mellitus | 102/337 (30.3) | 116/335 (34.6) |
| Previous myocardial infarction — no./total no. (%) | 60/339 (17.7) | 53/335 (15.8) |
| Previous stroke — no./total no. (%) | 29/341 (8.5) | 20/336 (6.0) |
| Known peripheral artery disease — no./total no. (%) | 43/341 (12.6) | 37/337 (11.0) |
| Previous PCI — no./total no. (%) | 64/339 (18.9) | 63/335 (18.8) |
| Previous coronary-artery bypass grafting — no./total no. (%) | 20/341 (5.9) | 13/337 (3.9) |
| Signs of impaired organ perfusion — no./total no. (%) | | |
| Altered mental status | 237/341 (69.5) | 224/341 (65.7) |
| Cold, clammy skin and limbs | 233/338 (68.9) | 236/335 (70.4) |
| Oliguria | 80/334 (24.0) | 93/326 (28.5) |
| Arterial lactate >2.0 mmol/liter | 216/334 (64.7) | 224/330 (67.9) |
| Fibrinolysis <24 hr before randomization — no./total no. (%) | 19/341 (5.6) | 15/341 (4.4) |
| Resuscitation before randomization — no./total no. (%) | 177/341 (51.9) | 189/342 (55.3) |
| ST-segment elevation myocardial infarction — no./total no. (%) | 206/335 (61.5) | 209/330 (63.3) |
| Anterior ST-segment elevation myocardial infarction — no./total no. (%) | 108/205 (52.7) | 114/206 (55.3) |
| Left bundle-branch block — no./total no. (%) | 52/335 (15.5) | 47/331 (14.2) |
| Systolic blood pressure — mm Hg | | |
| Median | 100 | 100 |
| Interquartile range | 83–120 | 85–130 |
| Diastolic blood pressure — mm Hg | | |
| Median | 60 | 61 |
| Interquartile range | 50–80 | 50–80 |
| Mean blood pressure — mm Hg | | |
| Median | 76 | 76 |
| Interquartile range | 63–92 | 63–93 |

**Table 1. (Continued.)**

| Characteristic | Culprit-Lesion-Only PCI Group (N = 344) | Multivessel PCI Group (N = 342) |
|---|---|---|
| Heart rate — beats/min | | |
| Median | 90 | 91 |
| Interquartile range | 73–109 | 72–107 |
| Creatinine — mg/dl‡ | | |
| Median | 1.17 | 1.20 |
| Interquartile range | 0.90–1.66 | 0.90–1.68 |
| Creatinine clearance — ml/min | | |
| Median | 64 | 66 |
| Interquartile range | 42–95 | 43–93 |
| No. of affected vessels — no./total no. (%) | | |
| 1 | 3/343 (0.9) | 2/342 (0.6) |
| 2 | 122/343 (35.6) | 124/342 (36.3) |
| 3 | 218/343 (63.6) | 216/342 (63.2) |
| Vessel related to the infarction — no./total no. (%) | | |
| Left anterior descending artery | 132/343 (38.5) | 156/342 (45.6) |
| Left circumflex artery | 76/343 (22.2) | 70/342 (20.5) |
| Right coronary artery | 102/343 (29.7) | 89/342 (26.0) |
| Left main artery | 31/343 (9.0) | 22/342 (6.4) |
| Bypass graft | 2/343 (0.6) | 5/342 (1.5) |
| ≥1 Chronic total occlusion — no./total no. (%) | 77/344 (22.4) | 82/342 (24.0) |
| Left ventricular ejection fraction — % | | |
| Median | 33 | 30 |
| Interquartile range | 25–40 | 21–40 |

* PCI denotes percutaneous coronary intervention.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

### STATISTICAL ANALYSIS

To calculate the sample size, we estimated an event rate of the composite primary end point of death or renal-replacement therapy of 38% in the culprit-lesion-only PCI group and 50% in the multivessel PCI group.[4] A sequential statistical design was chosen; one interim analysis was performed after 50% of all the patients who could be evaluated had completed 30 days of follow-up. The global type I error level was 0.05. We calculated that a sample of 684 patients would give the trial 80% power to rule out the null hypothesis of no difference between the two treatment groups in the event rate for the primary end point (at a two-sided alpha level of 0.048 for the final analysis). To allow for a withdrawal rate of 3%, 706 patients were recruited. The software used for sample-size calculation was nQuery Advisor, version 7.0 (Statistical Solutions).

