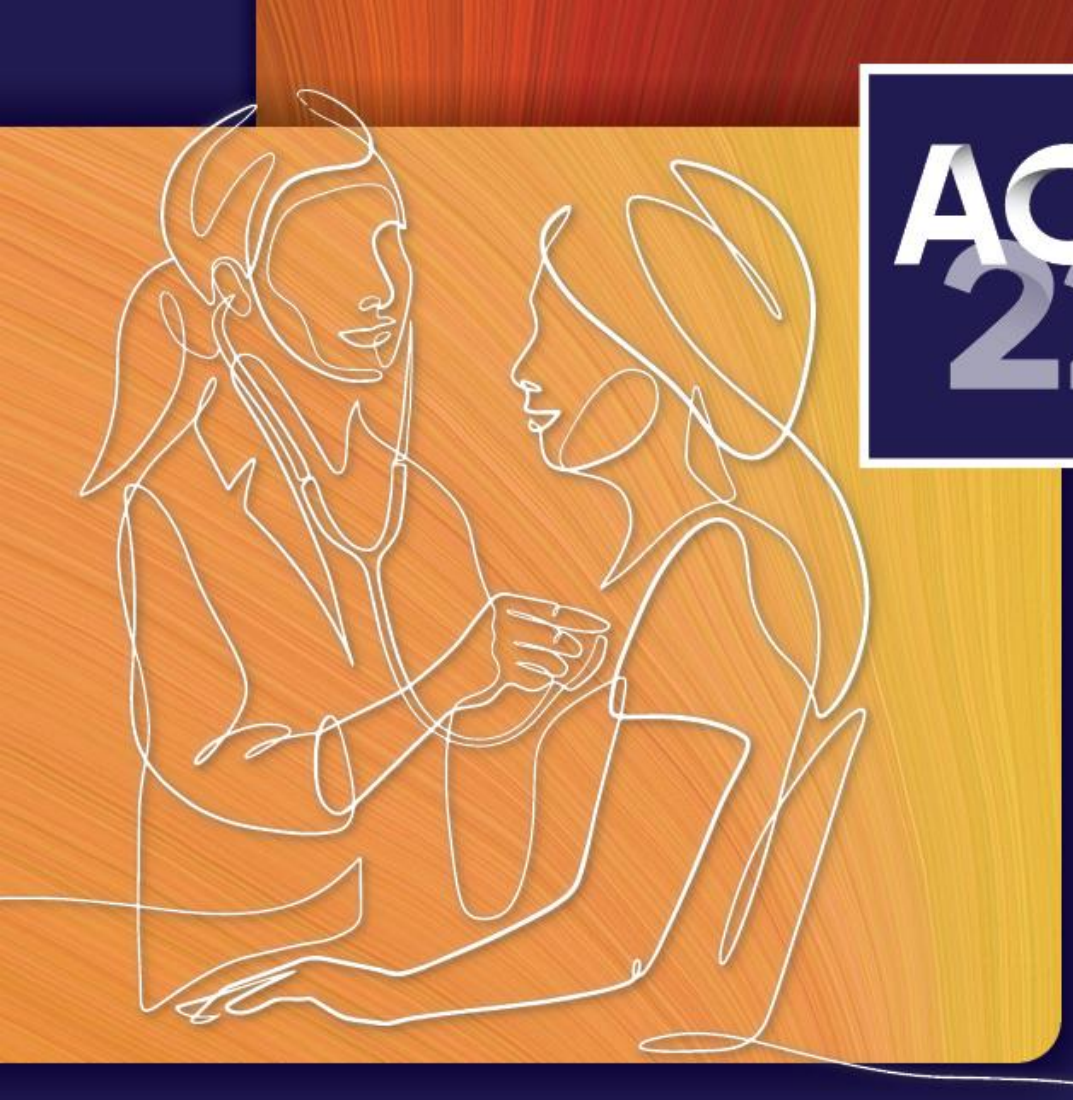

ACC 22

Late Breaking Clinical Trial - 4 April 2022

Sodium Thiosulfate in Myocardial Infarction (GIPS-IV)

