UNIVERSITÄT LEIPZIG
HERZZENTRUM

CULPRIT-SHOCK

CULPRIT-SHOCK: A Randomized Trial of Multivessel PCI in Cardiogenic Shock

Holger Thiele, MD

on behalf of the CULPRIT-SHOCK Investigators

Disclosure Statement of Financial Interest

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

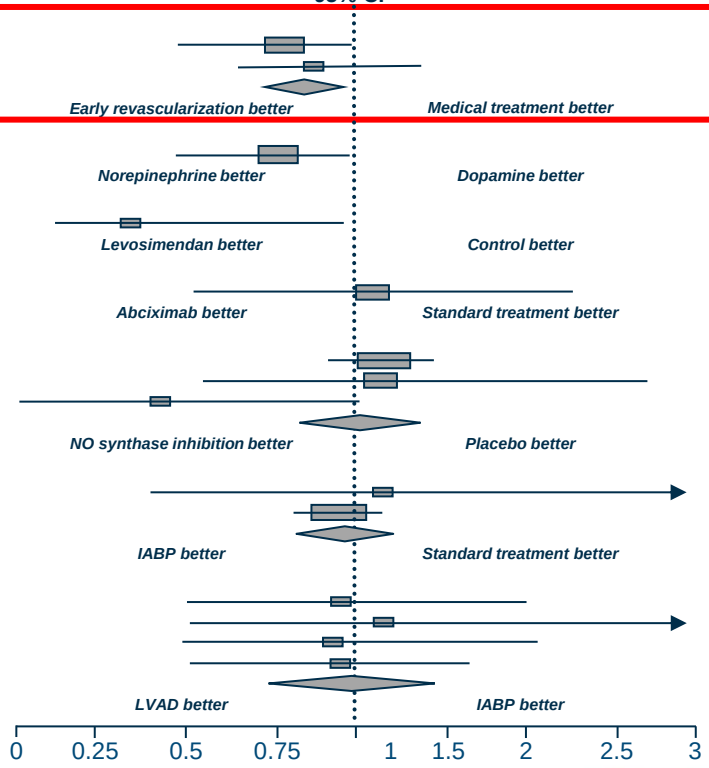
Affiliation/Financial Relationship	Company
• Grant/Research Support	• European Union, German Cardiac Society German Heart Research Foundation
• Consulting Fees/Honoraria	• None
• Major Stock Shareholder/Equity	• None
• Royalty Income	• None
• Ownership/Founder	• None
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

UNIVERSITÄT LEIPZIG
HERZZENTRUM

Randomized Trials Cardiogenic Shock

CULPRIT-SHOCK

Trial	Follow-up	n/N	n/N	Relative Risk Mortality 95% CI	Relative Risk 95% CI
Revascularization					
SHOCK	1 year	81/152	100/150		0.72 (0.54;0.95)
SMASH	30 days	22/32	18/23		0.87 (0.66;1.29)
Total		***103/184***	***118/173***		***0.82 (0.69;0.97)***
Vasopressors					
SOAP-2 (CS subgroup)	28 days	64/145	50/135		0.75 (0.55;0.93)
Inotropes					
Unverzagt et al.	30 days	5/16	10/16		0.33 (0.11;0.97)
Glycoprotein IIb/IIIa inhibitors					
PRAGUE-18	In-hospital	15/40	13/40		1.15 (0.59;2.27)
NO synthase inhibitors					
TRIUMPH	30 days	97/201	76/180		1.14 (0.91;1.45)
SHOCK II	30 days	24/59	7/20		1.16 (0.59;2.69)
Cotter et al.	30 days	4/15	10/15		0.40 (0.13;1.05)
Total		***125/275***	***93/215***		***1.05 (0.85;1.29)***
IABP					
IABP-SHOCK I	30 days	7/19	6/21		1.28 (0.45;3.72)
IABP-SHOCK II	30 days	119/300	123/298		0.96 (0.79;1.17)
Total		***126/319***	***129/319***		***0.98 (0.81;1.18)***
LVAD					
Thiele et al.	30 days	9/21	9/20		0.95 (0.48;1.90)
Burkhoff et al.	30 days	9/19	5/14		1.33 (0.57;3.10)
ISAR-SHOCK	30 days	6/13	6/13		1.00 (0.44;2.29)
IMPRESS in Severe Shock	30 days	11/24	12/24		0.92 (0.51;1.66)
Total		***35/77***	***32/71***		***1.01 (0.70;1.44)***



Thiele et al. Eur Heart J 2015;36:1223-1230

Multivessel PCI in Cardiogenic Shock
European and American Recommendations 2017

Multivessel coronary artery disease present in up to 80% → higher mortality

Guidelines

ESC

I IIa IIb III

C

ACC/AHA/SCAI

American Heart Association

No recommendation

Appropriate Use Criteria

ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS

American Heart Association

A (9)

Ibanez et al. ESC STEMI Guidelines 2017. Eur Heart J 2017; epub
Levine et al. J Am Coll Cardiol 2016;67:1235-1250
Patel et al. J Am Coll Cardiol 2016; in press

Multivessel PCI in Cardiogenic Shock

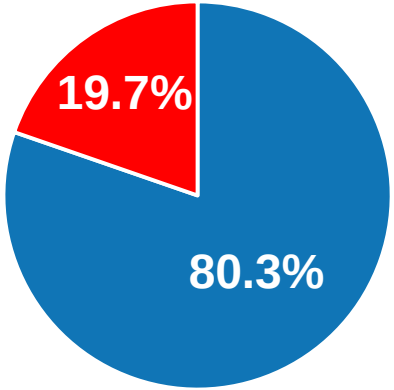
Metaanalysis Mortality – Registry-Data:

10 observational studies published between 2003 and 2016

↓

6,051 patients:

IABP-SHOCK II, ALKK, KAMIR, Yang et al., Cavender et al.; Mylotte et al., van der Schaaf et al., EHS-PCI, NCDR, SHOCK



- Culprit only-PCI (n=4,857)
- Multivessel-PCI (n=1,194)

de Waha et al. Eur Heart J Acute Cardiovasc Care. 2017; epub

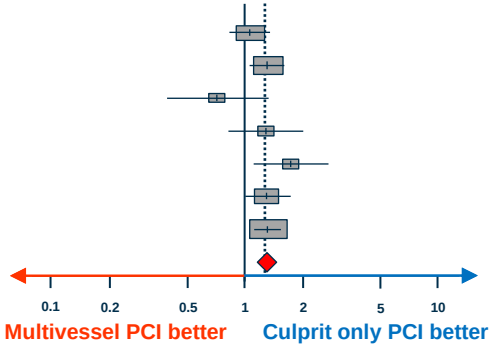
UNIVERSITÄT LEIPZIG
HERZZENTRUM

Multivessel PCI in Cardiogenic Shock?

