Supplemental Online Content

Blauenfeldt RA, Hjort N, Valentin JB, et al. Remote ischemic conditioning for acute stroke and functional outcome: The RESIST randomized clinical trial. *JAMA*. doi:10.1001/jama.2023.16893

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

Supplement 3 - eMethods/eResults/eTables/eFigures

Contents

eMethods

Site and Investigators

Aarhus University Hospital (15.03.2018 – 11.11.2022):

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Regional Hospital Gødstrup (17.09.2018 – 11.11.2022):

Site PI: Birgitte Forsom Sandal. Contributors: Margrét Katrín Hreiðarsdóttir, Paul Von Weitzel Mudersbach, Morten Stilund, Mohammad Ahmad Al-jazi, Iwona Nowak Malczynska, Søren Kjær, Ivan Sonnenschein

Odense University Hospital (29.06.2020-11.11.2022):

Site PI: Anne-Mette Homburg. Contributors: Alex Alban Christensen, David Gaist, Karen Ægidius, Sjofn Thorisdottir, Nasir Musa Al-Mashkur, Sanaz Shoja Gharehbagh

Aalborg University Hospital (14.01.2021-11.11.2022):

Site PI: Boris Modrau. Contributors: Krystian Figlewski, Niels Degn, Rolf Ankerlund Blauenfeldt, Lars H. Markvardsen, Sidsel Gaarn Hastrup, Jakob Schäfer, Lotte Vinge, Victoria Russo, Kimmo Jensen

Prehospital Emergency Medical Services, Central Denmark Region (15.03.2018 – 11.11.2022):

Site PI: Hans Kirkegaard. Contributors: Martin F. Gude, Ulla Væggemose, Palle Juelsgaard

Prehospital Emergency Medical Services, Northern region of Denmark (14.01.2021– 11.11.2022):

Site PI: Martin Rostgaard

Prehospital Emergency Medical Services, Southern region of Denmark (29.06.2020– 11.11.2022):

Site PI: Søren Mikkelsen. Contributors: Daniel Wittrock, Henning Morthorst Lassesen.

Enrolling centers (study period; number of patients enrolled/randomized)

Aarhus University Hospital (15.03.2018 – 11.11.2022):

Randomized patients: 1315

Regional Hospital Gødstrup (17.09.2018 – 11.11.2022):

Randomized patients: 104

Odense University Hospital (29.06.2020-11.11.2022):

Randomized patients: 83

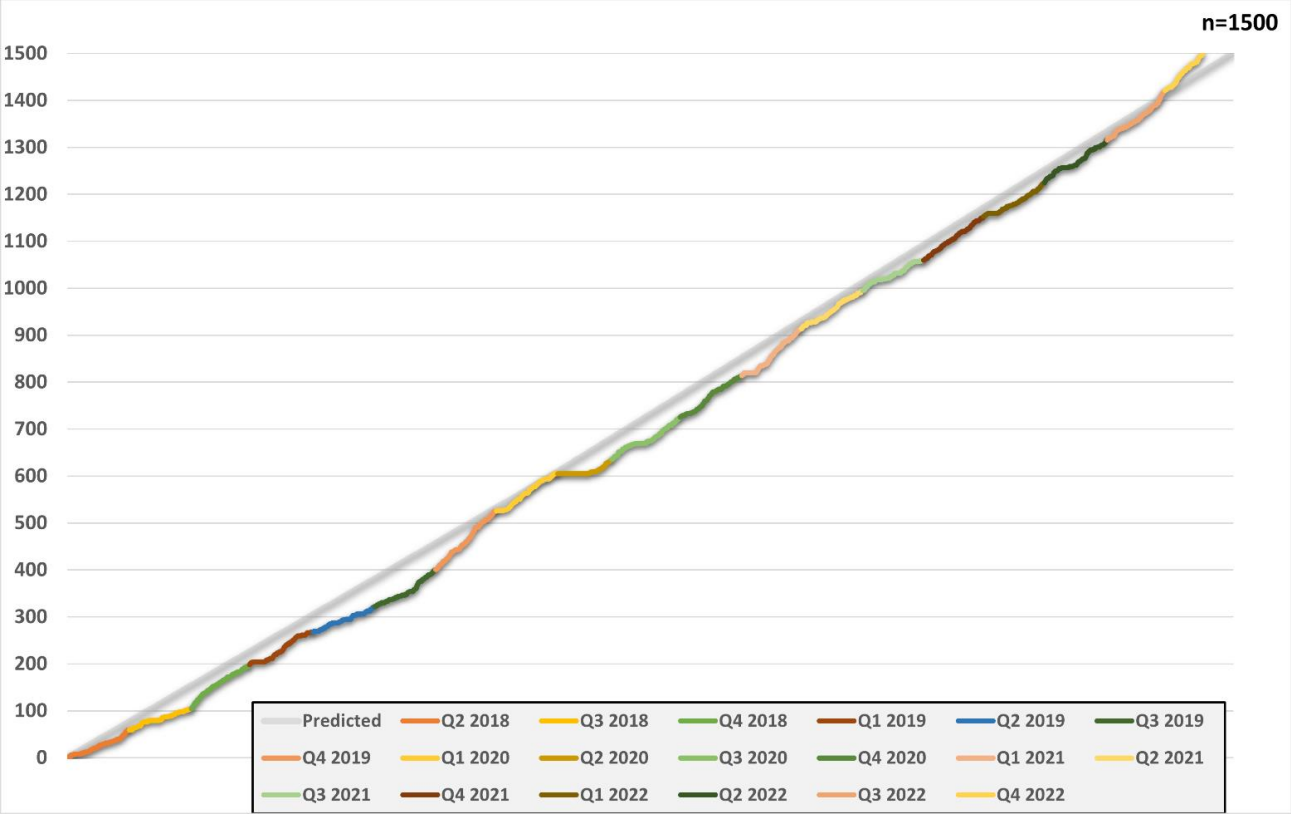
Aalborg University Hospital (14.01.2021-11.11.2022):

Randomized patients: 110

Non-Enrolling centers

Non-initiated site: Department of Neurology, Zealand University Hospital, DK-4000 Roskilde, Denmark

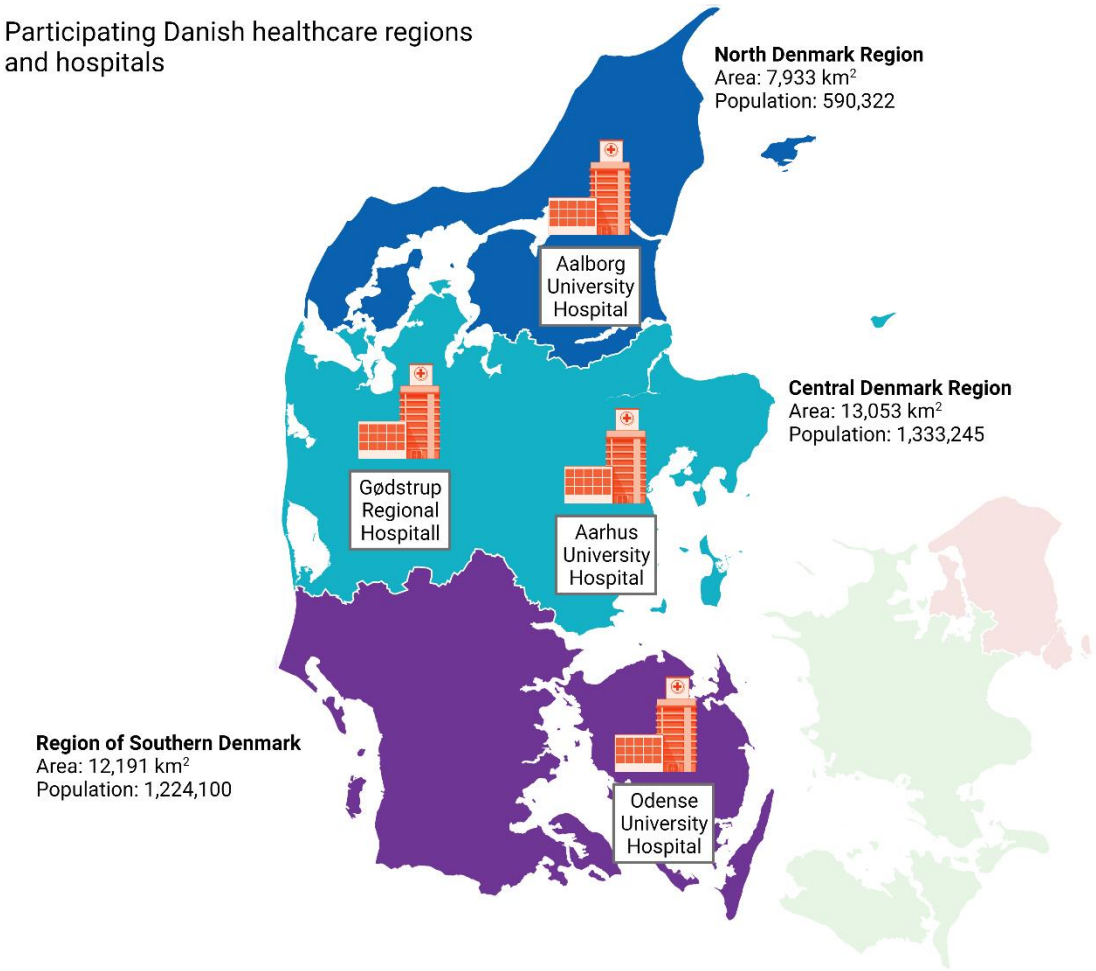
Enrolment rate



Enrolment is visualized as randomized patients per yearly quarter. Grey line is anticipated inclusion rate.

Enrolment started on March 16, 2018 and was completed on November 11, 2022. Last patient last visit was completed on February 3, 2023.

Participating Danish regions and hospitals



Created with BioRender.com

Participating ambulances and trained paramedics at trial completion

	Trained paramedics/EMT	Ambulances
Central Region Denmark		
Driven by the region	396	70
Falck®	209	26
Region of Southern Denmark		
Driven by the region	563	56
Responce®	170	15
North Denmark Region		
Driven by the region	220	23
PreMed ®	139	10
Total	**1697**	**200**

EMT = Emergency Medical Technician

Falck, Response and PreMed are private contractors delivering prehospital emergency medical services on behalf of the healthcare region.