Marie-Sophie L.Y. de Koning, Paulien van Dorp, Solmaz Assa, Michiel Voskuil, Rutger L. Anthonio, D. Veen, Tim Leiner, Anita J. Sibeijn-Kuiper, Harry van Goor, Dirk J. van Veldhuisen, Peter van der Meer, Robin Nijveldt, Erik Lipšic, Pim van der Harst, and the GIPS-IV investigators

University Medical Center Groningen
the Netherlands

#GIPSIV
@profpim
@MarieSophiedeK1

AMERICAN COLLEGE of CARDIOLOGY

Disclosures and funding

- M.L.Y. de Koning has no conflicts of interest
- Discusses off-label and investigational use of sodium thiosulfate
- Funded by:

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Hartstichting
SIEMENS Healthineers
umcg

Background

Myocardial infarction still major risk factor for heart failure development and early mortality

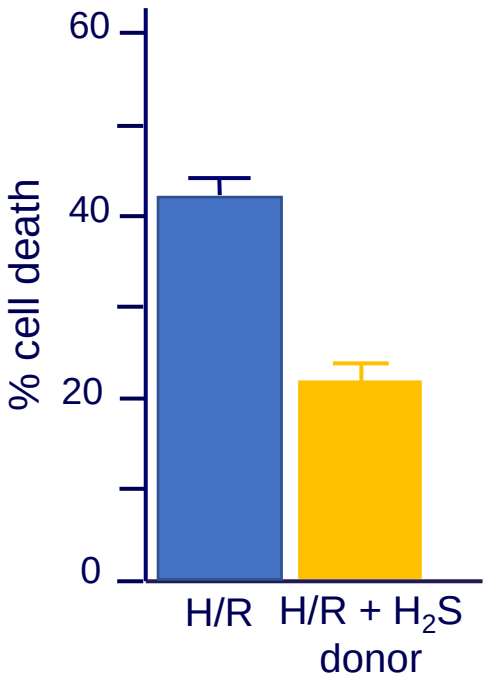
- Infarct size: strongest predictor of clinical outcomes

Residual target to limit infarct size: ischemia-reperfusion injury

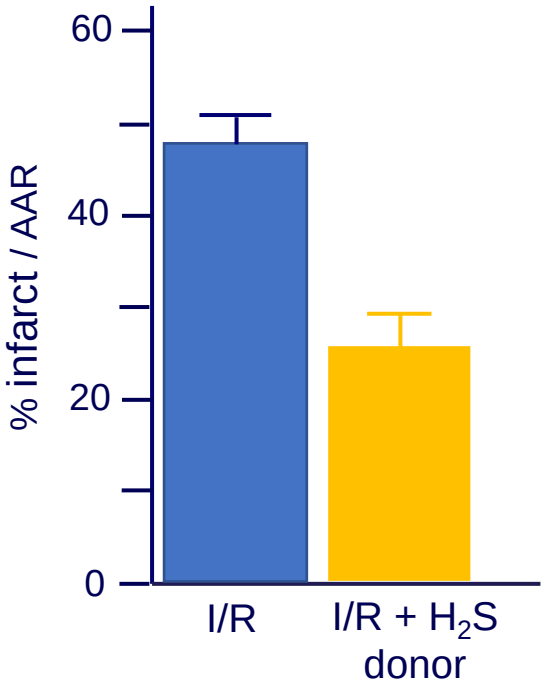
Hydrogen Sulfide (H_2S) very promising cardioprotective therapy