Metaanalysis Mortality – Registry-Data

CULPRIT-SHOCK

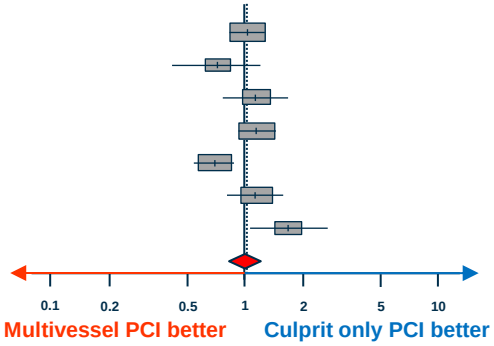
	MV-PCI		C-PCI		Short-term follow-up	RR	95%CI
	Events	Total	Events	Total			
IABP-SHOCK II	75	167	119	284		1.07	[0.86-1.33]
ALKK	81	173	201	562		1.31	[1.08-1.33]
KAMIR	13	124	56	386		0.72	[0.41-1.28]
Yang et al.	19	60	68	278		1.29	[0.85-1.98]
Cavender et al.	20	43	42	156		1.73	[1.14-2.61]
EHS-PCI	40	82	95	254		1.30	[0.99-1.71]
NCDR	158	433	737	2654		1.31	[1.14-1.51]
Overall	**406**	**1082**	**1318**	**4574**		**1.26**	**[1.12-1.41]**



Heterogeneity: τ^2=0.007, I^2=31.0%, p=0.19

Test for overall effect: p=0.001

	MV-PCI		C-PCI		Long-term follow-up	RR	95%CI
	Events	Total	Events	Total			
IABP-SHOCK II	91	167	149	284		1.04	[0.87-1.24]
KAMIR	16	124	69	386		0.72	[0.43-1.19]
Yang et al.	21	60	85	278		1.14	[0.78-1.69]
Cavender et al.	32	43	101	156		1.15	[0.93-1.42]
Mylotte et al.	37	66	82	103		0.70	[0.56-0.89]
van der Schaaf et al.	22	37	66	124		1.12	[0.82-1.53]
SHOCK	7	9	26	57		1.71	[1.09-2.67]
Overall	**226**	**506**	**578**	**1387**		**1.03**	**[0.85-1.25]**



Heterogeneity: τ^2=0.043, I^2=67.8%, p=0.005

Test for overall effect: p=0.77

de Waha et al. Eur Heart J Acute Cardiovasc Care. 2017; epub

Hypothesis

Culprit lesion only PCI (with possible staged revascularization)
is superior to
immediate multivessel PCI
in multivessel coronary artery disease (≥2 mm in diameter, >70% stenosis incl. CTO) patients with cardiogenic shock complicating acute myocardial infarction.

Thiele et al. Am Heart J. 2016;172:160-169

Statistical Methodology

Primary Study Endpoint:

- 30-day all-cause mortality or renal replacement therapy

Secondary Study Endpoints:

- 30-day all-cause mortality
- Renal failure with requirement of renal replacement therapy
- Time to hemodynamic stabilization
- Duration of catecholamine therapy
- Serial creatinine-clearance
- Length of ICU-stay
- SAPS-II score
- Requirement and length of mechanical ventilation
- All-cause death within 6 and 12 months follow-up
- Recurrent infarction within 30-days, 6 and 12 months follow-up
- Death or recurrent infarction at 6 and 12 months follow-up
- Rehospitalization for congestive heart failure within 30 days, 6-, and 12-months follow-up
- Death/recurrent infarction/rehospitalization for congestive heart failure within 30 days, 6-, and 12-months follow-up
- Need for repeat revascularization (PCI and/or CABG) within 30 days, 6-, and 12-months follow-up
- Peak creatine kinase, creatine kinase-MB and troponin level during hospital stay

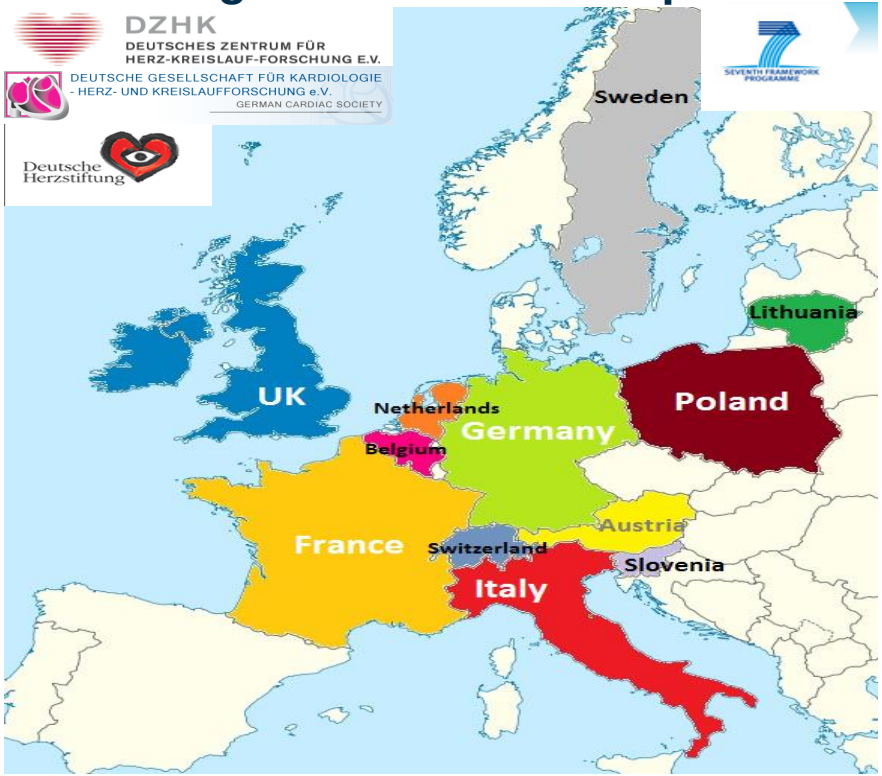
Sample Size:

- Estimated 50% event rate in multivessel PCI versus 38% in culprit lesion only group for primary endpoint
- 1 interim analysis (50% of patients)
- 2-sided test Chi^2-test; power: 80%, alpha=0.048 for final analysis → 684 patients
- To compensate losses in follow-up → 706 patients

Thiele et al. Am Heart J. 2016;172:160-169

CULPRIT-SHOCK Trial

Investigator-initiated European multicenter trial; 1:1 randomization



PI + Coordination:
Holger Thiele

Co-PI:
Uwe Zeymer
Steffen Desch

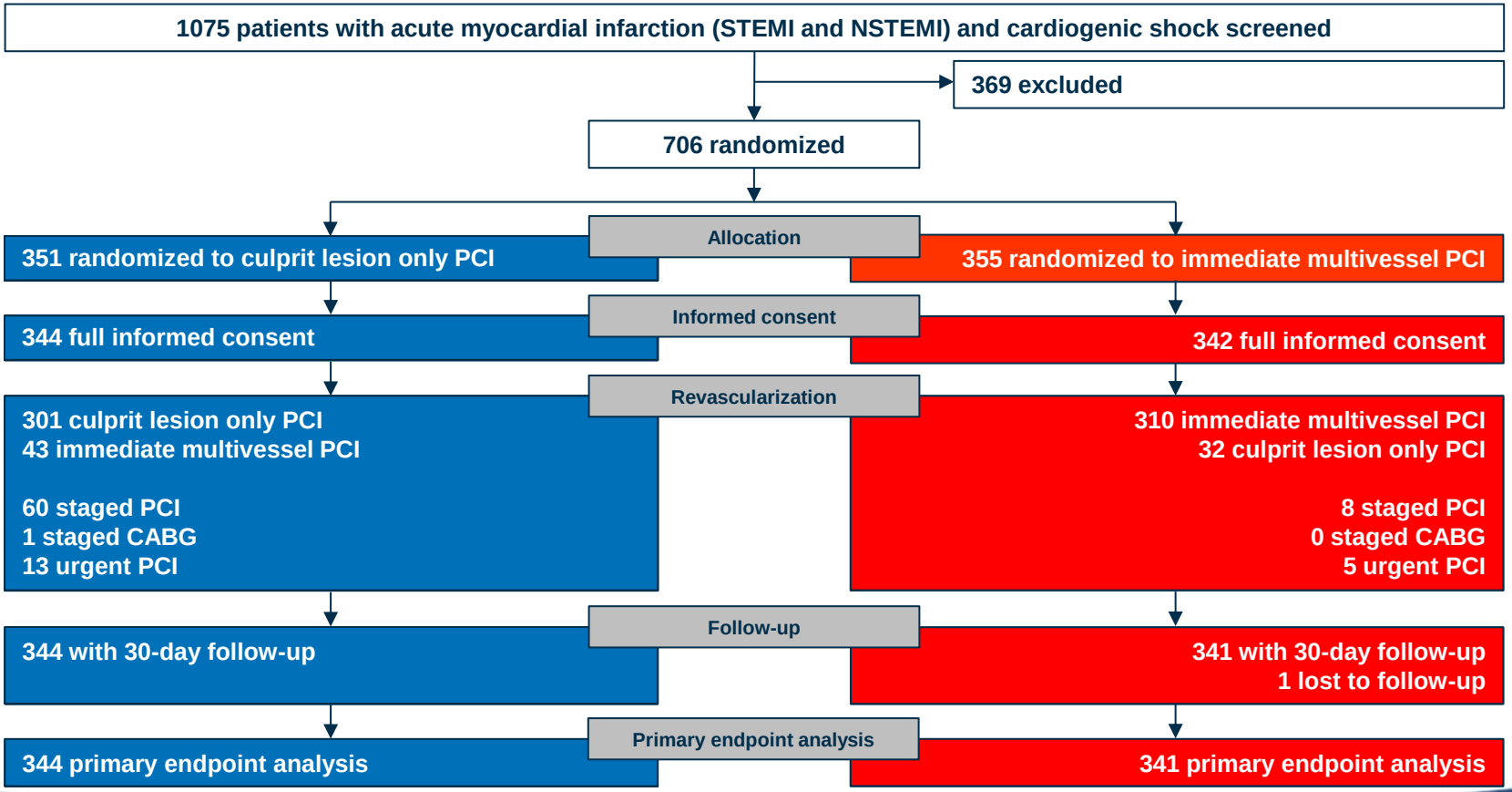
National Coordinators (83 centers):
- Kurt Huber
- Gilles Montalescot
- Jan Piek
- Holger Thiele
- Pranas Serpytis
- Janina Stepinska
- Christiaan Vrints
- Marko Noc
- Keith Oldroyd
- Stefan Windecker
- Stefano Savonitto