All data were analyzed according to the intention-to-treat principle. In addition, sensitivity analyses were performed in the per-protocol and as-treated populations (defined in Fig. S1 in the Supplementary Appendix) to evaluate data robustness. For the primary end point, chi-square testing was performed to compare event rates. Binary secondary end points were assessed by means of Fisher's exact tests or chi-square tests, and quantitative secondary end points were assessed by means of Mann–Whitney U tests. No correction for multiple testing was performed. Analyses were performed in subgroups that were defined accord-

**Table 2. Procedural Characteristics.**

| Variable | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=342) | P Value |
|---|---|---|---|
| Arterial access — no./total no. (%) | | | |
| Femoral | 287/343 (83.7) | 277/342 (81.0) | 0.36 |
| Radial | 61/343 (17.8) | 66/342 (19.3) | 0.61 |
| Brachial | 2/343 (0.6) | 1/342 (0.3) | >0.99 |
| Stent in culprit lesion — no./total no. (%) | | | |
| Any | 326/343 (95.0) | 324/342 (94.7) | 0.86 |
| Bare metal | 20/326 (6.1) | 17/324 (5.2) | 0.63 |
| Drug eluting | 305/326 (93.6) | 308/324 (95.1) | 0.41 |
| Bioresorbable scaffold in culprit lesion — no./total no. (%) | 2/326 (0.6) | 3/324 (0.9) | 0.69 |
| Aspiration thrombectomy of culprit lesion — no./total no. (%) | 60/343 (17.5) | 39/342 (11.4) | 0.02* |
| TIMI grade for blood flow — no./total no. (%)† | | | |
| Before PCI of culprit lesion | | | |
| 0 | 189/339 (55.8) | 178/337 (52.8) | |
| I | 37/339 (10.9) | 45/337 (13.4) | |
| II | 56/339 (16.5) | 50/337 (14.8) | |
| III | 57/339 (16.8) | 64/337 (19.0) | 0.49 |
| After PCI of culprit lesion | | | |
| 0 | 13/342 (3.8) | 16/338 (4.7) | |
| I | 12/342 (3.5) | 8/338 (2.4) | |
| II | 28/342 (8.2) | 21/338 (6.2) | |
| III | 289/342 (84.5) | 293/338 (86.7) | 0.46 |
| Immediate PCI of nonculprit lesions — no./total no. (%) | 43/344 (12.5) | 310/342 (90.6) | <0.001 |
| Immediate complete revascularization achieved — no./total no. (%) | 26/344 (7.6) | 277/342 (81.0) | <0.001 |
| Total dose of contrast material — ml | | | <0.001 |
| Median | 190 | 250 | |
| Interquartile range | 140–250 | 200–350 | |
| Total duration of fluoroscopy — min | | | <0.001 |
| Median | 13 | 19 | |
| Interquartile range | 7–20 | 12–29 | |
| Staged PCI of nonculprit lesions — no./total no. (%) | 60/344 (17.4) | 8/341 (2.3) | <0.001 |
| Staged coronary-artery bypass grafting — no./total no. (%) | 1/344 (0.3) | 0/341 | >0.99 |
| Mechanical circulatory support — no./total no. (%) | | | |
| Any | 99/344 (28.8) | 95/342 (27.8) | 0.77 |
| Intraaortic balloon pump | 25/99 (25.3) | 26/95 (27.4) | 0.74 |
| Impella 2.5 percutaneous ventricular assist device | 16/99 (16.2) | 18/95 (18.9) | 0.61 |
| Impella CP percutaneous ventricular assist device | 30/99 (30.3) | 18/95 (18.9) | 0.07 |
| TandemHeart percutaneous ventricular assist device | 2/99 (2.0) | 0/95 | 0.50 |
| Extracorporeal membrane oxygenation | 18/99 (18.2) | 27/95 (28.4) | 0.09 |
| Other | 12/99 (12.1) | 8/95 (8.4) | 0.40 |
| Heart transplantation — no./total no. (%) | 1/343 (0.3) | 0/340 | >0.99 |
| Mild hypothermia — no./total no. (%) | 111/344 (32.3) | 118/340 (34.7) | 0.50 |