Pre-clinical evidence

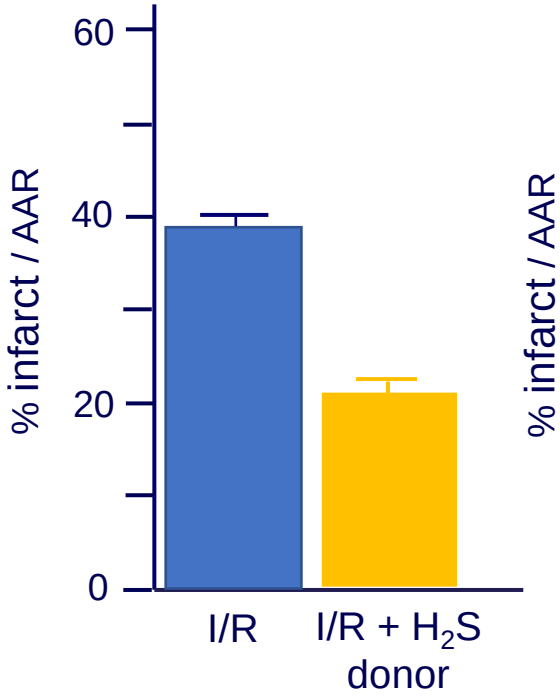
Myocardial I/R



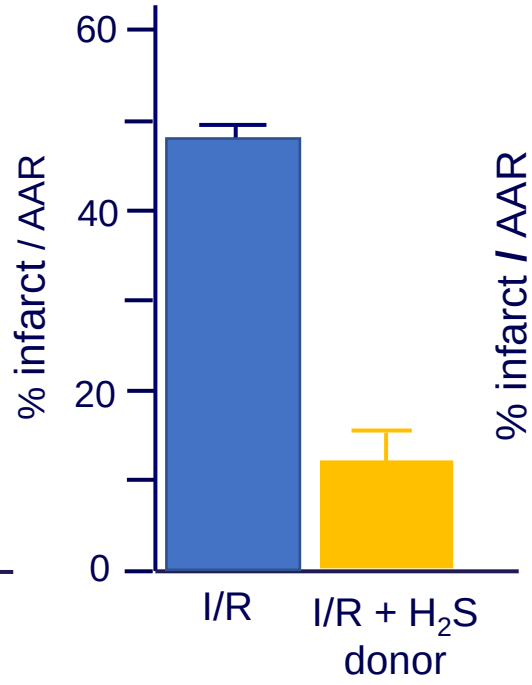
cellular[1] cardiomyocytes



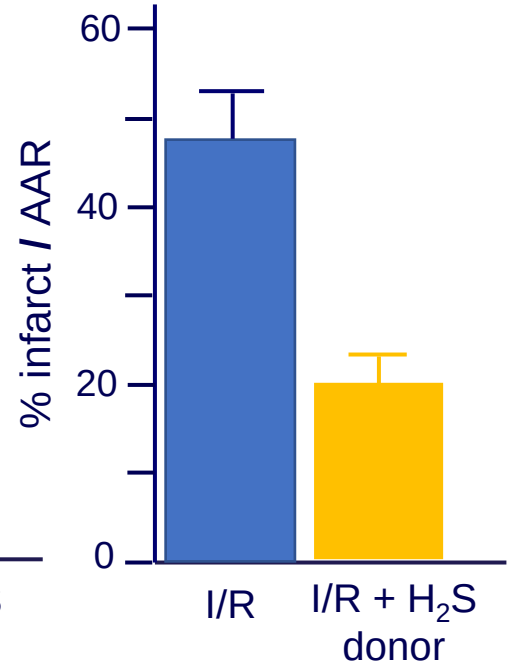
mouse[2]



rat[3]