Codebreak

There were no cases where the randomization code was compromised during the study period

Trial Boards and Committees

Steering Committee

Grethe Andersen (Chair, Aarhus University Hospital), Rolf Ankerlund Blauenfeldt (Aarhus University Hospital), Niels Hjort (Aarhus University Hospital), Hans Erik Bøtker (Aarhus University Hospital), David C. Hess (Medical College of Georgia, USA), Hans Kirkegaard (Aarhus University Hospital). Rikke Bay Thomsen (Aarhus University Hospital), Birgitte Forsom Sandal (Regional Hospital West Jutland, Holstebro) and Marc Fisher (Beth Israel Deaconess Medical Centre, Harvard Medical School, USA), Claus Ziegler Simonsen (Aarhus University Hospital), Anne-Mette Homburg (Odense University Hospital) and Boris Modrau (Aalborg University Hospital), Søren Paaske Johnsen (Aalborg University)

Data and Safety Monitoring Board (DSMB)

Jesper Petersson (Skåne University Hospital, Sweden) – chair. Jan Brink Valentin (Aalborg University Hospital, Denmark) Thomas Christensen (Nordsjællands Hospital, Denmark)

Central functional outcome assessment:

Andreas D. Gammelgaard, Ane B. Iversen, Sigrid Vestergaard, Marie Plesner, Vibeke Bock, Janne K. Mortensen, Grethe Andersen.

Clinical Endpoint Adjudication Committee

Janne K. Mortensen, Erik L. Grove, Krystian Figlewski, Kristina D. Hougaard.

Biostatistician

Jan B. Valentin (Aalborg University)

Independent data Monitoring organization

Good Clinical practice units of Aalborg/Aarhus and Odense.

Funding

The study was funded by

- TrygFonden (ID: 120636)

- Manufacturer Vilhelm Pedersen and Wife's foundation (ID: NNF16OC0023474)
- Aase Ejnar Danielsens Foundation (ID:10–002120)
- Novo Nordisk Foundation (ID: NNF00052924)
- Novo Nordisk Foundation (ID: NNF0060998)
- National Institute of Health (grant number: 1R01NS112511-01A1)

Supplementary Methods

Inclusion and Exclusion Criteria

Inclusion criteria (prehospital):

The initial treatment regime will be applied in the acute prehospital phase in setting of an acute research study

- Male and female patients (≥ 18 years)
- Prehospital putative stroke
- Onset of stroke symptoms < 4 hours before remote ischemic conditioning (RIC)
- Independent in daily living before symptom onset (mRS ≤ 2)

Final in-hospital inclusion criteria (defining target population)

- Acute ischemic stroke including documented TIA

  or

- ICH

Exclusion criteria

Exclusion criteria, to be established during the teleconference between ambulance and on call neurologist

- Intracranial aneurisms, arteriovenous (AV) malformation, cerebral neoplasm abscess or progressive neurodegenerative disease
- Pregnancy
- Severe peripheral arterial disease in the upper extremities
- AV shunt in the arm selected for RIC
- Concomitant acute life-threatening medical or surgical condition

Device description

Automatic remote ischemic conditioning devices

Both the RIC and sham-RIC device were developed in collaboration with Aarhus University, Faculty of Biomedical Engineering, 8200-DK, Aarhus N, Denmark; Seagull Aps, 4200-DK, Slagelse, Denmark and the Department of Neurology, Aarhus University Hospital, 8000-DK, Aarhus C, Denmark.

The devices were manufactured by Shenzhen Raycome Health Technology Co., Ltd, 3F, 51 Building, No.5 Qiong Yu Road, Hi-Tech Industrial Park, Nanshan District, Shenzhen, China 518057.

*The **Investigator's Brochure (IB)** contains a detailed description of the investigational devices including risk analysis assessment.*

A brief user's manual was found in each device bag. No preexisting experience was necessary in order to operate the device. Written and oral information combined (Healthcare professional at participating hospitals) with RESIST trial e-learning material (prehospital personnel) were offered to familiarize the clinical personnel in using the investigational devices. Patients and relatives were instructed using written and oral information.

Remote Ischemic Conditioning device (RIC device)

The device was programmed to five cycles (50 minutes), each consisting of five minutes of cuff inflation followed by five minutes with a deflated cuff. The cuff pressure was 200mmHg; but if initial systolic blood pressure was above 175 mmHg, the cuff was automatically inflated to 35 mmHg above the systolic blood pressure. This was done to account for a maximum cuff air leakage of 6mmHg per minute and maximum deviation in blood pressure measurement of 10mmHg. The maximum cuff pressure was 285 mmHg.

Sham – remote ischemic conditioning device (Sham device)

The device was programmed to five cycles (50 minutes), each consisting of five minutes of cuff inflation followed by five minutes with a deflated cuff. The cuff pressure during inflation was 20mmHg.

Timestamps, blood pressure before RIC/sham-RIC and total RIC/sham-RIC cycles were recorded and stored on the device (accessible by *universal serial bus*, USB). The RIC and sham-RIC devices were pre-programmed before being delivered to collaborating centers/ambulances. No data on conditioning cuff pressure was displayed on the device screen.

In cases of short transport time, the RIC/sham-RIC protocol continued during the initial assessment at the stroke centre. RIC/sham-RIC stimulation was discontinued just prior to the MRI and continued afterwards if the protocol was insufficient (< 4 cycles). In the cases of insufficient treatment before MRI a complete RIC/sham-RIC protocol was performed (5 cycles) as soon as possible after MRI. This was done to ensure that all participants received at least 4 consecutive cycles of RIC/sham-RIC. In centers using CT, the RIC/sham-RIC protocol was continued (if possible) during the scan until a total of 5 cycles was reached. The device automatically stopped treatment when the 5 cycles were completed. Except for RIC/sham-RIC, the prehospital observation and treatment were according to standard procedures in the ambulance.

The use of Stroke RIC/Sham devices in the trial was approved by the Danish Medicines Agency (DMA id 2017114177, EUDAMED CIV-ID 17-11-022324).

Initial remote ischemic conditioning *(All patients)*

RIC/sham-RIC cuff was placed on the non-paretic upper arm. The cuff was placed on the upper extremity on the same side of the suspected side of cerebral stroke, e.g. in right hemiparesis the cuff on the left arm, and in monosymptomatic aphasia the cuff was placed on the left arm.

Remote ischemic conditioning at +6 hours *(All patients with AIS, ICH – all centers)*

At 6 hours after the first RIC/sham-RIC protocol (6 hours from the last cuff-off, respectively), another series of RIC/sham-RIC was performed; five cycles each consisting of 5 minutes of ischemia are followed by 5 minutes of reperfusion. *In the case of mechanical thrombectomy the +6 hour treatment could be delayed and was started as soon as possible after the procedure.*

Remote ischemic <u>post</u>conditioning (twice daily for 7 days) (AIS and ICH – only at Aarhus University Hospital)

The post-conditioning stimulus was applied twice daily in the first week. This occured at pre-specified times: 08.00 PM and AM. However, RIC/sham-RIC could be applied no sooner than 10 hours and not later than 21 hours after the initial perconditioning stimulus (last cuff).

Aarhus University Hospital: RIC/sham-RIC treatment was continued for a total of 7 days. If patients were discharged to their home or to another department, they continued treatment according to written instructions, including application of the device for 7 days. After RIC/sham-RIC on day 7, the device was then returned to the Stroke Centre.

RIC/sham-RIC protocol	**Accepted time frame**
Prehospital RIC	< 4 hours from symptom onset
RIC at +6 h	4 to 8h from last cuff of the initial RIC
RIC twice daily for 7 days – 08.00 PM and AM[a]	06.00 to 10.00 PM and 06.00 to 10.00 AM

[a] RIC/sham-RIC could be applied no sooner than 10 hours and no later than 21 hours after the initial perconditioning stimulus.

eResults - Supplementary Results

Primary Endpoint Analysis without Imputation of Missing Data

No imputation of the primary outcome variable has been performed as no patients were lost to follow-up.

eTable1 - Primary Endpoint – Post hoc Sensitivity Analyses

Primary Outcome (Sensitivity analysis) *Target population (n=902)*	**RIC** (n=436)	**Sham**[a] (n=466)	**Value, 95% CI**	**p-value**
Modified Rankin Scale 0 vs 1 to 6 at 90 days, n(%)	87 (20.0%)	102 (21.9%)	OR 0.88 (0.64-1.23)	0.46
Modified Rankin Scale 0 to 1 vs 2 to 6 at 90 days, n(%)	215 (49.3%)	240 (51.5%)	OR 0.90 (0.64-1.27)	0.45
Modified Rankin Scale 0 to 2 vs 3 to 6 at 90 days, n(%)	296 (67.9%)	310 (66.5%)	OR 1.06 (0.74-1.52)	0.71
Modified Rankin Scale 0 to 3 vs 4 to 6 at 90 days, n(%)	359 (82.3%)	377 (80.9%)	OR 1.07 (0.69-1.66)	0.72
Modified Rankin Scale 0 to 4 vs 5 to 6 at 90 days, n(%)	380 (87.2%)	398 (85.4%)	OR 1.11 (0.74-1.69)	0.61
Modified Rankin Scale 0 to 5 vs 6 at 90 days, n(%)	398 (91.3%)	419 (89.9%)	OR 1.15 (0.71-1.87)	0.56

Abbreviation: OR Odds ratio
[a] Reference is Sham

eTable2 - Safety Analysis – Serious Adverse Events at 90 days

Serious adverse events	**RIC**	**Sham**[a]	**Relative difference, 95% CI**	**p-value**
All randomized (n=1500)[b]	169 (23.7%)	175 (24.3%)	RR 0.98 (0.86-1.11)	0.73
Target population (n=902)	157 (36.0%)	164 (35.1%)	RR 1.02 (0.86-1.18)	0.76
Per-Protocol population (n=565)	77 (29.4%)	90 (29.7%)	RR 0.99 (0.76-1.29)	0.93

Abbreviations: RR Relative risk
[a] Reference is Sham
[b] All adverse events occurring until the patient/relative withdrew his/her consent were registered (mandatory for acute research studies in Denmark).

eTables - Supplementary Tables

eTable 3: Baseline characteristics of the all included (safety population)