**Table 2. (Continued.)**

| Variable | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=342) | P Value |
|---|---|---|---|
| Mechanical ventilation — no./total no. (%) | 273/344 (79.4) | 282/339 (83.2) | 0.20 |
| Duration of mechanical ventilation — days | | | 0.97 |
| Median | 3 | 3 | |
| Interquartile range | 1–7 | 1–7 | |
| Duration of intensive care treatment — days | | | 0.61 |
| Median | 5 | 5 | |
| Interquartile range | 2-12 | 2-11 | |
| Antiplatelet and anticoagulant drugs administered in the catheterization laboratory — no./total no. (%) | | | |
| Aspirin | 259/344 (75.3) | 240/341 (70.4) | 0.15 |
| Clopidogrel | 65/344 (18.9) | 61/341 (17.9) | 0.73 |
| Prasugrel | 47/344 (13.7) | 41/341 (12.0) | 0.52 |
| Ticagrelor | 76/344 (22.1) | 83/341 (24.3) | 0.49 |
| Glycoprotein IIb/IIIa inhibitor | 74/344 (21.5) | 73/341 (21.4) | 0.97 |
| Cangrelor | 8/344 (2.3) | 11/341 (3.2) | 0.47 |
| Unfractionated heparin | 276/344 (80.2) | 281/341 (82.4) | 0.47 |
| Low-molecular-weight heparin | 50/344 (14.5) | 49/341 (14.4) | 0.95 |
| Bivalirudin | 16/344 (4.7) | 24/341 (7.0) | 0.18 |
| Subsequent medications in those who survived until hospital discharge — no./total no. (%) | | | |
| Statin | 184/195 (94.4) | 152/165 (92.1) | 0.40 |
| Beta-blocker | 181/195 (92.8) | 148/165 (89.7) | 0.29 |
| Angiotensin-converting–enzyme inhibitor or angiotensin II type 1 receptor antagonist | 176/195 (90.3) | 140/165 (84.8) | 0.12 |
| Aspirin | 191/195 (97.9) | 163/165 (98.8) | 0.54 |
| Clopidogrel | 89/195 (45.6) | 73/165 (44.2) | 0.79 |
| Prasugrel | 67/195 (34.4) | 56/165 (33.9) | 0.93 |
| Ticagrelor | 78/195 (40.0) | 65/165 (39.4) | 0.91 |
| Catecholamine therapy — no./total no. (%) | 304/344 (88.4) | 309/339 (91.2) | 0.23 |
| Duration of catecholamine therapy — days | | | 0.43 |
| Median | 2 | 2 | |
| Interquartile range | 1–4 | 1–5 | |
| Time to hemodynamic stabilization — days | | | 0.56 |
| Median | 3 | 3 | |
| Interquartile range | 1–6 | 1–6 | |

* The difference between the two groups in the rate of aspiration thrombectomy would most likely not remain significant after adjustment for multiple testing.
† Thrombolysis in Myocardial Infraction (TIMI) grades for blood flow range from 0 to III, with higher grades indicating better flow. TIMI grades were reported by the investigator.

ing to sex, age (<50 years, 50 to 75 years, or >75 years), location of the infarction (anterior or nonanterior), number of affected vessels (two or three), type of myocardial infarction (ST-segment elevation or non–ST-segment elevation), and the presence or absence of diabetes, arterial hypertension, previous infarction, and chronic total occlusion.

## RESULTS

### PATIENTS

From April 2013 through April 2017, a total of 1075 patients with cardiogenic shock were screened at 83 European centers, and 706 of those patients (65.6%) were randomly assigned to the culprit-lesion-only PCI group (351 patients) or the multivessel PCI group (355 patients). Data could be evaluated for 344 patients in the culprit-lesion-only PCI group and for 342 patients in the multivessel PCI group (Fig. S1 in the Supplementary Appendix). Baseline characteristics were well balanced between the two treatment groups (Table 1).

### TREATMENT

Procedural characteristics are shown in Table 2. Crossover from the culprit-lesion-only PCI group to the multivessel PCI group was reported in 43 patients (12.5%); reasons for crossover are shown in Table S1 in the Supplementary Appendix. Staged revascularization was performed in 61 of the 344 patients (17.7%) in the culprit-lesion-only PCI group. Crossover from the multivessel PCI group to the culprit-lesion-only PCI group was reported in 32 patients (9.4%); reasons for crossover are shown in Table S2 in the Supplementary Appendix.

The Thrombolysis in Myocardial Infarction (TIMI) grades for blood flow obtained before and after PCI of the culprit artery did not differ significantly between the two groups. More patients underwent aspiration thrombectomy in the culprit-lesion-only group than in the multivessel PCI group. The overall dose of contrast material was significantly higher and the duration of fluoroscopy was significantly longer in the multivessel PCI group than in the culprit-lesion-only group. There was no significant difference between the two groups with respect to the use of adjunctive medications or devices for mechanical circulatory support. Most patients were treated with multiple antiplatelet and anticoagulant drugs, including aspirin, $P2Y_{12}$ inhibitors, glycoprotein IIb/IIIa inhibitors, and unfractionated heparin.

### PRIMARY AND SECONDARY END POINTS

One patient in the multivessel PCI group was lost to follow-up before 30 days. Therefore, 344 patients in the culprit-lesion-only PCI group and 341 patients in the multivessel PCI group were included in the analysis of the primary and secondary end points (Fig. S1 in the Supplementary Appendix).

At 30 days, the rate of the composite primary end point of death or renal-replacement therapy was significantly lower in the culprit-lesion-only PCI group than in the multivessel PCI group (45.9% vs. 55.4%; relative risk, 0.83; 95% confidence interval [CI], 0.71 to 0.96; P=0.01) (Table 3 and Fig. 1A). Only minor variation in the relative risk was observed when the analysis was performed in the per-protocol population (44.8% in the culprit-lesion-only PCI group vs. 55.1% in the multivessel PCI group; relative risk, 0.81; 95% CI, 0.69 to 0.96; P=0.01) or the as-treated population (46.0% in the culprit-lesion-only PCI group vs. 55.1% in the multivessel PCI group; relative risk, 0.83; 95% CI, 0.72 to 0.97; P=0.02). Prespecified subgroup analyses revealed consistent results across all the subgroups (Fig. 2).