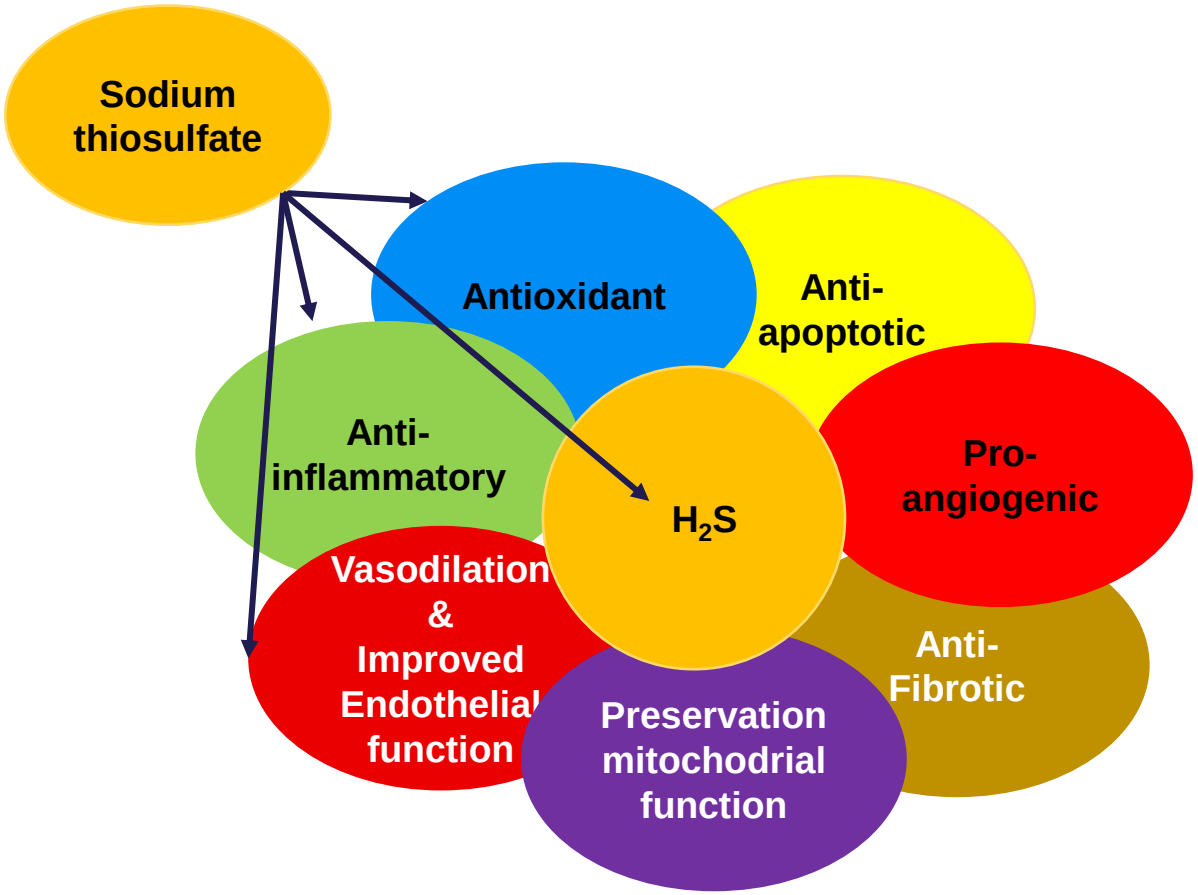
rabbit[4]



swine[5]

1. Kannan et al. *Cell Biochemistry and* Biophysics *2019*
2. Calvert et al. *Circ Res 2009*
3. Ravindran et al. *J. Cardiovasc Transl Res 2018*
4. Bibli et al. *Cardiovasc Res 2015*
5. Sodha et al. *Eur J. Cardiothoracic surgery 2008*

Mechanisms and safety profile



Clinical safety

- Cyanide poisoning
- Cisplatin-related ototoxicity[1,2] (children)
- Calciphylaxis[3]
- Pilot study, acute coronary syndrome[4]

1. Brock et al. *NEJM 2018*
2. Freyer et al. *Lancet Oncol 2017*
3. Peng et al. *Nephrology 2017*
4. De Koning et al. *J. Interv Cardiol 2020*