	All included	RIC	Sham	p-value
All included, n	1433	713	720	
Age, median (IQR)	71 (59, 78)	71 (59, 79)	72 (59, 78)	0.87
Sex				0.59
Female, n (%)	591 (41.2%)	289 (40.5%)	302 (41.9%)	
Male, n (%)	842 (58.8%)	424 (59.5%)	418 (58.1%)	
Hypertension, n/N (%)	810/1430 (56.5%)	398/711 (55.8%)	412/719 (57.1%)	0.61
Diabetes, n/N (%)	183/1432 (12.8%)	90/712 (12.6%)	93/720 (12.9%)	0.88
Atrial fibrillation, n/N (%)	190/1432 (13.3%)	105/712 (14.7%)	85/720 (11.8%)	0.10
Prior AIS, n/N (%)	256/1428 (17.9%)	125/709 (17.5%)	131/719 (18.2%)	0.77
Prior TIA, n/N(%)	121/1422 (8.4%)	57/707 (8.0%)	64/716 (8.9%)	0.56
Prehospital systolic blood pressure, median (IQR) mmHg	180 (155-202)	179 (155-200)	180 (154-203)	0.68
Prehospital diastolic blood pressure, median (IQR) mmHg	91 (79-105)	92 (79-105)	87 (79-105)	0.56
PreSS, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.77
Onset to randomization, median (IQR) minutes	60 (36-108)	61 (36-110)	59 (36-107)	0.29
Symptoms at randomization on PreSS				
Facial palsy present, n(%)	618 (43.1%)	302 (42.4%)	316 (43.9%)	0.56
Arm drift present, n(%)	817 (57.0%)	399 (56.0%)	418 (58.1%)	0.42
Speech difficulty present, n(%)	795 (55.5%)	384 (53.9%)	411 (57.1%)	0.22
Eye deviation and/or eye muscle palsy present, n(%)	155 (10.8%)	79 (11.1%)	76 (10.7%)	0.75
Incorrect correct month and age present, n(%)	323 (22.5%)	157 (22.0%)	166 (23.2%)	0.64
Other symptoms of stroke present, n(%)[a]	670 (46.8%)	353 (49.5%)	317 (44.1%)	0.038
Target population				
AIS, n(%)	737 (51.4%)	349 (48.9%)	388 (53.9%)	
ICH, n(%)	165 (11.5%)	87 (12.2%)	78 (10.8%)	
Non-target population				
TIA, n(%)	149 (10.4%)	79 (11.1%)	70 (9.7%)	
Stroke mimic, n(%)	382 (26.7%)	198 (27.8%)	184 (25.5%)	

Abbreviations: AIS acute ischemic stroke, ICH intracerebral hemorrhage, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale score, PreSS Prehospital Stroke Score, TIA transient ischemic attack
Information on missing data (if present) are listed under each variable.
[a] Including: sudden onset of leg weakness, sensory changes, ataxia, visual field defects, and diplopia

eTable 4: Primary and Secondary Efficacy Outcomes – Per-Protocol Population

Per protocol analysis (treatment adherence ≥ 80%)	Remote ischemic conditioning (RIC)	Sham	Absolute difference (95% CI)	Relative difference, 95% CI	p-value
Target population (per-protocol)	**RIC** (n=262)	**Sham** (n=303)			
Modified Rankin Scale score at 90 days, median (IQR)	1(0-2)	1(0-2)	0 (-0.24-0.24) [d]	OR 1.09 (0.80-1.47)	0.58
Difference in PreSS during 24hours, median (IQR)[a]	-1(-2-0)	-1(-2-0)	-0.52 (-1.68-0.64) [d]	OR 0.85 (0.63-1.14)	0.27
≥4 point NIHSS improvement during 24 hours, n(%)[b]	68 (26.5%)	85 (28.1%)	2.0 % (-8.6-4.7)	OR 0.92 (0.66-1.29)	0.64
Acute ischemic stroke	**RIC** (n=215)	**Sham** (n=265)			
Modified Rankin Scale score at 90 days, median (IQR)	1(0-2)	1(0-2)	0 (-0.26-0.26) [d]	OR 1.17 (0.84-1.63)	0.36
Difference in PreSS during 24hours, median (IQR)	-1 (-2-0)	-1(2-0)	0 (-0.29-0.29) [d]	OR 0.96 (0.74-1.24)	0.74
≥4 point NIHSS improvement during 24 hours, n(%)[b]	73 (27.7%)	59 (27.7%)	0.05 % (-7.9-8.0) [e]	OR 1.10 (0.75-1.62)	0.63
Treated with IVT	**RIC** (n=150)	**Sham** (n=174)			
Modified Rankin Scale score at 90 days, median (IQR)	1(0-2)	1(0-2)	0 (-0.48-0.48) [d]	OR 1.30 (0.86-.1.96)	0.21
Treated with EVT	**RIC** (n=30)	**Sham** (n=43)			
Modified Rankin Scale score at 90 days median (IQR)	1(1-3)	1(1-3)	0 (-0.97-0.97) [d]	OR 1.21 (0.50-2.93)	0.67
Treated with reperfusion therapy[c]	**RIC** (n=157)	**Sham** (n=195)			
Modified Rankin Scale score at 90 days, median (IQR)	1(1-2)	1(1-2)	0 (-0.46-0.46) [d]	OR 1.24 (0.84-1.85)	0.28
Not treated with reperfusion therapy[e]	**RIC** (n=58)	**Sham** (n=70)			
Modified Rankin Scale score at 90 days, median (IQR)	1(1-2)	1(1-2)	0 (-0.30-0.30) [d]	OR 0.99 (0.52-1.88)	0.98
Intracerebral hemorrhage patients	**RIC** (n=47)	**Sham** (n=38)			
Modified Rankin Scale score at 90 days, median (IQR)	3(2-4)	2(1-4)	1 (0.21-1.79) [d]	OR 1.57 (0.69-3.55)	0.28

Abbreviations: AIS acute ischemic stroke, EVT endovascular therapy/thrombectomy, ICH intracerebral hemorrhage, IVT Intravenous thrombolysis, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale score, mRS modified Rankin Scale, OR Odds ratio, PreSS Prehospital Stroke Score, TIA transient ischemic attack

[a] Difference in PreSS between Prehospital and 24-hour were missing in 36 (2.5%) patients of all randomized (n=1433) and were imputed for the ordinal logistic regression analyses. Difference in PreSS = 24 hour PreSS – Prehospital PreSS.

[b] NIHSS baseline and/or 24hour were missing in 26 (2.9%) patients of the target population (n=902) and were imputed for the ordinal logistic regression analysis on ≥4 point NIHSS improvement during 24 hours. For the IVT treated AIS, imputation of missing NIHSS values were not performed due to large statistical uncertainty of the estimates.

[c] Reperfusion therapy: Treatment with IVT and/or EVT.

[d] Difference in medians (95% CI)

[e] Absolute difference in risk (in percent) (95% CI)

eTable 5: Additional Efficacy and Safety Outcomes – Target population

Secondary efficacy in subgroups	Remote ischemic conditioning (RIC)	Sham	Relative difference, 95% CI	p-value
Acute ischemic stroke patients	**RIC** (n=349)	**Sham** (n=388)		
90-day all-cause mortality (post hoc), n(%)	16 (4.6%)	27 (7.0%)	HRR 0.67 (0.36-1.24)	0.20
24-hour NIHSS, median (IQR)	2 (0-4)	2 (0-4)	N/A	0.13
Treated with IVT	**RIC** (n=233)	**Sham** (n=240)		
≥4 point NIHSS improvement during 24 hours, n(%) [b]	69 (31.2%)	79 (31.9%)	OR 1.09 (0.81-1.47)	0.56
Difference in PreSS during 24hours, median (IQR) [a]	-1 (-2-0)	-1 (-2-0)	OR 1.01 (0.72-1.40)	0.98
90-day all-cause mortality (post hoc), n(%)	6 (2.7%)	13 (5.4%)	HRR 0.48 (0.18-1.28)	0.14
Treated with EVT	**RIC** (n=65)	**Sham** (n=69)		
Difference in PreSS during 24hours, median (IQR) [a]	-1 (-3-0)	-1 (-3-0)	OR 1.04 (0.56-1.93)	0.90
90-day all-cause mortality (post hoc), n(%)	7 (10.8%)	8 (11.6%)	HRR 0.96 (0.35-2.67)	0.94
Treated with reperfusion therapy [c]	**RIC** (n=247)	**Sham** (n=274)		
Difference in PreSS during 24hours, median (IQR) [a]	-1 (-2-0)	-1 (-2-0)	OR 0.90 (0.66-1.24)	0.53
90-day all-cause mortality (post hoc), n(%)	10 (4.0%)	19 (6.9%)	HRR 0.59 (0.27-1.28)	0.18
Not treated with reperfusion therapy [c]	**RIC** (n=102)	**Sham** (n=114)		
Difference in PreSS during 24hours, median (IQR) [a]	-1 (-1-0)	-1 (-2-0)	OR 1.04 (0.64-1.68)	0.87
90-day all-cause mortality (post hoc), n(%)	6 (5.9%)	8 (7.0%)	HRR 0.79 (0.27-2.30)	0.67
Intracerebral hemorrhage patients	**RIC** (n=87)	**Sham** (n=78)		
Difference in PreSS during 24hours, median (IQR) [a]	1 (0-1)	0 (-1-1)	OR 0.81 (0.44-1.50)	0.50
90-day all-cause mortality (post hoc), n(%)	21 (24.1%)	19 (24.4%)	HRR 0.93 (0.49-1.77)	0.82
Target diagnosis	**RIC** (n=436)	**Sham** (n=466)		
Bed days at the stroke unit, median (IQR)	2(1-5)	2(1-4)	N/A	0.45

Abbreviations: AIS acute ischemic stroke, EVT endovascular therapy/thrombectomy, HRR Hazard Rate Ratio, ICH intracerebral hemorrhage, IVT Intravenous thrombolysis, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale score, mRS modified Rankin Scale, OR Odds ratio, PreSS Prehospital Stroke Score, RR Relative Risk, TIA transient ischemic attack

[a] Difference in PreSS between Prehospital and 24-hour were missing in 36 (2.5%) patients of all randomized (n=1433) and were imputed for the ordinal logistic regression analyses. Difference in PreSS = 24 hour PreSS – Prehospital PreSS.