The rate of death from any cause was significantly lower in the culprit-lesion-only PCI group than in the multivessel PCI group (43.3% vs. 51.6%; relative risk, 0.84; 95% CI, 0.72 to 0.98; P=0.03) (Table 3 and Fig. 1B). The causes of death are shown in Table S3 in the Supplementary Appendix. The rate of renal-replacement therapy did not differ significantly between the culprit-lesion-only PCI group and the multivessel PCI group (11.6% and 16.4%, respectively; relative risk, 0.71; 95% CI, 0.49 to 1.03; P=0.07) (Table 3 and Fig. 1C). The rates of recurrent myocardial infarction, rehospitalization for congestive heart failure, bleeding, and stroke did not differ significantly between the two groups (Table 3). Event rates for the primary end point and its components among patients in the CULPRIT-SHOCK registry are shown in Table S4 in the Supplementary Appendix.

The time to hemodynamic stabilization, the use of catecholamine therapy and the duration of such therapy, the duration of the ICU stay, and the use of mechanical ventilation and the duration of such therapy did not differ significantly between the two groups (Table 2). There was also no significant difference between the two groups in the SAPS-II score. The creatinine clearance and levels of arterial lactate, troponin, and creatine kinase were similar in the two treatment groups. (See Figs. S2 through S6 in the Supplementary Appendix.)

**Table 3. Clinical Outcomes at 30 Days.**

| Outcome | Culprit-Lesion-Only PCI Group (N=344) | Multivessel PCI Group (N=341) | Relative Risk (95% CI) | P Value |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Primary end point: death from any cause or renal-replacement therapy | 158/344 (45.9) | 189/341 (55.4) | 0.83 (0.71–0.96) | 0.01 |
| Death from any cause* | 149/344 (43.3) | 176/341 (51.6) | 0.84 (0.72–0.98) | 0.03 |
| Renal-replacement therapy | 40/344 (11.6) | 56/341 (16.4) | 0.71 (0.49–1.03) | 0.07 |
| Indication for renal-replacement therapy | | | | |
| Hyperkalemia | 7/40 (17.5) | 9/56 (16.1) | | |
| Metabolic acidosis | 18/40 (45.0) | 20/56 (35.7) | | |
| Uremia | 13/40 (32.5) | 20/56 (35.7) | | |
| Volume overload | 12/40 (30.0) | 17/56 (30.4) | | |
| Other cause | 6/40 (15.0) | 4/56 (7.1) | | |
| Recurrent myocardial infarction | 4/344 (1.2) | 3/341 (0.9) | 1.32 (0.30–5.86) | 1.00 |
| Rehospitalization for congestive heart failure | 1/344 (0.3) | 1/342 (0.3) | 0.99 (0.10–9.50) | 0.99 |
| Death, recurrent myocardial infarction, or rehospitalization for congestive heart failure | 151/344 (43.9) | 179/342 (52.3) | 0.84 (0.72–0.98) | 0.03 |
| Staged or urgent repeat revascularization | 74/344 (21.5) | 13/341 (3.8) | 7.43 (3.61–15.31) | <0.001 |
| Stroke | 12/344 (3.5) | 10/341 (2.9) | 1.19 (0.52–2.72) | 0.68 |
| BARC type 2, 3, or 5 bleeding† | | | | |
| Any | 57/344 (16.6) | 75/341 (22.0) | 0.75 (0.55–1.03) | 0.07 |
| BARC 2 | 14/57 (24.6) | 23/75 (30.7) | | |
| BARC 3a | 21/57 (36.8) | 28/75 (37.3) | | |
| BARC 3b | 17/57 (29.8) | 19/75 (25.3) | | |
| BARC 3c | 0/57 | 2/75 (2.7) | | |
| BARC 5a | 4/57 (7.0) | 1/75 (1.3) | | |
| BARC 5b | 1/57 (1.8) | 2/75 (2.7) | | |

* Causes of death are shown in Table S3 in the Supplementary Appendix.

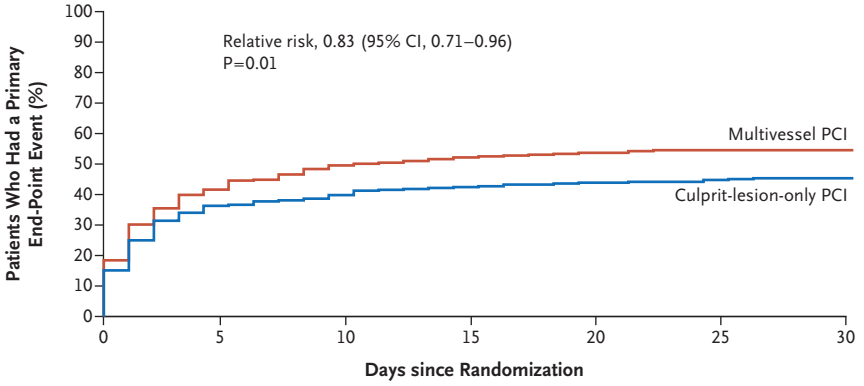
† On the Bleeding Academic Research Consortium (BARC) scale, type 2 indicates any overt, actionable sign of bleeding; type 3a, overt bleeding with a decrease in the hemoglobin level of 3 to less than 5 g per deciliter or any transfusion; type 3b, overt bleeding with a decrease in the hemoglobin level of 5 g or more per deciliter, cardiac tamponade, or surgical intervention; type 3c, intracranial hemorrhage or intraocular bleeding; type 5a, probable fatal bleeding; and type 5b, definite fatal bleeding.