Thiele et al. Am Heart J. 2016;172:160-169

UNIVERSITÄT LEIPZIG
HERZZENTRUM

Study Flow Chart

CULPRIT-SHOCK



Baseline Characteristics

Characteristic	Culprit only PCI (n=344)	Multivessel PCI (n=342)
Age (years); median (IQR)	70 (60-78)	70 (60-77)
Male sex; n/total (%)	257/343 (74.9)	267/342 (78.1)
Prior myocardial infarction; n/total (%)	60/339 (17.7)	53/335 (15.8)
Prior PCI; n/total (%)	64/339 (18.9)	63/335 (18.8)
Prior coronary arterial bypass surgery; n/total (%)	20/341 (5.9)	13/337 (3.9)
Signs of impaired organ perfusion; n/total (%)		
Altered mental status	237/341 (69.5)	224/341 (65.7)
Cold, clammy skin and extremities	233/338 (68.9)	236/335 (70.4)
Oliguria	80/334 (24.0)	93/326 (28.5)
Arterial lactate >2.0 mmol/l	216/334 (64.7)	224/330 (67.9)
Fibrinolysis <24 h before randomization; n/total (%)	19/341 (5.6)	15/341 (4.4)
Resuscitation before randomization; n/total (%)	177/341 (51.9)	189/342 (55.3)
ST-elevation myocardial infarction; n/total (%)	206/335 (61.5)	209/330 (63.3)
No. of diseased vessels; n/total (%)		
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)
Patients with at least one CTO; n/total (%)	77/344 (22.4)	82/342 (24.0)
Left ventricular ejection fraction (%); median (IQR)	33 (25-40)	30 (21-40)

Treatment

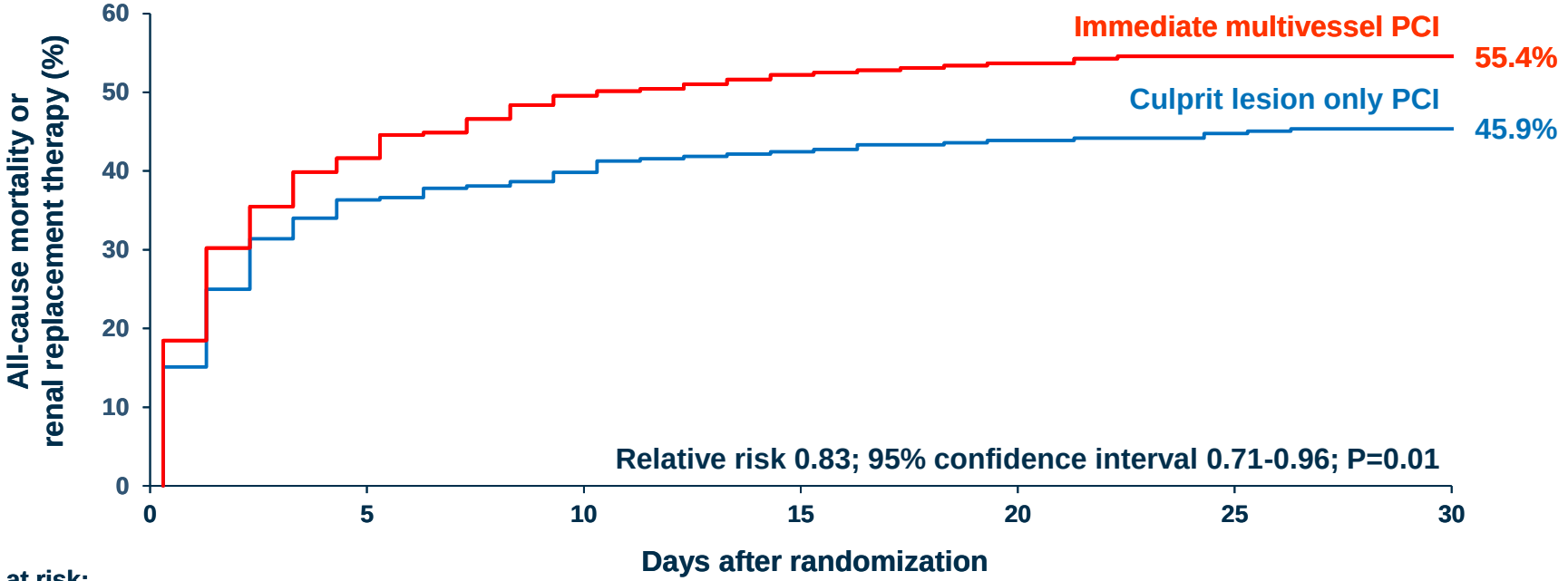
Characteristic	Culprit only PCI (n=344)	Multivessel PCI (n=342)	
Femoral access; n/total (%)	287/343 (83.7)	277/342 (81.0)	0.36
Radial access; n/total (%)	61/343 (17.8)	66/342 (19.3)	0.61
Stent implanted in culprit lesion; n/total (%)	326/343 (95.0)	324/342 (94.7)	0.86
Drug-eluting stent in culprit lesion; n/total (%)	305/326 (93.6)	308/324 (95.1)	0.41
TIMI-flow III post PCI of culprit lesion; n/total (%)	289/342 (84.5)	293/338 (86.7)	0.46
Immediate PCI of non-culprit lesions; n/total (%)	43/344 (12.5)	310/342 (90.6)	<0.001
Immediate complete revascularization; n/total (%)	26/344 (7.6)	277/342 (81.2)	<0.001
Total amount of contrast agent (ml); median (IQR)	190 (140-250)	250 (200-350)	<0.001
Staged PCI of non-culprit lesions; n/total (%)	60/344 (17.4)	8/341 (2.3)	<0.001
Staged coronary artery bypass surgery; n/total (%)	1/344 (0.3)	0/341	>0.99
Mechanical circulatory support; n/total (%)	99/344 (28.8)	95/342 (27.8)	0.77
Intraaortic balloon pump; n/total (%)	25/99 (25.3)	26/95 (27.4)	0.74
Impella 2.5; n/total (%)	16/99 (16.2)	18/95 (18.9)	0.61
Impella CP; n/total (%)	30/99 (30.3)	18/95 (18.9)	0.07
TandemHeart; n/total (%)	2/99 (2.0)	0/95	0.50
ECMO; n/total (%)	18/99 (18.2)	27/95 (28.4)	0.09
Mild hypothermia; n/total (%)	111/344 (32.3)	118/340 (34.7)	0.50
Mechanical ventilation; n/total (%)	273/344 (79.4)	282/339 (83.2)	0.20
Duration of mechanical ventilation (days); median (IQR)	3 (1-7)	3 (1-7)	0.97
Duration of intensive care treatment (days); median (IQR)	5 (2-12)	5 (2-11)	0.61