[b] NIHSS baseline and/or 24hour were missing in 26 (2.9%) patients of the target population (n=902) and were imputed for the ordinal logistic regression analysis on ≥4 point NIHSS improvement during 24 hours. For the IVT treated AIS, imputation of missing NIHSS values were not performed due to large statistical uncertainty of the estimates.

[c] Reperfusion therapy: Treatment with IVT and/or EVT.

eTable 6: Sensitivity analysis on primary and secondary endpoints adjusted for sex, age, diagnosis, site of inclusion, and prehospital PreSS

Sensitivity analysis on primary and secondary endpoints	Remote ischemic conditioning (RIC)	Sham	Absolute difference (95% CI)	Relative difference, 95% CI	p-value
Target diagnosis	**RIC** (n=436)	**Sham** (n=466)			
Modified Rankin Scale score at 90 days, median (IQR)	2 (1-3)	1 (1-3)	0 (-0.26-0.26) [d]	OR 1.02 (0.81-1.30)	0.85
≥4 point NIHSS improvement during 24 hours, n(%)[b]	131 (29.0%)	108 (25.4%)	-2.4 % % (-7.9-3.0) [e]	OR 0.87 (0.66-1.16)	0.36
Difference in PreSS during 24 hours, median (IQR) [a]	-1 (-2-0)	-1 (-2-0)	-0.14 (-0.46-0.19) [d]	OR 0.94 (0.74-1.19)	0.61
Complete remission of symptoms within 24 hours, n (%)	96 (18.6%)	90 (16.8%)	-0.2 % (-1.6-1.1)[e]	RR 0.98 (0.90-1.06)	0.56
Acute ischemic stroke patients	**RIC** (n=349)	**Sham** (n=388)			
Median score on mRS at 90 days, (IQR)	1 (1-2)	1 (0-3)	0 (-0.24-0.24) [d]	OR 1.00 (0.78-1.31)	0.96
Treated with IVT	**RIC** (n=233)	**Sham** (n=240)			
Median score on mRS at 90 days, (IQR)	1 (0-2)	1 (0-2)	0 (-0.34-0.34) [d]	OR 1.24 (0.89-1.73)	0.20
Treated with EVT	**RIC** (n=65)	**Sham** (n=69)			
Median score on mRS at 90 days, (IQR)	2 (1-3)	2 (1-3)	0 (-1.76-1.76) [d]	OR 1.26 (0.68-2.4)	0.46
Treated with reperfusion therapy [c]	**RIC** (n=247)	**Sham** (n=274)			
Median score on mRS at 90 days, (IQR)	1 (1-3)	1 (1-3)	0 (-0.33-0.33) [d]	OR 1.12 (0.82-1.53)	0.49
Not treated with reperfusion therapy [c]	**RIC** (n=102)	**Sham** (n=114)			
Median score on mRS at 90 days, (IQR)	2 (1-3)	1 (1-3)	0 (-1.0-1.0) [d]	OR 0.82 (0.50-1.33)	0.42
Intracerebral hemorrhage patients	**RIC** (n=87)	**Sham** (n=78)			
Median score on mRS at 90 days, (IQR)	3 (2-5)	3 (2-5)	0 (-1.0-1.0) [d]	OR 1.13 (0.64-1.99)	0.67
Entire population	**RIC** (n=713)	**Sham** (n=720)			
Serious adverse event (≥1 SAE), n (%)	169 (23.7%)	175 (24.3%)	0.1% (-3-2) [e]	HRR 1.01 (0.89-1.14)	0.91
Difference in PreSS during 24 hours, median (IQR) [a]	-1 (-2-0)	-1 (-2-0)	0 (-0.16-0.16) [d]	OR 1.00 (0.82-1.20)	0.96
90-day mortality, n(%)	41 (5.8%)	47 (6.5%)	-1.1 % (-3-0.9) [d]	RR 0.89 (0.63-1.24)	0.47

Abbreviations: AIS acute ischemic stroke, EVT endovascular therapy/thrombectomy, HRR Hazard Rate Ratio, ICH intracerebral hemorrhage, IVT Intravenous thrombolysis, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale score,
mRS modified Rankin Scale, OR Odds ratio, PreSS Prehospital Stroke Score, RR Relative Risk, TIA transient ischemic attack

[a] Difference in PreSS between Prehospital and 24-hour were missing in 36 (2.5%) patients of all randomized (n=1433) and were imputed for the ordinal logistic regression analyses. Difference in PreSS = 24 hour PreSS – Prehospital PreSS.

[b] NIHSS baseline and/or 24hour were missing in 26 (2.9%) patients of the target population (n=902) and were imputed for the ordinal logistic regression analysis on ≥4 point NIHSS improvement during 24 hours. For the IVT treated AIS, imputation of missing NIHSS values were not performed due to large statistical uncertainty of the estimates.

[c] Reperfusion therapy: Treatment with IVT and/or EVT.

[d] Difference in medians (95% CI) [e] Absolute difference in risk (in percent) (95% CI)

eTable 7: Device treatment adherence

Overall adherence (n=902)	**Total (n=902)**	**RIC (n=436)**	**Sham (n=466)**	**p-value**
Adherence to treatment ≥80%, n (%)	565 (62.6%)	262 (60.1%)	304 (65.1%)	0.087
Overall adherence, median (IQR) percentage	90 (65-100)	89 (51-100)	90 (71-100)	0.026
Hyperacute treatment (n=902)				
Prehospital cuff pressure, median (IQR) mmHg	N/A	216 (200-237)	20 (20-20)	N/A
Cycles received, median (IQR) cycles[a]	5 (4-6)	5 (4-6)	5 (4-6)	0.35
Adherence, median (IQR) percentage	100 (80-120)	100 (80-120)	100 (80-120)	0.32
Prehospital systolic blood pressure, median (IQR) mmHg[b]	182 (157-203)	181 (156-202)	182 (157-205)	0.58
Prehospital diastolic blood pressure, median (IQR) mmHg[b]	92 (79-106)	93 (79-106)	92 (80-106)	0.70
If RIC/sham was interrupted (eg. MRI):				
Cycles received before scan, median (IQR) cycles	3 (2-4)	3 (2-4)	3 (2-4)	0.85
Cycles received after scan, median (IQR) cycles	1 (0-4)	1 (0-3)	2 (0-5)	0.17
Duration of interruption, mean (SD) minutes	24 (0-41)	24 (0-40)	25 (0-41)	0.72
6-hour treatment (n=902)				
Cycles received, median (IQR) cycles	5 (0-5)	5 (0-5)	5 (0-5)	0.40
Adherence, median (IQR) percentage	100 (0-100)	100 (0-100)	100 (0-100)	0.22
Twice daily for one week (n=714)				
Cycles received, median (IQR) cycles	60 (38-70)	60 (20-69)	62 (49-70)	<0.001
Adherence, median (IQR) percentage	87 (57-100)	86 (29-99)	90 (71-100)	<0.001
Systolic blood pressure at day 7, median (IQR) mmHg[c]	147 (132-165)	146 (130-162)	148 (134-166)	0.12
Diastolic blood pressure at day 7, median (IQR) mmHg[c]	80 (73-93)	79 (70-93)	81 (73-93)	0.30

Abbreviations: IQR interquartile range, MRI Magnetic Resonance Imaging

In cases of transport time under 50 min, the RIC/sham protocol continued during the initial assessment at the stroke center until completed. If treatment had to be stopped (e.g. due to MRI, magnetic resonance imaging) a full treatment series was given after imaging if less than four cycles had been completed before discontinuation. All received treatments were registered on the devices. In 16 (3.4%) in the Sham group and 12 (2,8%) in the RIC group no device adherence data were available

[a] One cycle equals 5min of cuff inflation and 5 minutes of cuff deflation

[b] No prehospital blood-pressures were available in 24 (5.1%) of the Sham group and 15 (3.4%) of the RIC group.

[c] Blood pressure on day 7 only available for patients treated with 7-day RIC/sham day.

eTable 8: Events assessed and adjudicated by the clinical event committee[a]

CEC assessment	RIC	Sham
Serious Events, n	159	186
Disabling Stroke – Hemorrhagic	1 (0.6%)	2 (1.1%)
Disabling Stroke – Ischemic	12 (7.5%)	9 (4.8%)
Intracerebral Haemorrhage (Non-Stroke)	1 (0.6%)	0 (0.0%)
Non-Disabling Stroke – Ischemic	8 (5.0%)	19 (10.2%)
Subarachnoid hemorrhage (SAH)	1 (0.6%)	0 (0.0%)
Transient Ischemic Attack (TIA)	8 (5.0%)	6 (3.2%)
Neurovascular - Other (Specify)	4 (2.5%)	2 (1.1%)
Coma	1 (0.6%)	1 (0.5%)
Headache	1 (0.6%)	0 (0.0%)
Neurological - Other (Specify)	11 (6.9%)	9 (4.8%)
Prehospital stroke deterioration	6 (3.8%)	10 (5.4%)
In-hospital stroke deterioration	29 (18.2%)	38 (20.4%)
Prehospital non-stroke deterioration	2 (1.3%)	3 (1.6%)
In-hospital non- stroke deterioration	6 (3.8%)	8 (4.3%)
ACS: Myocardial Infarction – NSTEMI	1 (0.6%)	1 (0.5%)
Stable Angina	1 (0.6%)	0 (0.0%)
Claudication (Chronic extremity ischemia)	0 (0.0%)	1 (0.5%)
Peripheral Vascular – Other (DVT or PE)	5 (3.1%)	4 (2.2%)
Cardiopulmonary Bypass	1 (0.6%)	0 (0.0%)
Chest Pain	3 (1.9%)	5 (2.7%)
Electrocardiogram – Other Abnormal Findings (Specify)	0 (0.0%)	1 (0.5%)
Endovascular Or Surgical Intervention – Planned (Specify Site)	1 (0.6%)	2 (1.1%)
Cardiovascular – Other (Specify)	1 (0.6%)	5 (2.7%)
Bleeding - Severe or Life-threatening	2 (1.3%)	0 (0.0%)
Bleeding - Mild	0 (0.0%)	1 (0.5%)
Bleeding – Severe (symptomatic intracranial bleeding after reperfusion therapy)	10 (6.3%)	7 (3.8%)
Death, Cardiovascular, Non-Coronary Vascular Conditions – Neurological Event	29 (18.2%)	27 (14.5%)
Death, Cardiovascular, Non-Coronary Vascular Conditions – Other	2 (1.3%)	0 (0.0%)
Death, Cardiovascular – Sudden Or Unwitnessed	3 (1.9%)	0 (0.0%)
Death, Cardiovascular – Death Of Unknown Cause	2 (1.3%)	5 (2.7%)
Death, Non-Cardiovascular – Malignancy	3 (1.9%)	4 (2.2%)
Death, Non-Cardiovascular – Infection/Sepsis	1 (0.6%)	8 (4.3%)
Death, Non-Cardiovascular – COPD	1 (0.6%)	0 (0.0%)
Death, Non-Cardiovascular – Other (Specify)	1 (0.6%)	2 (1.1%)
Infection – Pulmonary	1 (0.6%)	1 (0.5%)
Infection – Other (Specify)	0 (0.0%)	1 (0.5%)
Paraclinical - Other (Specify)	0 (0.0%)	1 (0.5%)
Neoplasm - Other (Specify)	0 (0.0%)	2 (1.1%)
Carotid Endarectomy (rescue)	0 (0.0%)	1 (0.5%)