## DISCUSSION

In this randomized, multicenter trial involving patients with multivessel coronary artery disease and acute myocardial infarction with cardiogenic shock, PCI of the culprit lesion only (with the option of staged revascularization of nonculprit lesions) was superior to immediate multivessel PCI with respect to a composite end point of death or renal-replacement therapy at 30 days. The difference was driven mainly by significantly lower mortality in the culprit-lesion-only PCI group.

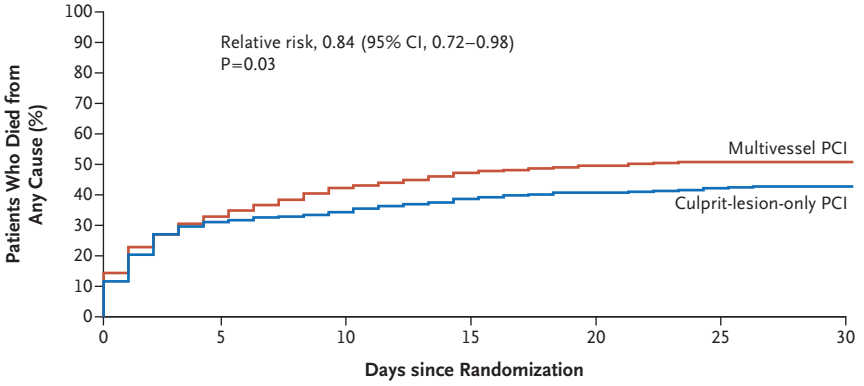
Multivessel coronary artery disease is present in the vast majority of patients who have acute myocardial infarction with cardiogenic shock and is associated with higher mortality than single-vessel disease.[5] Thus, mortality at 30 days was higher in this trial than in other randomized trials involving patients with cardiogenic shock, despite similar inclusion criteria regarding cardiogenic shock.[2,17-19] Although PCI of the culprit lesion is the established standard of care, the management of nonculprit lesions is the subject of intense debate. Complete revascularization has been thought

**A Composite Primary End Point**



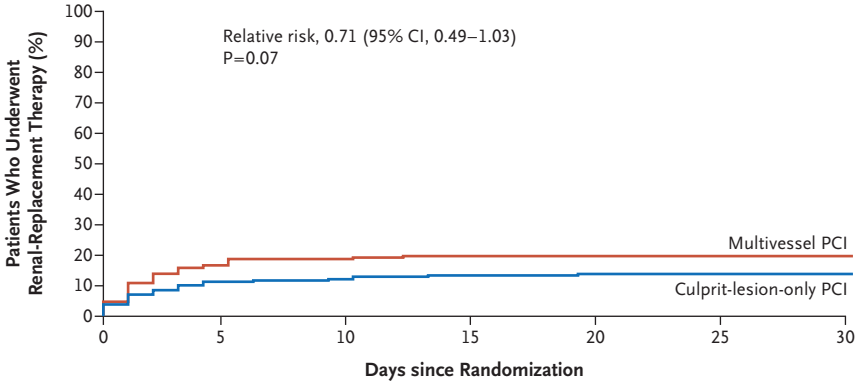

| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multivessel PCI | 341 | 199 | 172 | 162 | 156 | 153 | 152 |
| Culprit-lesion-only PCI | 344 | 219 | 207 | 198 | 192 | 189 | 184 |

**B Death from Any Cause**




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multivessel PCI | 341 | 229 | 197 | 179 | 170 | 166 | 165 |
| Culprit-lesion-only PCI | 344 | 237 | 226 | 211 | 203 | 198 | 193 |

**C Renal-Replacement Therapy**




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multivessel PCI | 341 | 199 | 172 | 162 | 156 | 153 | 152 |
| Culprit-lesion-only PCI | 344 | 219 | 207 | 198 | 192 | 189 | 184 |

**Figure 1 (facing page). Event Rates of the Primary End Point and Its Components at 30 Days.**

Shown are Kaplan–Meier time-to-event curves for the primary end point of a composite of death from any cause or severe renal failure leading to renal-replacement therapy (Panel A), as well as the individual components of death from any cause (Panel B) and renal-replacement therapy (Panel C), within 30 days after randomization. PCI denotes percutaneous coronary intervention.

to be beneficial in improving ventricular function and hemodynamic status.[13] However, the results of this trial and of nonrandomized studies have shown lower mortality with PCI of the culprit lesion only than with multivessel PCI.[12]

The lack of benefit of immediate multivessel PCI in this trial might be related to the significantly higher dose of contrast material that was used in the multivessel PCI group than in the culprit-lesion-only PCI group and a consequent decline in renal function. However, the incidence of severe renal failure leading to renal-replacement therapy did not differ significantly between the two groups. The higher dose of contrast material that was used in the multivessel PCI group than in the culprit-lesion-only PCI group may have also led to acute left ventricular volume overload and a subsequent 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.