UNIVERSITÄT LEIPZIG
HERZZENTRUM

Primary Study Endpoint

All-Cause Mortality or Renal Replacement Therapy

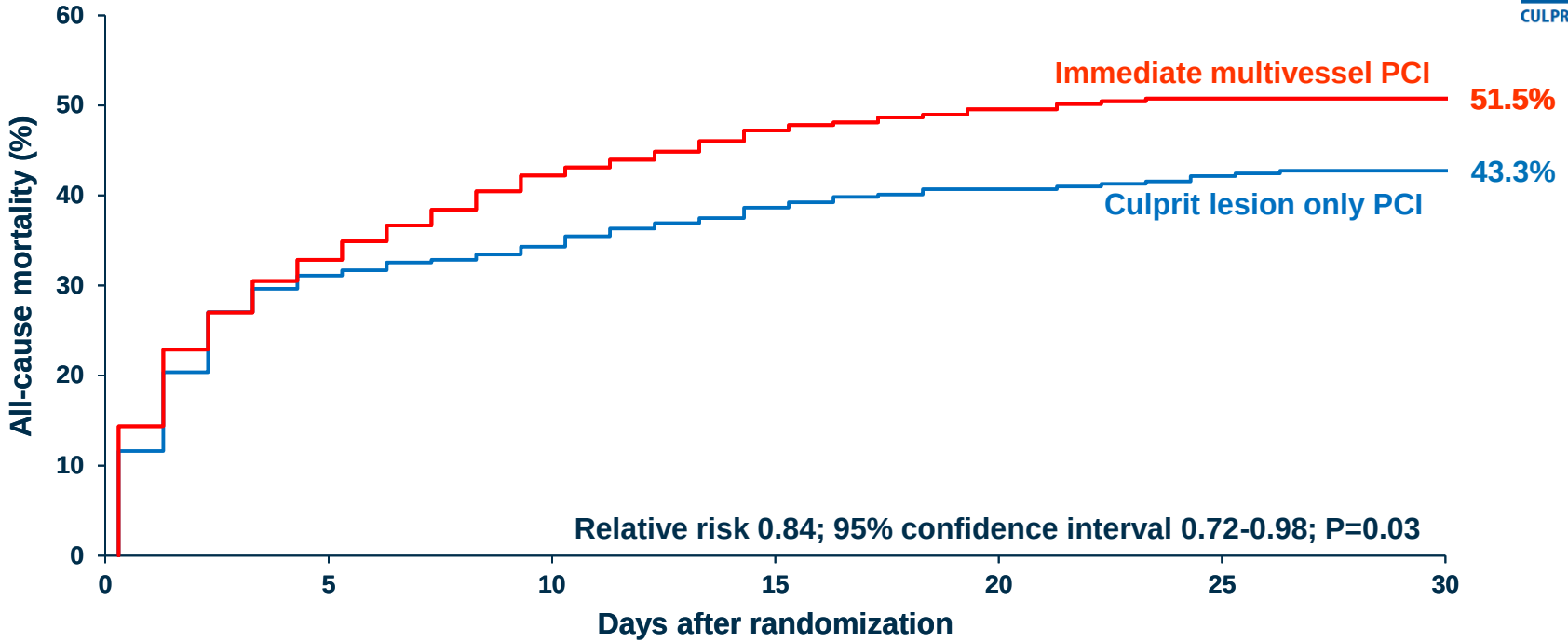
CULPRIT-SHOCK



Number at risk:

Culprit lesion only PCI	344	219	207	198	192	189	184
Immediate multivessel PCI	341	199	172	162	156	153	152

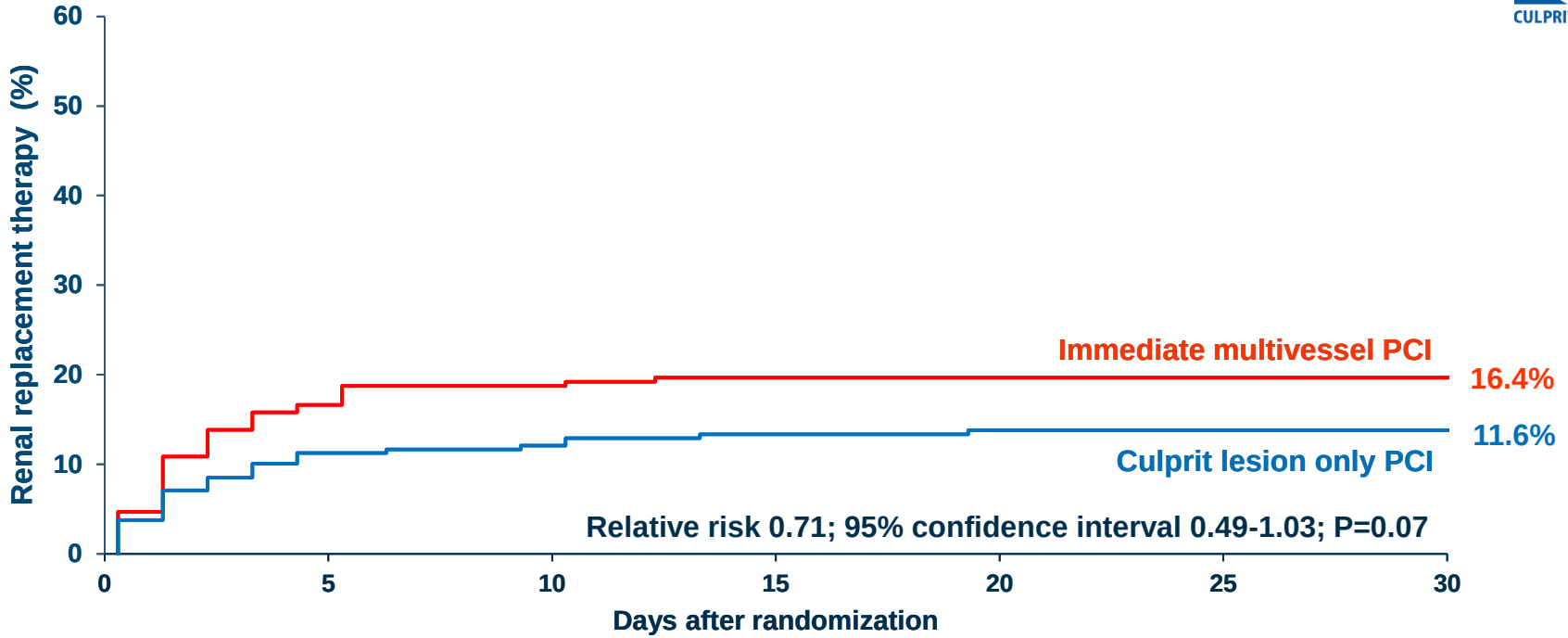
All-Cause Mortality



Number at risk:

Culprit lesion only PCI	344	237	226	211	203	198	193
Immediate multivessel PCI	341	229	197	179	170	166	165

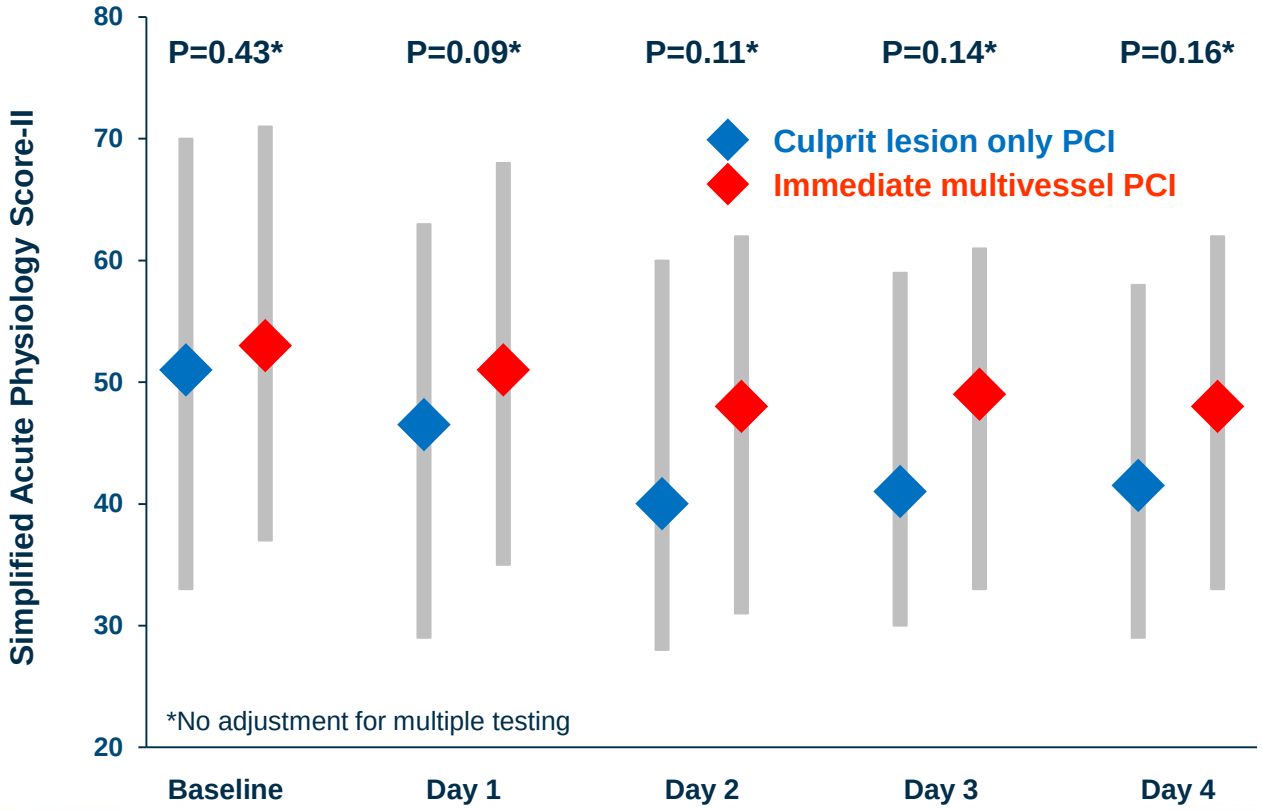
Renal Replacement Therapy



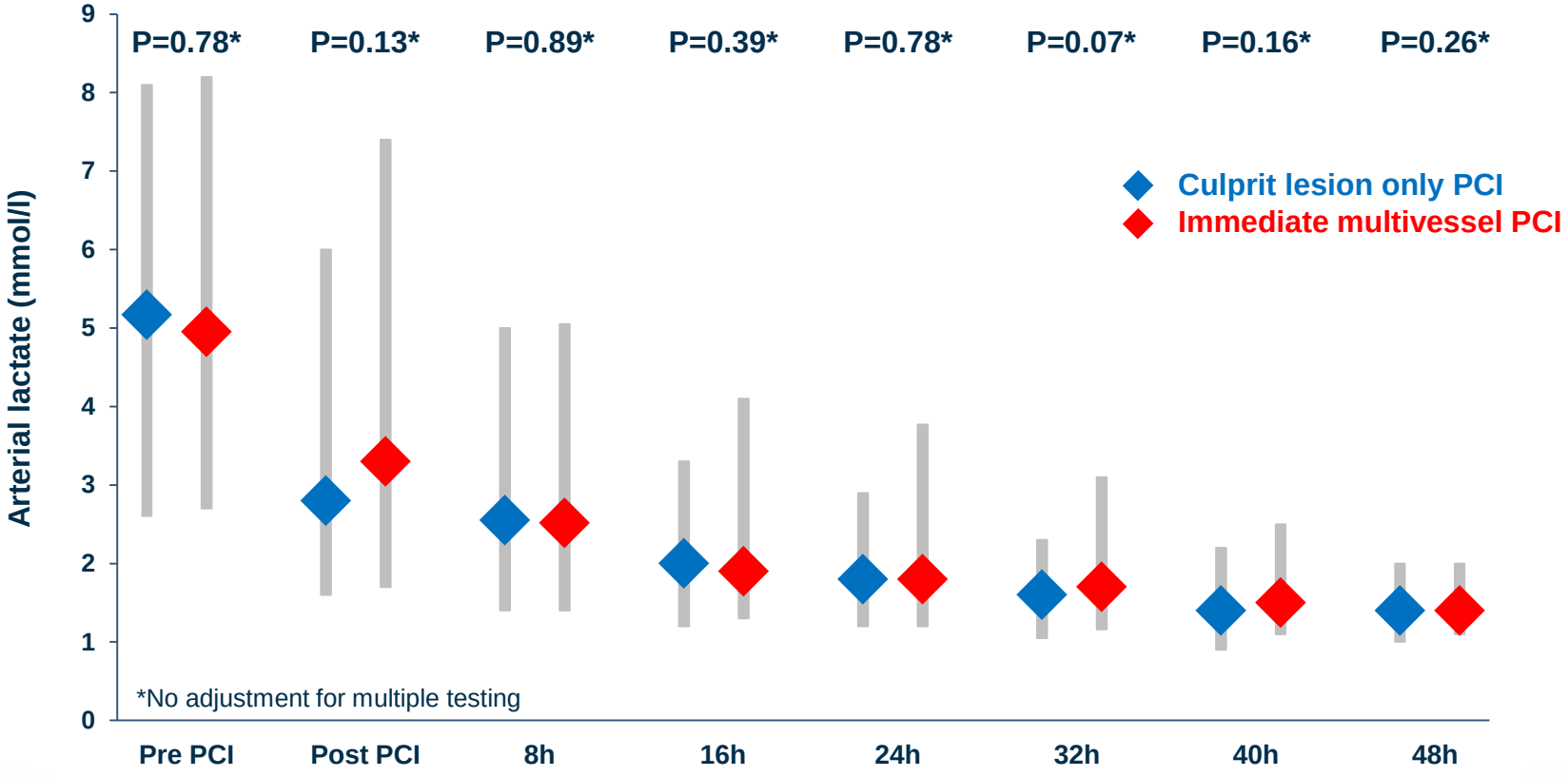
Number at risk:

Culprit lesion only PCI	344	219	207	198	192	189	184
Immediate multivessel PCI	341	199	172	162	156	153	152

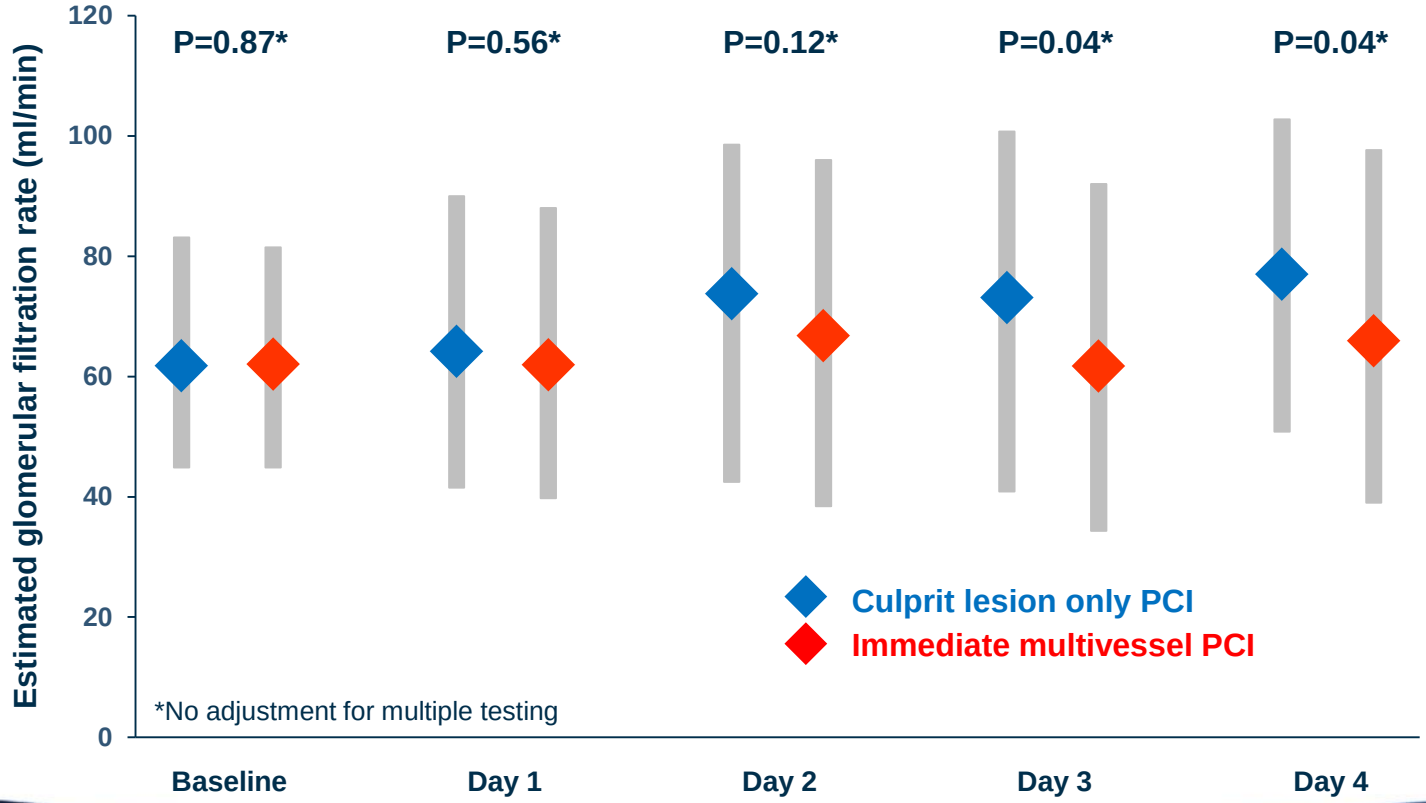
SAPS II-Score



Arterial Lactate



Glomerular Filtration Rate

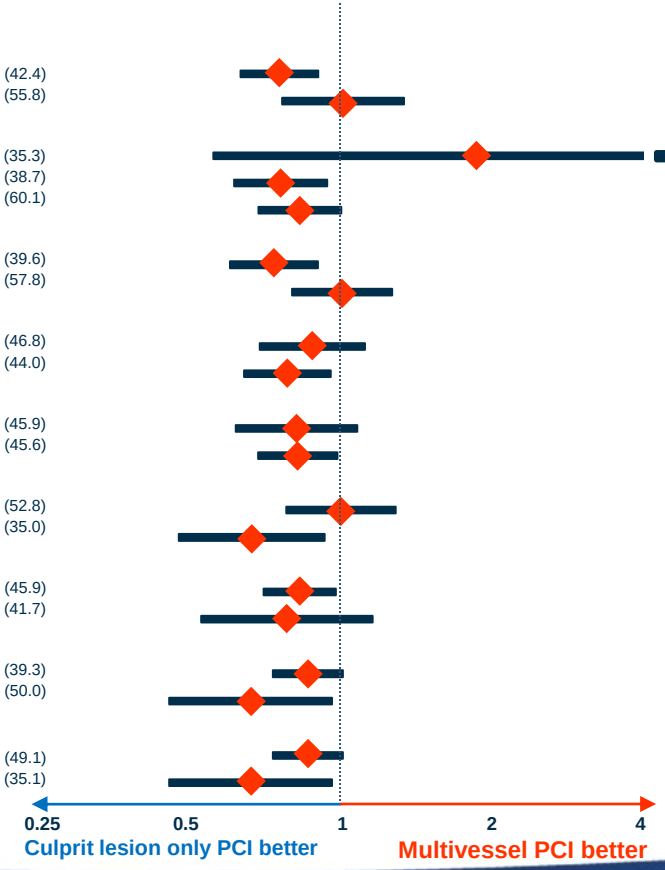


UNIVERSITÄT LEIPZIG
HERZZENTRUM

Subgroup Analysis – Primary Endpoint

CULPRIT-SHOCK

Baseline Variable	Multivessel PCI	Culprit lesion only PCI	Relative Risk (95% CI)	P Value for Interaction
Sex				
Male	148/266 (55.6)	109/257 (42.4)	0.76 (0.64-0.91)	**0.11**
Female	41/75 (54.7)	48/86 (55.8)	1.02 (0.77-1.35)	
Age				
<50 years	3/16 (18.8)	6/17 (35.3)	1.88 (0.56-6.29)	**0.24**
50-75 years	114/226 (50.4)	82/212 (38.7)	0.77 (0.62-0.95)	
>75 years	72/99 (72.7)	70/115 (60.1)	0.84 (0.69-1.01)	
Diabetes				
No	116/218 (53.2)	93/235 (39.6)	0.74 (0.61-0.91)	**0.08**
Yes	66/116 (56.9)	59/102 (57.8)	1.02 (0.81-1.28)	
Hypertension				
No	68/129 (52.7)	65/139 (46.8)	0.89 (0.70-1.13)	**0.47**
Yes	114/205 (55.6)	88/200 (44.0)	0.79 (0.65-0.97)	
Type of infarction				
NSTEMI	54/97 (55.7)	45/98 (45.9)	0.82 (0.62-1.09)	**0.96**
STEMI	128/233 (54.9)	108/237 (45.6)	0.83 (0.69-0.99)	
STEMI type				
Anterior infarction	59/113 (52.2)	57/108 (52.8)	1.01 (0.79-1.30)	**0.07**
Non-anterior infarction	48/92 (52.2)	34/97 (35.0)	0.67 (0.48-0.94)	
Previous infarction				
No	154/281 (54.8)	128/279 (45.9)	0.84 (0.71-0.99)	**0.83**
Yes	28/53 (52.8)	25/60 (41.7)	0.79 (0.53-1.17)	
Coronary artery disease				
2-vessel disease	64/124 (51.6)	48/122 (39.3)	0.76 (0.58-1.01)	**0.56**
3-vessel disease	124/215 (57.7)	109/218 (50.0)	0.87 (0.73-1.03)	
Chronic total occlusion				
No	146/259 (56.4)	131/267 (49.1)	0.87 (0.74-1.02)	**0.26**
Yes	43/82 (52.4)	27/77 (35.1)	0.67 (0.46-0.97)	