[a] All events that qualified, or if there were any doubt, as MACCE, recurrent ischemic events or death were assessed and adjudicated by CEC.
Abbreviations: CEC Clinical event committee, COPD Chronic obstructive pulmonary disease, NSTEMI non-ST-elevation myocardial infarction, DVT Deep vein thrombosis, PE Pulmonary embolism

eTable 9: All registered events as assessed by the investigators

Serious adverse events	RIC	Sham	Adverse events	RIC	Sham
Related events[a]			**Related events**[a]		
Serious adverse events assessed as possible related to intervention	11	21	**Adverse events assessed as possible related to intervention**	43	9
Prehospital stroke deterioration	2	4	Neurological - Other (sensory disturbances)	1	1
In-hospital stroke deterioration	5	10	Minor hematoma at the extremity	1	0
Myocardial Infarction – NSTEMI	0	1	Mild To Moderate Bruising Or Ecchymosis/Petechial rash in the extremity	1	1
Peripheral Vascular – Other (superficial vein thrombosis)	0	1	Peripheral edema at the extremity	1	0
Death, Cardiovascular, Non-Coronary Vascular Conditions – Neurological index disease	2	5	Pain in the extremity	36	7
Pain and pettechial rash in the extremity that leads to prolonged admission	1	0			
Surgery – Other (hematoma evacuation in ICH)	1	0			
Serious adverse events	**RIC**	**Sham**	**Adverse events**	**RIC**	**Sham**
Unrelated events[b]			**Unrelated events**[b]		
Serious adverse events assessed as unrelated to intervention	324	304	Adverse events assessed as unrelated to intervention	114	66
Disabling Stroke – Hemorrhagic	2	2	Non-Disabling Stroke – Ischemic	2	0
Disabling Stroke – Ischemic	7	5	Transient Ischemic Attack (TIA)	1	2
Intracerebral Haemorrhage (Non-Stroke)	0	2	Neurovascular - Other (Specify)	3	3
Non-Disabling Stroke – Hemorrhagic	2	2	Reduced consciousness/coma	0	1
Non-Disabling Stroke – Ischemic	12	23	Delirium	1	1
Transient Ischemic Attack (TIA)	8	5	Seizure	1	0
Neurovascular - Other	7	6	Pathological Crying	2	1
Reduced consciousness/coma	3	1	Psychiatric - Other	3	2
Delirium	0	2	Headache	4	1
Seizure	16	11	Dizziness – non-cardiovascular	2	0
Encephalopathy - Other	0	1	Syncope – non-cardiovascular	0	1
Depression	1	2	Neurological - Other	10	2
Pathological Crying	0	3	In-hospital stroke deterioration	0	2
Headache	3	1	In-hospital non- stroke deterioration	2	4
Dizziness – non-cardiovascular	0	1	Stable Angina	1	1
Syncope – non-cardiovascular	0	1	Arrhythmia – Major	1	2
Neurological - Other	14	8	Arrhythmia – Minor	5	3
Prehospital stroke deterioration	3	5	Atrial Fibrillation	2	1
In-hospital stroke deterioration	26	26	Left Ventricular Insufficiency	1	0
Prehospital non-stroke deterioration	1	2	Peripheral Vascular – Other	2	0
In-hospital non- stroke deterioration	8	7	Chest Pain	3	3
Myocardial Infarction – NSTEMI	1	1	Orthoestatism	2	0
Arrhythmia – Severe	2	4	Syncope – cardiovascular	3	0
Arrhythmia – Major	7	0	Cardiovascular – Other	2	1
Arrhythmia – Minor	0	1	Bleeding - Moderate	1	0
Permanent Pacemaker Implant	4	4	Bleeding - Mild	5	7

Serious adverse events	RIC	Sham
Atrial Fibrillation requiring acute treatment	4	4
Left Ventricular Insufficiency	1	1
Heart Failure (other)	1	0
Claudication (Chronic extremity ischemia)	1	1
Peripheral Vascular – Other (DVT or PE)	7	5
Cardiopulmonary Bypass (unplanned)	1	0
Chest Pain	1	2
Endovascular Or Surgical Intervention – Planned	7	4
Endovascular Or Surgical Intervention – Unplanned	4	2
Orthoestatism	1	0
Pulmonary Edema	1	0
Syncope – cardiovascular	0	1
Cardiovascular – Other (Specify)	1	8
Arterial hypotension	3	4
Bleeding - Severe or Life-threatening	3	1
Bleeding - Moderate	1	1
Bleeding - Mild	3	0
Bleeding – Severe (symptomatic intracranial bleeding after reperfusion therapy)	9	5
Death, Cardiovascular, Non-Coronary Vascular Conditions – Neurological Event	27	21
Death, Cardiovascular, Non-Coronary Vascular Conditions – Other (Specify)	2	0
Death, Cardiovascular – Sudden Or Unwitnessed	3	0
Death, Cardiovascular – Death Of Unknown Cause	3	5
Death, Non-Cardiovascular – Malignancy	3	5
Death, Non-Cardiovascular – Infection/Sepsis	1	9
Death, Non-Cardiovascular – COPD	1	0
Death, Non-Cardiovascular – Other	1	2
Gastro-Intestinal - Other	4	2
Respiratory Insufficiency/Failure	6	9
Respiratory - Other (Specify)	6	0
Renal Insufficiency (newly diagnosed)	0	3
Urinary And Genital Organs - Other (Specify)	4	1
Infection – Pulmonary	31	29
Infection – Urinary	12	5
Infection – Gastrointestinal	7	1
Infection – Other	9	15
Peripheral Edema	1	0
Skin - Other	3	0
Fall causing bone fracture	1	3
Paraclinical - Other (Specify)	2	4
Serious adverse events	**RIC**	**Sham**
Benign Neoplasms	1	0
Neoplasm - Other	1	7
Anaemia	0	1

Adverse events	RIC	Sham
Bleeding – asymptomatic intracranial bleeding (found on routine imaging)	0	1
Diarrhoea	1	0
Biochemical - Hepatic Dysfunction	0	1
Gastro-Intestinal - Other	2	2
Respiratory - Other	2	0
Renal Insufficiency	0	2
Urinary And Genital Organs	1	2
Infection – Urinary	15	8
Infection – Gastrointestinal	1	0
Infection – Other	6	3
Peripheral Edema	1	0
Sweating	1	0
Skin – Other	7	3
Paraclinical - Other	11	6
Neoplasm - without treatment consequences	2	0
Anaemia	0	1
Endocrine, nutritional and metabolic	1	0
Other	2	1

eTable 9: All registered events as assessed by the investigators (continued)

Diseases In Blood And Blood Forming Organs	0	1
Endocrine, nutritional and metabolic	2	0
Surgery – Other	13	14
Other	4	2

[a] Related events: Assessed by investigator/sponsor as related, probably or possible related intervention
[b] Unrelated events: Assessed investigator/sponsor as unrelated, unlikely related to study intervention
Abbreviations: Abbreviations: CEC Clinical event committee, COPD Chronic obstructive pulmonary disease, NSTEMI non-ST-elevation myocardial infarction, DVT Deep vein thrombosis, PE Pulmonary embolism

eTable 10: Category of diagnosis in the stroke mimics group

Diagnosis in the stroke mimic group	All	RIC	Sham
ICD10 diagnosis categories, all are n(%)	382	198	184
A09 Other gastroenteritis and colitis of infectious and unspecified origin	1 (0.3%)	1 (0.5%)	0 (0.0%)
A41 Other sepsis	4 (1.0%)	2 (1.0%)	2 (1.1%)
A69 Other spirochaetal infections	1 (0.3%)	0 (0.0%)	1 (0.5%)
B99 Other and unspecified infectious diseases	1 (0.3%)	0 (0.0%)	1 (0.5%)
C71 Malignant neoplasm of brain	6 (1.6%)	5 (2.5%)	1 (0.5%)
C79 Secondary malignant neoplasm of other and unspecified sites	1 (0.3%)	0 (0.0%)	1 (0.5%)
D32 Benign neoplasm of meninges	2 (0.5%)	1 (0.5%)	1 (0.5%)
D43 Neoplasm of the brain and central nervous system (unspecified)	5 (1.3%)	2 (1.0%)	3 (1.6%)
E86 Volume depletion	1 (0.3%)	0 (0.0%)	1 (0.5%)
E87 Other disorders of fluid, electrolyte and acid-base balance	1 (0.3%)	0 (0.0%)	1 (0.5%)
F03 Unspecified dementia	2 (0.5%)	1 (0.5%)	1 (0.5%)
F05 Delirium, not induced by alcohol and other psychoactive substances	2 (0.5%)	1 (0.5%)	1 (0.5%)
F10 Mental and behavioural disorders due to use of alcohol	7 (1.8%)	2 (1.0%)	5 (2.7%)
F41 Other anxiety disorders	1 (0.3%)	1 (0.5%)	0 (0.0%)
F43 Reaction to severe stress, and adjustment disorders	4 (1.0%)	2 (1.0%)	2 (1.1%)
F44 Dissociative [conversion] disorders	4 (1.0%)	2 (1.0%)	2 (1.1%)
F45 Somatoform disorders	4 (1.0%)	1 (0.5%)	3 (1.6%)
F48 Other neurotic disorders	1 (0.3%)	0 (0.0%)	1 (0.5%)
F80 Specific developmental disorders of speech and language	2 (0.5%)	1 (0.5%)	1 (0.5%)
G04 Encephalitis, myelitis and encephalomyelitis	2 (0.5%)	1 (0.5%)	1 (0.5%)
G25 Other extrapyramidal and movement disorders	3 (0.8%)	1 (0.5%)	2 (1.1%)
G37 Other demyelinating diseases of central nervous system	1 (0.3%)	0 (0.0%)	1 (0.5%)
G41 Status epilepticus	2 (0.5%)	1 (0.5%)	1 (0.5%)
G43 Migraine	34 (8.9%)	18 (9.1%)	16 (8.7%)
G44 Other headache syndromes	4 (1.0%)	1 (0.5%)	3 (1.6%)
G47 Sleep disorders	1 (0.3%)	0 (0.0%)	1 (0.5%)
G51 Facial nerve disorders	11 (2.9%)	6 (3.0%)	5 (2.7%)
G54 Nerve root and plexus disorders	1 (0.3%)	1 (0.5%)	0 (0.0%)
G56 Mononeuropathies of upper limb	1 (0.3%)	1 (0.5%)	0 (0.0%)
G63 Polyneuropathy in diseases classified elsewhere	1 (0.3%)	1 (0.5%)	0 (0.0%)
G70 Myasthenia gravis and other myoneural disorders	2 (0.5%)	1 (0.5%)	1 (0.5%)
G81 Hemiplegia	1 (0.3%)	0 (0.0%)	1 (0.5%)
G83 Other paralytic syndromes	1 (0.3%)	1 (0.5%)	0 (0.0%)
G91 Hydrocephalus	1 (0.3%)	1 (0.5%)	0 (0.0%)
H53 Visual disturbances	7 (1.8%)	5 (2.5%)	2 (1.1%)