The findings of this trial are in contrast with the results of trials involving hemodynamically stable patients with myocardial infarction, which have shown a lower rate of major adverse cardiac events with either angiographically guided or FFR-guided early multivessel PCI than with PCI of the culprit lesion only.[8-11,20] However, these findings were driven mainly by the difference in the rate of repeat revascularization, which was counted as part of a composite end point, because repeat revascularization was usually performed during follow-up as staged revascularization procedures in patients who initially underwent PCI of the culprit lesion only. In our trial, staged revascularization was encouraged and not counted as a disadvantage of the culprit-lesion-only PCI strategy. In previous trials involving hemodynamically stable patients with myocardial infarction, there were no significant differences between the two treatment strategies in mortality or the rate of recurrent infarction. Among patients with cardiogenic shock, the acute hazards of a prolonged procedure time (including the increased dose of contrast material) seem to outweigh any potential negative aspects of repeat revascularization.

In contrast with previous trials involving highly selected patients with stable infarction, this trial did not specify the presence of a chronic total occlusion as an exclusion criterion.[8-11] This allowed for inclusion of a real-world cohort of patients with multivessel disease and cardiogenic shock. Chronic total occlusion is frequently present in patients with cardiogenic shock and is associated with adverse clinical outcomes.[21,22] Exclusion of patients with a chronic total occlusion would have led to a major selection bias and a lower-risk cohort. Therefore, in the multivessel PCI group, immediate recanalization of a chronic total occlusion was recommended. However, it was also advised to pursue recanalization attempts cautiously and to limit the total dose of contrast material to 300 ml. Complete revascularization was achieved in 81% of the patients in the multivessel PCI group. A previous trial involving patients with stable infarction showed no benefit of recanalization for chronic total occlusion of nonculprit lesions.[23]

This trial has several limitations. First, blinding was not possible because of the nature of the intervention. Management of cardiogenic shock involves a complex series of clinical decisions, and it is not possible to fully eliminate some bias during the actual course of treatment. Second, some patients could not be evaluated because of difficulties in obtaining final informed consent. The withdrawal rate was at the exact anticipated level of 3%. Third, 75 patients crossed over from their assigned treatment to the other treatment. Of these patients, 14 in the culprit-lesion-only PCI group underwent immediate multivessel PCI for multiple reasons, including lack of hemodynamic improvement, plaque shifts, and the presence of newly detected lesions after treatment of the culprit lesion; these reasons suggest that the treatment strategy may require adaptation to the specific clinical circumstances.

In conclusion, this randomized, multicenter trial showed that, among patients who had multi-