Groningen Intervention Study for the Preservation of cardiac function with Sodium thiosulfate after ST-segment elevation myocardial infarction (GIPS-IV)

Proof-of-principle trial

Randomized, double-blind, placebo-controlled, multicenter, phase 2 trial

Objective: to investigate whether sodium thiosulfate (STS) at reperfusion reduces infarct size in patients presenting with a first STEMI

NCT 02899364

Eligibility criteria

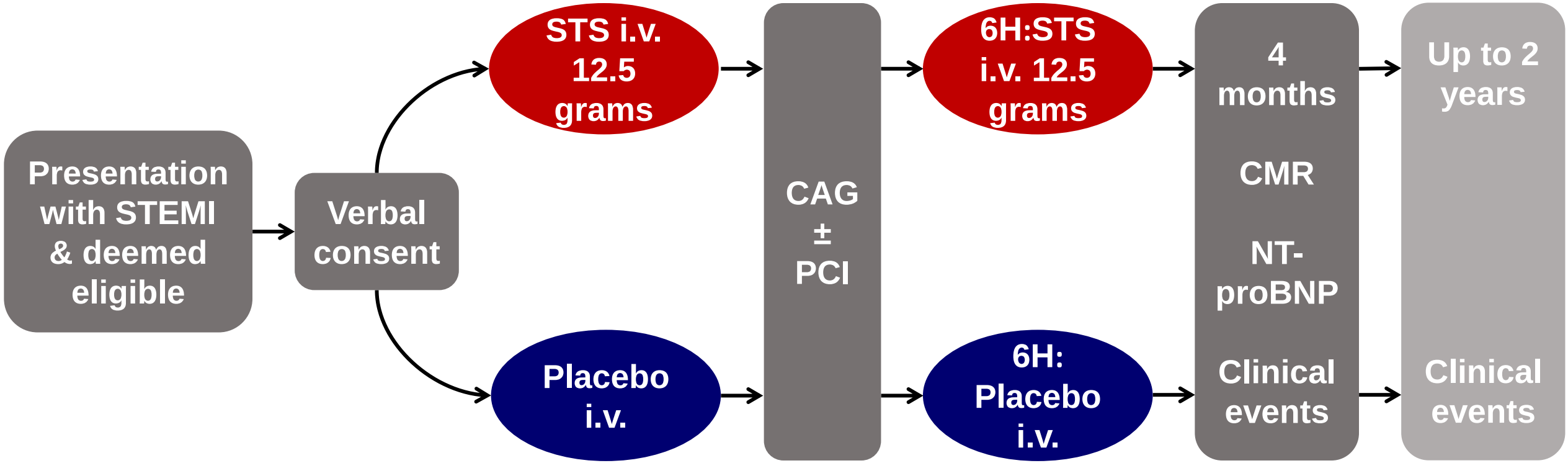
Key inclusion criteria

- Presentation with STEMI
- Age ≥ 18 years
- Ongoing ST-segment deviation and/or symptoms
- Onset complaints <12 hours before arrival at Cath Lab

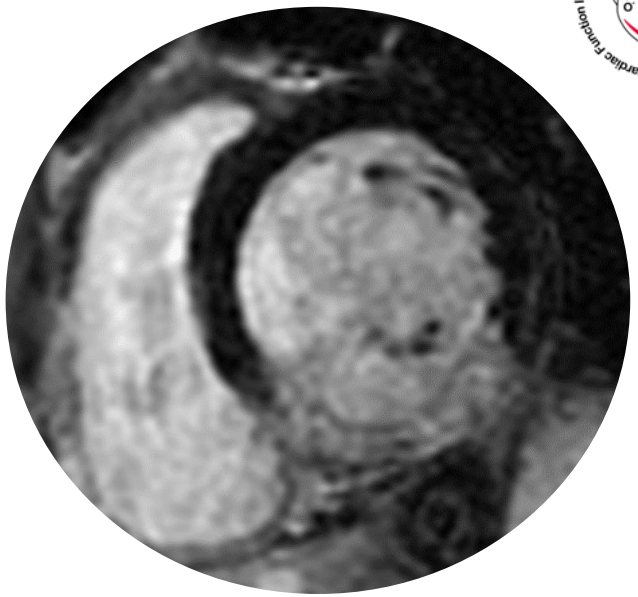
Key exclusion criteria

- Prior myocardial infarction, CABG, cardiomyopathy
- Conditions that would obscure CMR