H81 Disorders of vestibular function	11 (2.9%)	6 (3.0%)	5 (2.7%)
I10 Essential (primary) hypertension	2 (0.5%)	1 (0.5%)	1 (0.5%)
I43 Cardiomyopathy in diseases classified elsewhere	1 (0.3%)	1 (0.5%)	0 (0.0%)
I60 Subarachnoid haemorrhage	5 (1.3%)	3 (1.5%)	2 (1.1%)
S065 Subdural hematoma	1 (0.3%)	1 (0.5%)	0 (0.0%)
I62 Other nontraumatic intracranial haemorrhage	1 (0.3%)	0 (0.0%)	1 (0.5%)
I68 Cerebrovascular disorders in diseases classified elsewhere	2 (0.5%)	2 (1.0%)	0 (0.0%)
I69 Sequelae of cerebrovascular disease	11 (2.9%)	4 (2.0%)	7 (3.8%)
I71 Aortic aneurysm and dissection	1 (0.3%)	0 (0.0%)	1 (0.5%)
I77 Other disorders of arteries and arterioles	2 (0.5%)	2 (1.0%)	0 (0.0%)
J15 Bacterial pneumonia, not elsewhere classified	1 (0.3%)	1 (0.5%)	0 (0.0%)
J69 Pneumonitis due to solids and liquids	1 (0.3%)	1 (0.5%)	0 (0.0%)
M35 Other systemic involvement of connective tissue	1 (0.3%)	1 (0.5%)	0 (0.0%)
M54 Dorsalgia	2 (0.5%)	0 (0.0%)	2 (1.1%)
M62 Other disorders of muscle	2 (0.5%)	0 (0.0%)	2 (1.1%)
M87 Osteonecrosis	1 (0.3%)	1 (0.5%)	0 (0.0%)
N30 Cystitis	3 (0.8%)	2 (1.0%)	1 (0.5%)
N39 Other disorders of urinary system	1 (0.3%)	1 (0.5%)	0 (0.0%)
R00 Abnormalities of heart beat	1 (0.3%)	0 (0.0%)	1 (0.5%)
R11 Nausea and vomiting	1 (0.3%)	1 (0.5%)	0 (0.0%)
R20 Disturbances of skin sensation	43 (11.3%)	25 (12.6%)	18 (9.8%)
R25 Abnormal involuntary movements	6 (1.6%)	3 (1.5%)	3 (1.6%)
R26 Abnormalities of gait and mobility	2 (0.5%)	1 (0.5%)	1 (0.5%)
R27 Other lack of coordination	2 (0.5%)	2 (1.0%)	0 (0.0%)
R29 Other symptoms and signs involving the nervous and musculoskeletal systems	6 (1.6%)	2 (1.0%)	4 (2.2%)
R31 Unspecified haematuria	1 (0.3%)	0 (0.0%)	1 (0.5%)
R33 Retention of urine	1 (0.3%)	0 (0.0%)	1 (0.5%)
R41 Other symptoms and signs involving cognitive functions and awareness	8 (2.1%)	5 (2.5%)	3 (1.6%)
R42 Dizziness and giddiness	21 (5.5%)	8 (4.0%)	13 (7.1%)
R45 Symptoms and signs involving emotional state	1 (0.3%)	1 (0.5%)	0 (0.0%)
R47 Speech disturbances, not elsewhere classified	8 (2.1%)	4 (2.0%)	4 (2.2%)
R48 Dyslexia and other symbolic dysfunctions, not elsewhere classified	1 (0.3%)	1 (0.5%)	0 (0.0%)
R50 Fever of other and unknown origin	2 (0.5%)	1 (0.5%)	1 (0.5%)
R51 Headache	14 (3.7%)	9 (4.5%)	5 (2.7%)
R52 Pain, not elsewhere classified	4 (1.0%)	2 (1.0%)	2 (1.1%)
R53 Malaise and fatigue	18 (4.7%)	10 (5.1%)	8 (4.3%)
R55 Syncope and collapse	15 (3.9%)	3 (1.5%)	12 (6.5%)
R56 Convulsions, not elsewhere classified	2 (0.5%)	1 (0.5%)	1 (0.5%)

eTable 10: Category of diagnosis in the stroke mimics group

R68 Other general symptoms and signs	3 (0.8%)	1 (0.5%)	2 (1.1%)
R78 Findings of drugs and other substances, not normally found in blood	1 (0.3%)	0 (0.0%)	1 (0.5%)
S06 Intracranial injury	9 (2.4%)	4 (2.0%)	5 (2.7%)
S12 Fracture of neck	1 (0.3%)	1 (0.5%)	0 (0.0%)
S42 Fracture of shoulder and upper arm	1 (0.3%)	0 (0.0%)	1 (0.5%)
S44 Injury of nerves at shoulder and upper arm level	1 (0.3%)	0 (0.0%)	1 (0.5%)
S62 Fracture at wrist and hand level	1 (0.3%)	0 (0.0%)	1 (0.5%)
S84 Injury of nerves at lower leg level	1 (0.3%)	0 (0.0%)	1 (0.5%)
T42 Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs	1 (0.3%)	1 (0.5%)	0 (0.0%)
T51 Toxic effect of alcohol	3 (0.8%)	1 (0.5%)	2 (1.1%)
T85 Complications of other internal prosthetic devices, implants and grafts	1 (0.3%)	1 (0.5%)	0 (0.0%)
Z03 Medical observation and evaluation for suspected diseases and conditions	8 (2.1%)	5 (2.5%)	3 (1.6%)
Missing	1 (0.3%)	1 (0.5%)	0 (0.0%)

eTable 11: Baseline demographic, clinical and treatment characteristics of the target population stratified by duration of postconditioning

Characteristics	**Extended postconditioning** (7 days) - Aarhus (n=714)	**Postconditioning** (6 hour) – other sites (n=188)
Age, median (IQR)	73 (62, 79)	73 (63, 79.5)
Female, n(%)	265 (37.1%)	70 (37.2%)
Hypertension, n(%)[a]	440 (61.6%)	127 (67.6%)
Diabetes, n(%)[a]	79 (11.1%)	34 (18.1%)
Atrial fibrillation, n(%)[a]	109 (15.3%)	32 (17.0%)
PreSS, median (IQR)[b]	2 (2-4)	2 (2-3)
Onset to randomization, median (IQR) minutes	55 (33-98)	56 (35-100)
Admission NIHSS, median (IQR)[c]	5 (2-11)	5 (3-9)
24-hour NIHSS, median (IQR) [c]	2 (0-5)	2 (0-4)
Median score on modified Rankin Scale at 90 days, (IQR)	1 (1-3)	2 (1-3)
mRS 0	153 (21.4%)	36 (19.1%)
mRS 1	215 (30.1%)	51 (27.1%)
mRS 2	112 (15.7%)	39 (20.7%)
mRS 3	102 (14.3%)	28 (14.9%)
mRS 4	37 (5.2%)	5 (2.7%)
mRS 5	29 (4.1%)	10 (5.3%)
mRS 6 (dead)	66 (9.2%)	19 (10.1%)
Discharge diagnosis		
AIS	579 (81.1%)	158 (84.0%)
ICH	135 (18.9%)	30 (16.0%)
Patients with acute ischemic stroke		
Reperfusion therapy (IVT and/or EVT), n (%)	400 (69.1%)	121 (76.6%)
Intravenous thrombolysis, n(%)[d]	352 (49.6%)	110 (58.5%)
Admission to thrombolysis, median (IQR) min.	30 (25-38)	25 (17-32)
Thrombectomy, n(%)	111 (19.2%)	23 (14.6%)
Outcome		

Abbreviations: AIS acute ischemic stroke, EVT endovascular therapy/thrombectomy, ICH intracerebral hemorrhage, IVT Intravenous thrombolysis, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale score, mRS modified Rankin Scale, PreSS Prehospital Stroke Score, TIA transient ischemic attack

[a] Known or newly diagnosed

[b] Scores on the Prehospital Stroke Score (PreSS) range from 0 to 6, with higher scores indicating a greater deficit

[c] Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a greater deficit. NIHSS baseline and/or 24hour were missing in 26 (2.9%) patients

[d] Only intravenous thrombolysis with alteplase infusion was used during the study period

eTable 12: Pairwise consistency and agreement measure represented by relative and absolute intra-class agreement