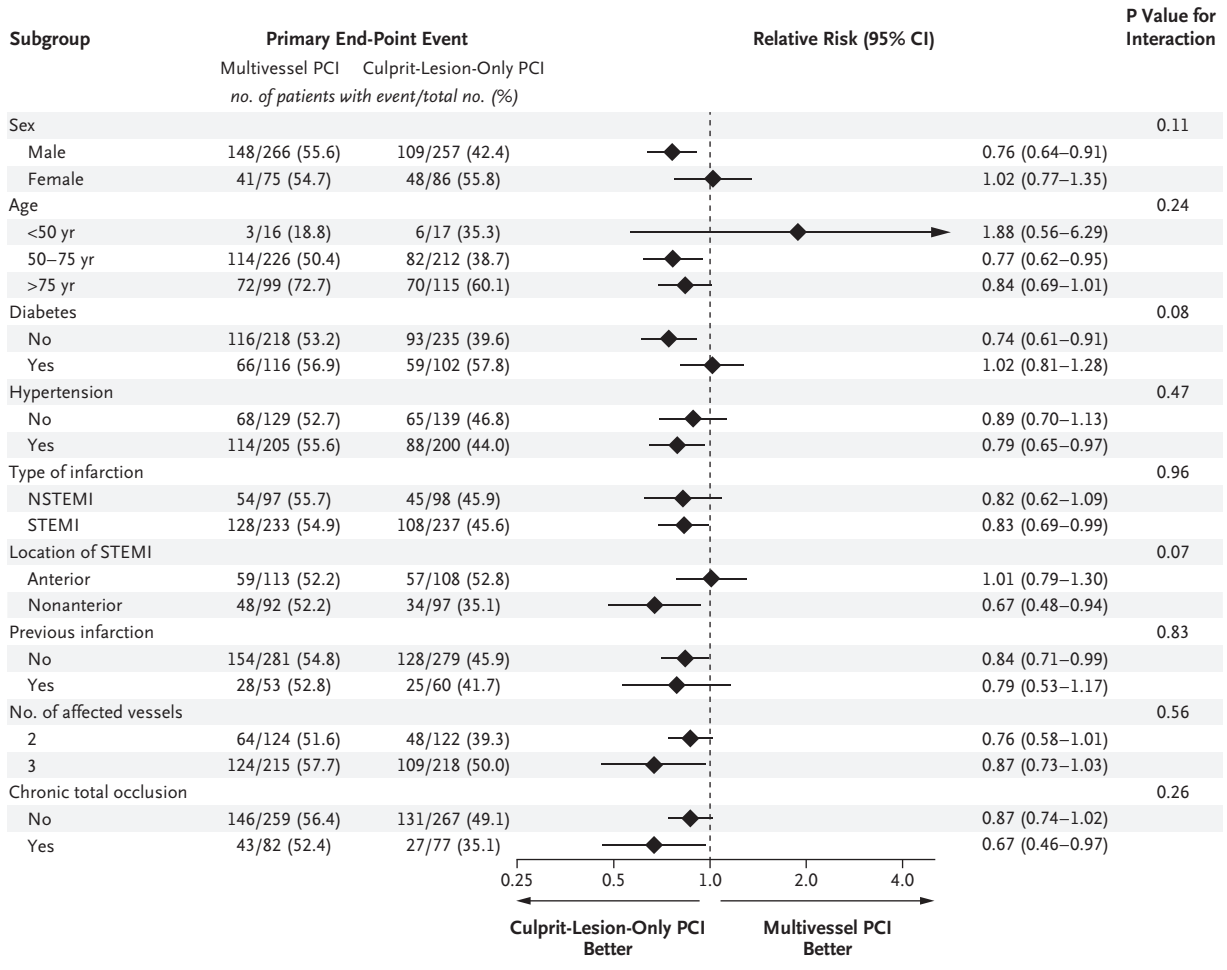



**Figure 2. Subgroup Analyses of the Primary End Point at 30 Days.**

NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

vessel coronary artery disease and acute myocardial infarction with cardiogenic shock, the risk of a composite of death or renal-replacement therapy was lower among those who initially underwent PCI of the culprit lesion only than among those who underwent multivessel PCI. This outcome was mainly driven by lower mortality among patients who underwent culprit-lesion-only PCI.

Supported by a grant (FP7/2007-2013) from the European Union 7th Framework Program and by the German Heart Research Foundation and the German Cardiac Society.

Dr. Landmesser reports receiving lecture fees and advisory-board fees from Abbott and Biotronik and grant support from the German Center for Cardiovascular Research; Dr. Piek, receiving travel support from Abbott Vascular and advisory-board fees and travel support from Philips Volcano; Dr. Noc, receiving consulting fees from ZOLL Circulation, lecture fees from Maquet Getinge, and grant support from AstraZeneca; Dr. Goslar, receiving lecture fees from AstraZeneca; Dr. Montalescot, receiving grant support paid to his institution, consulting fees, advisory-board fees, and lecture fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Medtronic, Merck Sharpe and Dohme, Pfizer, and Sanofi, grant support paid to his institution from Celladon, consulting fees from Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Menarini, the TIMI Study Group, and Actelion, lecture fees and education fees from the Cardiovascular Research Foundation, DME Resources, Europa, Lead-Up, WebMD, and Agence CCC, and review fees and education fees from Elsevier; Dr. Windecker, receiving grant support from Biotronik, Boston Scientific, Bracco, Edwards Lifesciences, Medtronic, Terumo, and St. Jude Medical; Dr. Savonitto, receiving grant support from Novartis, Daiichi Sankyo, and Eli Lilly and lecture fees from Pfizer, Bristol-Myers Squibb, AstraZeneca, and Bayer; and Dr. Zeymer,

receiving lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Sanofi, MSD, The Medicines Company, Pfizer, Daiichi Sankyo, Eli Lilly, and Abiomed. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who agreed to participate in this trial and their relatives, the trial contributors, and the investigators who recruited the patients.

## APPENDIX

The authors' full names and academic degrees are as follows: Holger Thiele, M.D., Ibrahim Akin, M.D., Marcus Sandri, M.D., Georg Fuernau, M.D., Suzanne de Waha, M.D., Roza Meyer-Saraei, Ph.D., Peter Nordbeck, M.D., Tobias Geisler, M.D., Ulf Landmesser, M.D., Carsten Skurk, M.D., Andreas Fach, M.D., Harald Lapp, M.D., Jan J. Piek, M.D., Ph.D., Marko Noc, M.D., Tomaž Goslar, M.D., Stephan B. Felix, M.D., Lars S. Maier, M.D., Janina Stepinska, M.D., Keith Oldroyd, M.D., Pranas Serpytis, M.D., Gilles Montalescot, M.D., Olivier Barthelemy, M.D., Kurt Huber, M.D., Stephan Windecker, M.D., Stefano Savonitto, M.D., Patrizia Torremante, B.Sc., Christiaan Vrints, M.D., Steffen Schneider, Ph.D., Steffen Desch, M.D., and Uwe Zeymer, M.D.