Trial design and intervention



Study outcomes



Primary outcome

- Infarct size (% of left ventricle), measured by CMR after 4 months

Secondary outcomes

- Peak Creatine-Kinase MB during index hospitalization
- LVEF at CMR after 4 months
- NT-proBNP levels after 4 months
- Safety endpoints, including MACE, up to 4 months

Sample size determination

Hypothesis: STS reduces infarct size

Sample size

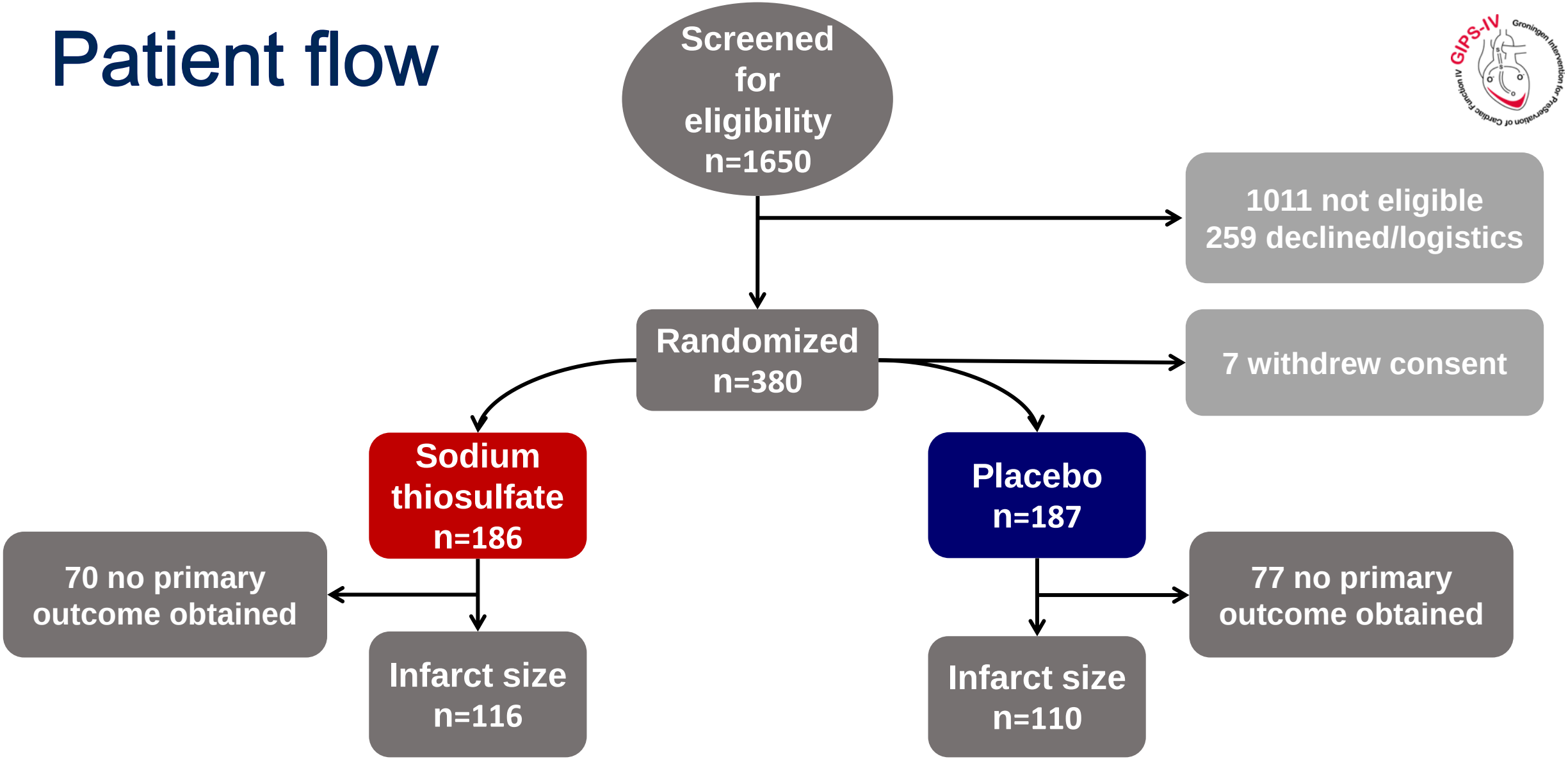
- 2-sided α=0.05
- anticipated infarct size: 9% (SD 7.9)
- anticipated drop-out: 33%