Characteristics	Relative intra-class agreement	Absolute intra-class agreement
Between assessor 1 and 2 (n=811)[a]	0.86	0.86
Between assessor 1 and 3 (n=254)[b]	0.69	0.69
Between assessor 2 and 3 (n=254)[b]	0.76	0.76

[a] The accepted timeframe for evaluation of assessments 1 and 2 were: 3 months +/- 2 weeks

[b] The accepted timeframe for evaluation of assessment 3: 3 months and 2 weeks +/- 2 weeks

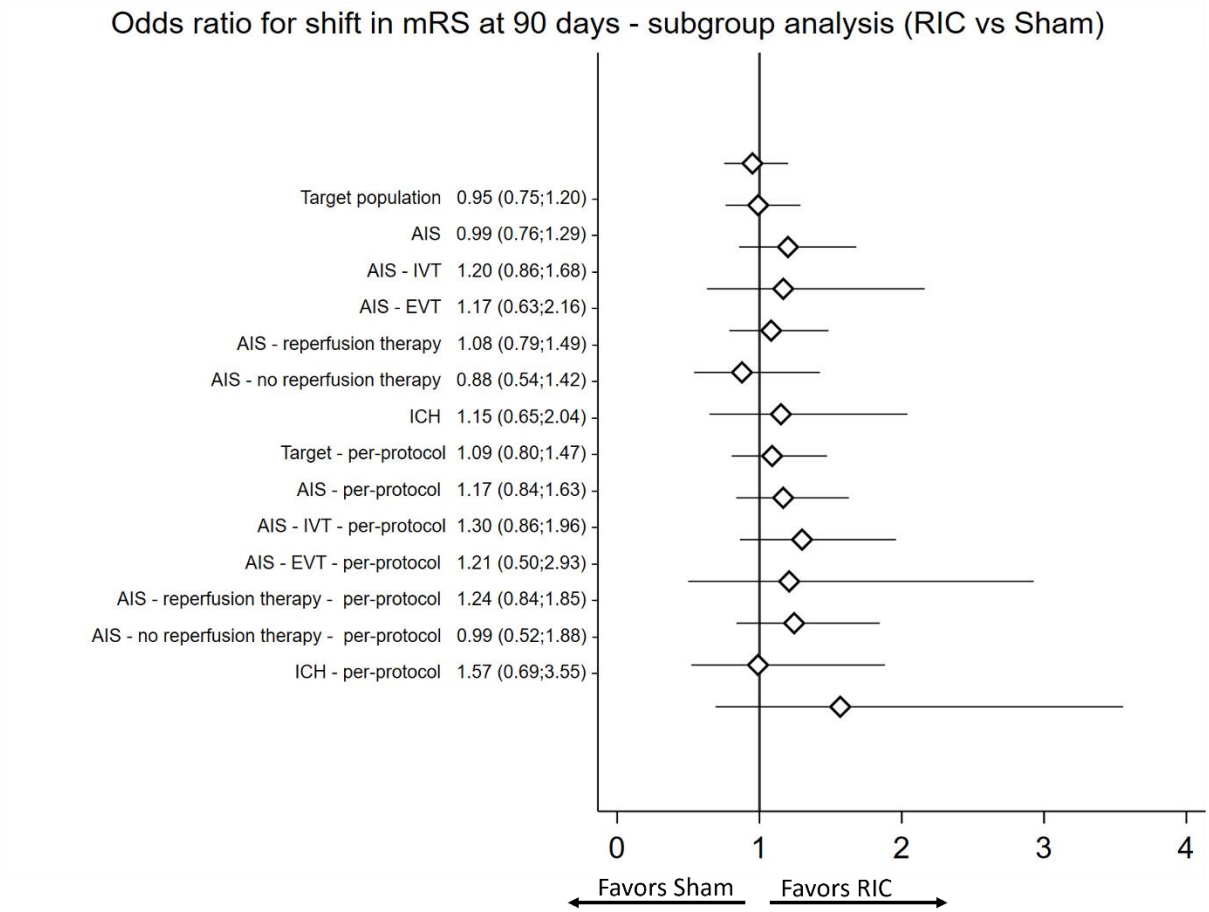
In 10 out of 902 (1.1%) patients only one assessor managed to contact the patient. . A total of 85 patients had died at the time of mRS follow-up (mRS=6) and in these cases only one assessment of mRS was required.

eFigures - Supplementary Figures

eFigure 1. Investigational device (RIC and Sham devices) photo.

A: Every ambulance was equipped with one RIC device and one sham-device. **B:** The devices were colorcoded and the patient was randomized to a device color (yellow device or blue device). Randomization was performed by the on-call stroke neurologist. **C:** Treatment was started immediately following randomization and the device and bag were secured during transport. RIC: ”yellow” and Sham: ”blue”

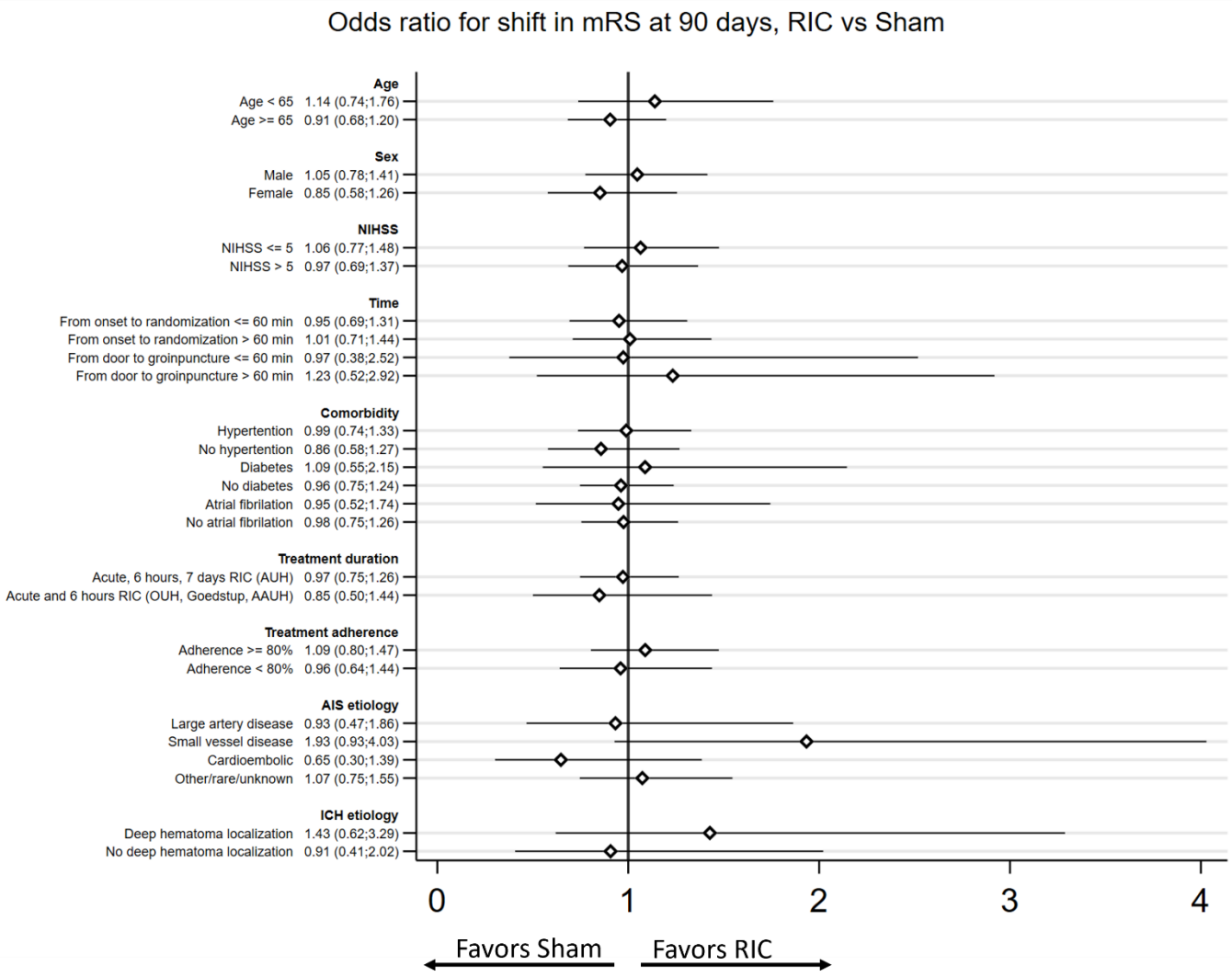
eFigure 2. Subgroup Analysis – Pre-Specified Subgroups (forestplot)



Abbreviations: AIS acute ischemic stroke, EVT endovascular therapy/thrombectomy, ICH intracerebral hemorrhage, IVT Intravenous thrombolysis, mRS modified Rankin Scale, RIC Remote Ischemic Conditioning

Forest plot on odds-ratios (OR) for shift in mRS at 90 days in different prespecified subgroups, with ORs above 1 favoring RIC.