Conclusions

- **In patients with multivessel coronary artery disease and cardiogenic shock complicating acute myocardial infarction culprit lesion only PCI with possible staged revascularization reduced the composite of mortality or requirement for renal replacement therapy at 30 days.**

- **This effect in the primary outcome was mainly driven by a 30-day mortality reduction.**

- **This largest randomized European multicenter trial in cardiogenic shock complicating myocardial infarction challenges current guideline recommendations.**

UNIVERSITÄT LEIPZIG
HERZZENTRUM

Acknowledgement and Thank You

CULPRIT-SHOCK Patients and Investigators

CULPRIT-SHOCK

Steering Committee

Holger Thiele, MD (Chair)
Steffen Desch, MD
Uwe Zeymer, MD
Gilles Montalescot, MD
Jan J. Piek, MD, PhD
Patrizia Torremante

Funding

German Heart Research Foundation
German Cardiac Society
European Union

DSMB

Peter Clemmensen, MD (Chair)
Ferenc Follath, MD
Karl Wegscheider, PhD

CRO

IHF Ludwigshafen
Steffen Schneider, PhD
Thomas Reimer, PhD
Christiane Lober
Alexander Neumer
Clemens Busch, PhD
Nathalie Pfeiffer

National Coordinators

Kurt Huber, MD
Gilles Montalescot, MD
Jan Piek, MD, PhD
Holger Thiele, MD
Pranas Serpytis, MD
Janina Stepinska, MD
Christiaan Vrints, MD
Marko Noc, MD
Keith Oldroyd, MD
Stefan Windecker, MD
Stefano Savonitto, MD

Project Management

Patrizia Torremante
Roza Meyer-Saraei, PhD

Angiographic Core Lab

ACTION Study Group
O. Barthelemy, MD
M. Zeitouni, MD
P. Overtchouk, MD
P. Guedeney, MD
G. Hage, MD
M. Hauguel-Moreau, MD

Association

German Cardiac Research Center (DZHK)

www.nejm.org

CULPRIT-SHOCK

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*