power: 85%
difference in infarct size: 3%

Study size

- 380 patients to obtain 250 evaluable primary outcomes

Patient flow



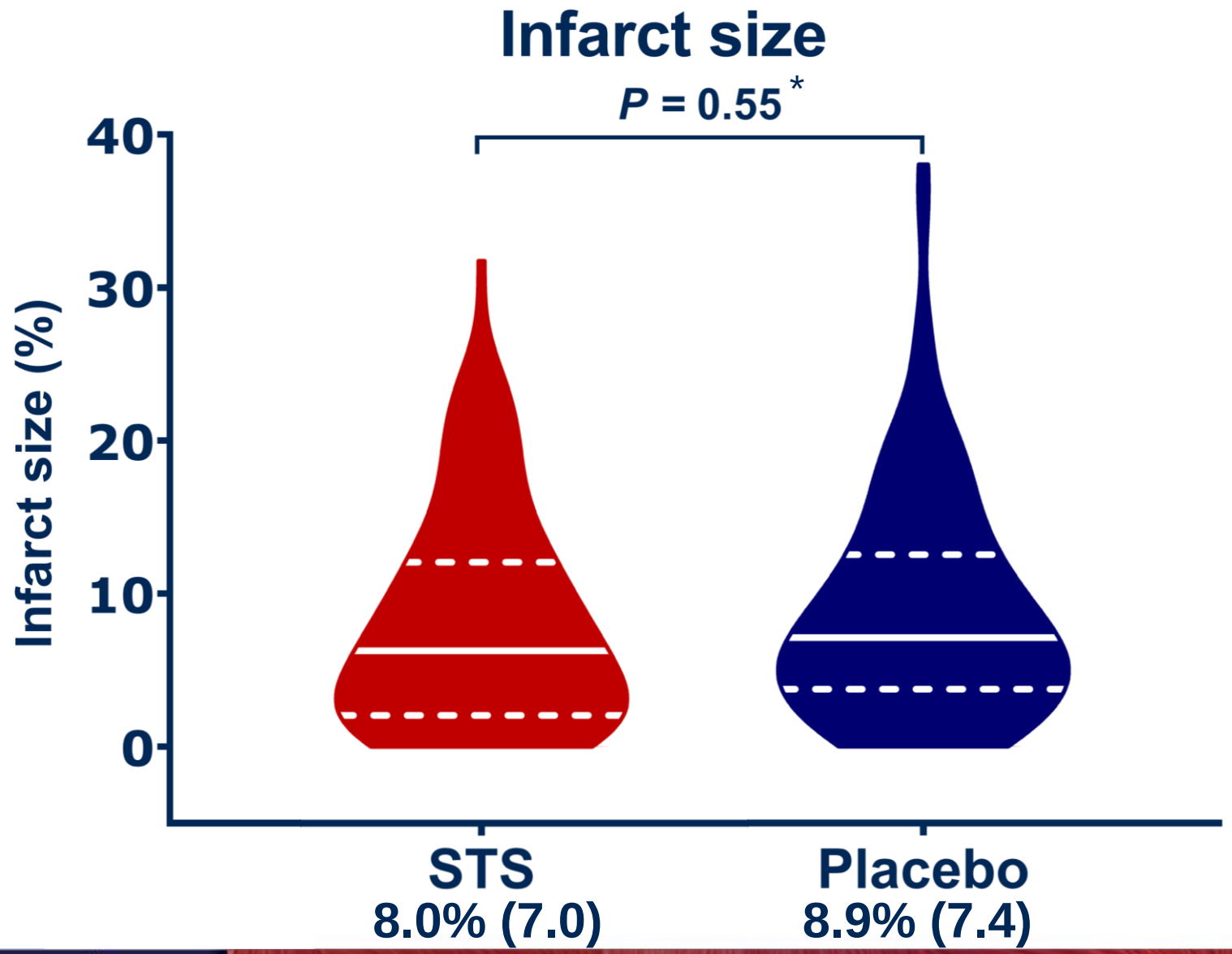
Baseline characteristics

	STS (n=186)	Placebo (n=187)
Age	62 (12)	62 (12)
Female sex	25%	21%
Caucasian ethnicity	97%	97%
Hypertension	46%	44%
Dyslipidemia	36%	36%
Diabetes Mellitus	12%	15%
Killip class I	97%	97%
Creatinine (µmol/L)	75 (65, 86)	75 (64, 86)
CK (U/L)	127 (82, 211)	134 (90, 232)