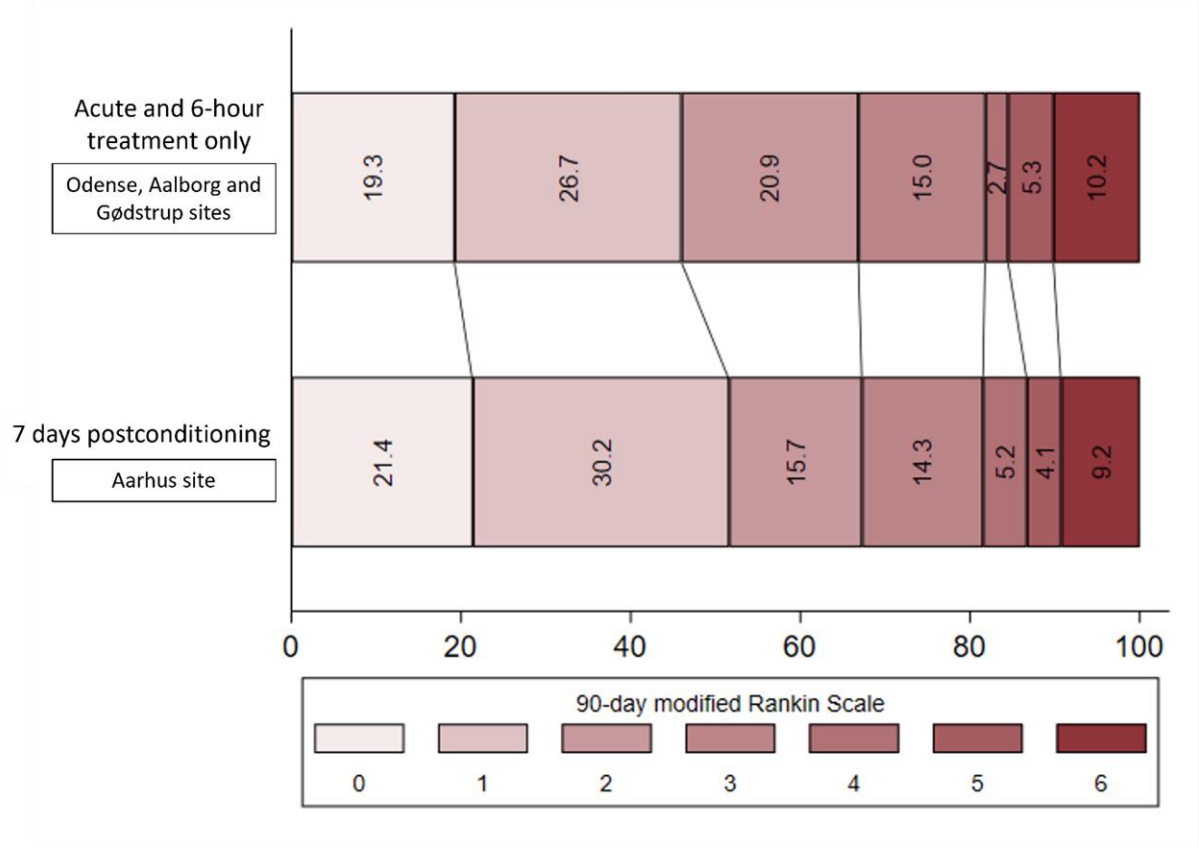
eFigure 3. Subgroup Analysis – Pre-Specified Subgroups on demographics (forestplot)



Abbreviations: AIS acute ischemic stroke, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale score, mRS modified Rankin Scale, PreSS Prehospital Stroke Score, RIC Remote Ischemic Conditioning

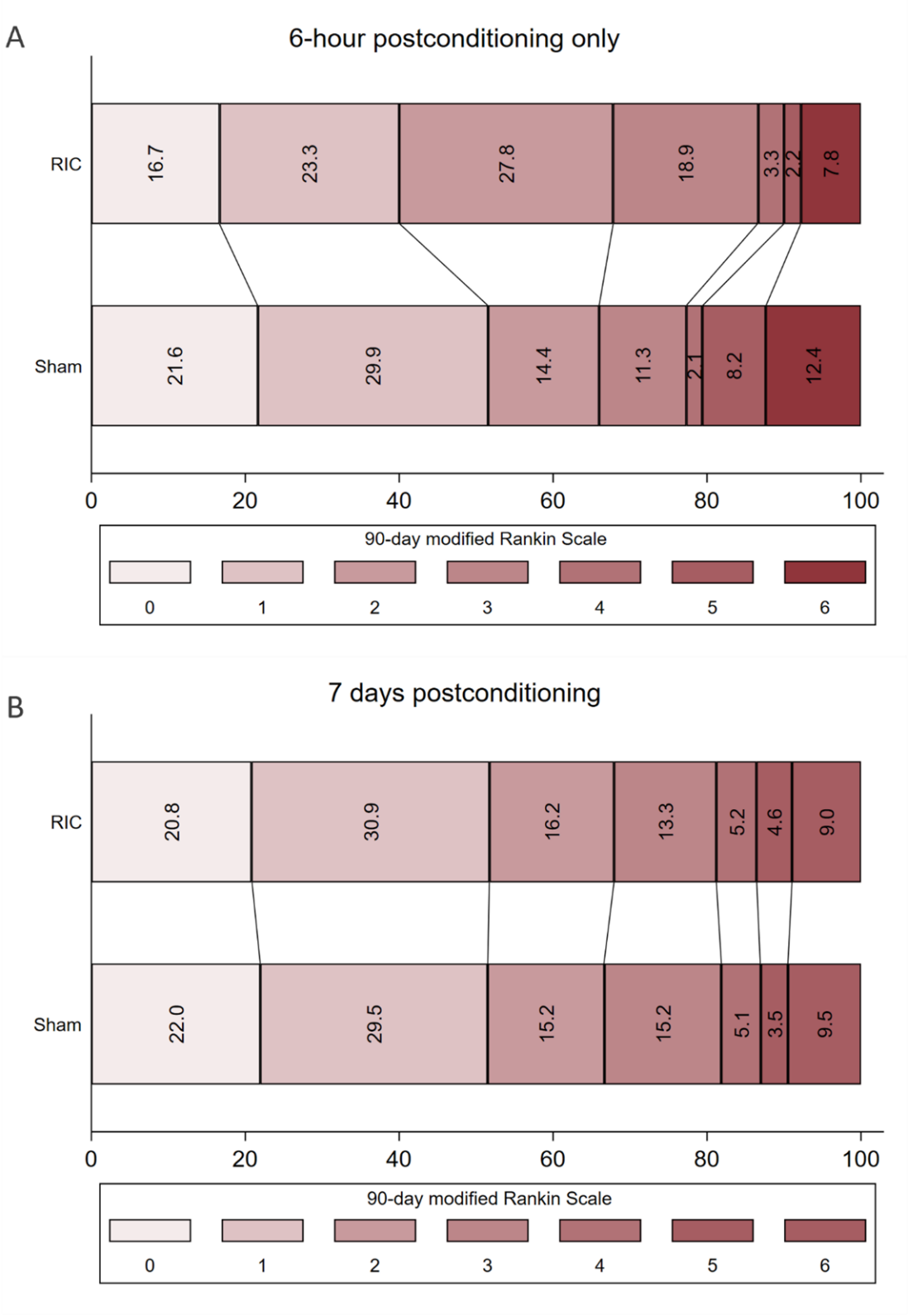
Forest plot on odds-ratios (OR) for a shift on mRS at 90 days in different prespecified subgroups, with ORs above 1 favoring RIC.

eFigure 4: Stacked barchart on the distribution of mRS score stratified by duration of postconditioning treatment



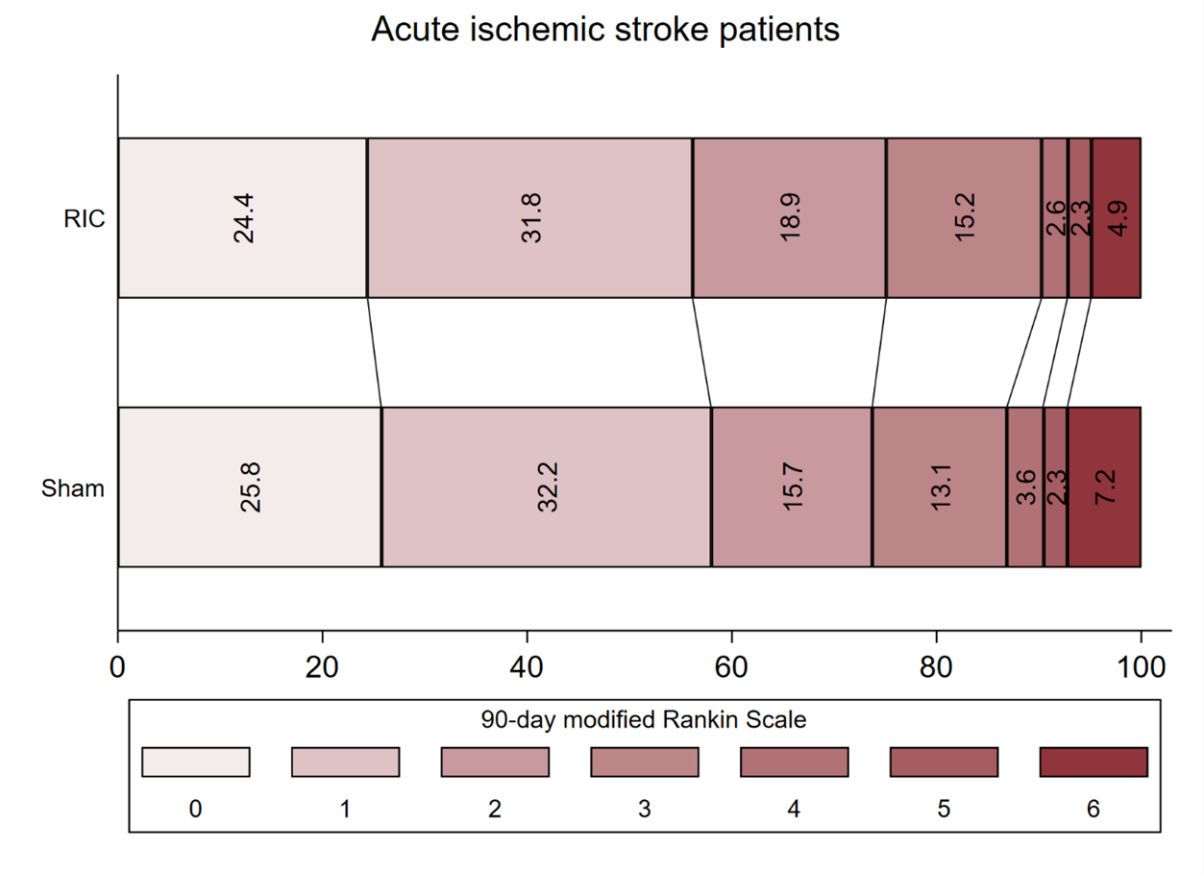
Differences in the scores on the modified Rankin scale (mRS) among target population patients treated with 6 hour and 7 days postconditioning . Each stratum is presented in percentage.

eFigure 5: Stacked barchart on the distribution of mRS score stratified by duration of postconditioning treatment



Differences in the scores on the modified Rankin scale (mRS) in the RIC and Sham group among target population patients treated with 6 hour (eFigure 5A) and 7 days postconditioning (eFigure 5B). Each stratum is presented in percentage.

eFigure 6: Stacked barchart on the distribution of mRS score in patients with acute ischemic stroke



Differences in the scores on the modified Rankin scale (mRS) in the RIC and Sham group among patients with acute ischemic stroke. Each stratum is presented in percentage.