The authors' affiliations are as follows: Heart Center Leipzig, University Hospital, Leipzig (H.T., M.S., S.D.), Universitätsmedizin Mannheim, Mannheim (I.A.), University Heart Center Lübeck, Lübeck (G.F., S. de Waha, R.M.-S.), German Center for Cardiovascular Research (DZHK) (G.F., S. de Waha, R.M.-S., U.L., C.S., S.B.F., S.D.) and Universitätsklinikum Charité, Campus Benjamin Franklin (U.L., C.S.), Berlin, Universitätsklinikum Würzburg, Würzburg (P.N.), Klinikum der Eberhard-Karls-Universität Tübingen, Tübingen (T. Geisler), Klinikum Links der Weser, Bremen (A.F.), Helios Klinik Erfurt, Erfurt (H.L.), Ernst-Moritz-Arndt-Universität, Greifswald (S.B.F.), Universitäres Herzzentrum Regensburg, Regensburg (L.S.M.), and Institut für Herzinfarktforschung (S. Schneider, U.Z.) and Klinikum Ludwigshafen (U.Z.), Ludwigshafen — all in Germany; Academic Medical Center, Amsterdam (J.J.P.); University Medical Center Ljubljana, Ljubljana, Slovenia (M.N., T. Goslar); Institute of Cardiology, Warsaw, Poland (J.S.); Golden Jubilee National Hospital, Glasgow, United Kingdom (K.O.); Vilnius University Hospital Santaros Klinikos and Faculty of Medicine, Vilnius University, Vilnius, Lithuania (P.S.); Sorbonne Université Paris 6, ACTION Study Group, Centre Hospitalier Universitaire Pitié–Salpêtrière (G.M., O.B.), and Applied Research, Technology Transfer, Industrial Collaboration, Société Par Actions Simplifiée (P.T.), Paris; Wilhelminenspital, Department of Cardiology, and Sigmund Freud University, Medical School, Vienna (K.H.); University of Bern, Inselspital, Bern, Switzerland (S. Windecker); Manzoni Hospital, Lecco, Italy (S. Savonitto); and Universitair Ziekenhuis Antwerp, Antwerp, Belgium (C.V.).

## REFERENCES

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295:2511-5.
2. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
3. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. Eur Heart J 2015;36:1223-30.
4. Thiele H, Desch S, Piek JJ, et al. Multivessel versus culprit lesion only percutaneous revascularization plus potential staged revascularization in patients with acute myocardial infarction complicated by cardiogenic shock: design and rationale of CULPRIT-SHOCK trial. Am Heart J 2016;172:160-9.
5. Sanborn TA, Sleeper LA, Webb JG, et al. Correlates of one-year survival inpatients with cardiogenic shock complicating acute myocardial infarction: angiographic findings from the SHOCK trial. J Am Coll Cardiol 2003;42:1373-9.
6. Webb JG, Lowe AM, Sanborn TA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol 2003;42:1380-6.
7. Wong SC, Sanborn T, Sleeper LA, et al. Angiographic findings and clinical correlates in patients with cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry: SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? J Am Coll Cardiol 2000;36: Suppl A:1077-83.
8. Smits PC, Abdel-Wahab M, Neumann F-J, et al. Fractional flow reserve–guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017;376:1234-44.
9. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115-23.
10. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963-72.
11. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3–PRIMULTI): an open-label, randomised controlled trial. Lancet 2015; 386:665-71.
12. de Waha S, Jobs A, Eitel I, et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2017 July 1 (Epub ahead of print).
13. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2017 August 26 (Epub ahead of print) (https://doi.org/10.1093/eurheartj/ehx393).
14. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol 2016;67:1235-50.
15. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:570-91.
16. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123: 2736-47.

**17.** Alexander JH, Reynolds HR, Stebbins AL, et al. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. JAMA 2007; 297:1657-66.
**18.** Thiele H, Zeymer U, Neumann F-J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of the randomised, open-label trial. Lancet 2013; 382:1638-45.
**19.** Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287-96.
**20.** Sardella G, Lucisano L, Garbo R, et al. Single-staged compared with multistaged PCI in multivessel NSTEMI patients: the SMILE Trial. J Am Coll Cardiol 2016;67:264-72.
**21.** van der Schaaf RJ, Claessen BE, Vis MM, et al. Effect of multivessel coronary disease with or without concurrent chronic total occlusion on one-year mortality in patients treated with primary percutaneous coronary intervention for cardiogenic shock. Am J Cardiol 2010; 105:955-9.
**22.** Hoebers LP, Vis MM, Claessen BE, et al. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. Eur J Heart Fail 2013;15: 425-32.
**23.** Henriques JPS, Hoebers LP, Råmunddal T, et al. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE Trial. J Am Coll Cardiol 2016;68:1622-32.