CK-MB activity (U/L)	15 (12, 20)	16 (13, 23)
NT-proBNP (ng/L)	106 (40, 221)	87 (43, 216)

Procedural characteristics

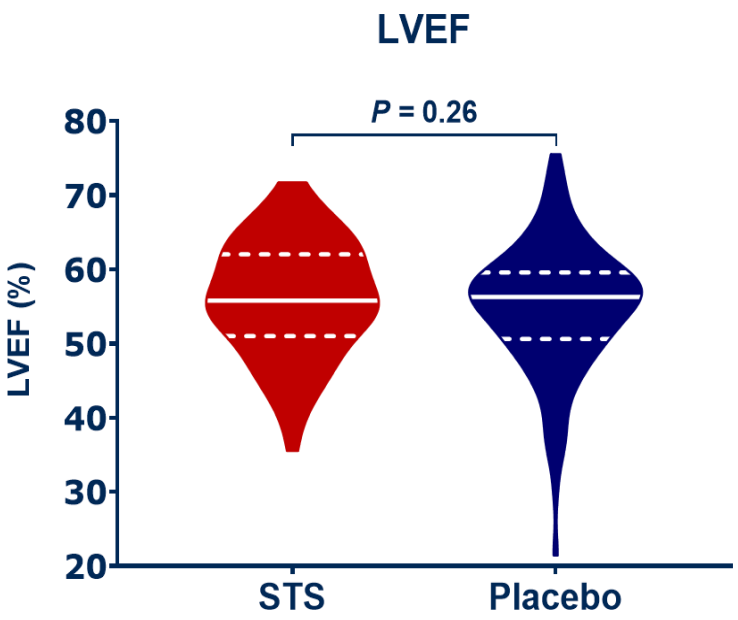
	STS (n=186)	Placebo (n=187)
Ischemic time (min)	133 (97, 203)	147 (104, 233)
Single vessel disease	55%	49%
Proximal laesion	41%	41%
Culprit in LAD	41%	41%
TIMI flow pre-PCI 0/1	67%	65%
Treated with PCI	97%	94%
TIMI flow post-PCI 3	93%	92%
Distal embolization	9%	6%

Primary outcome



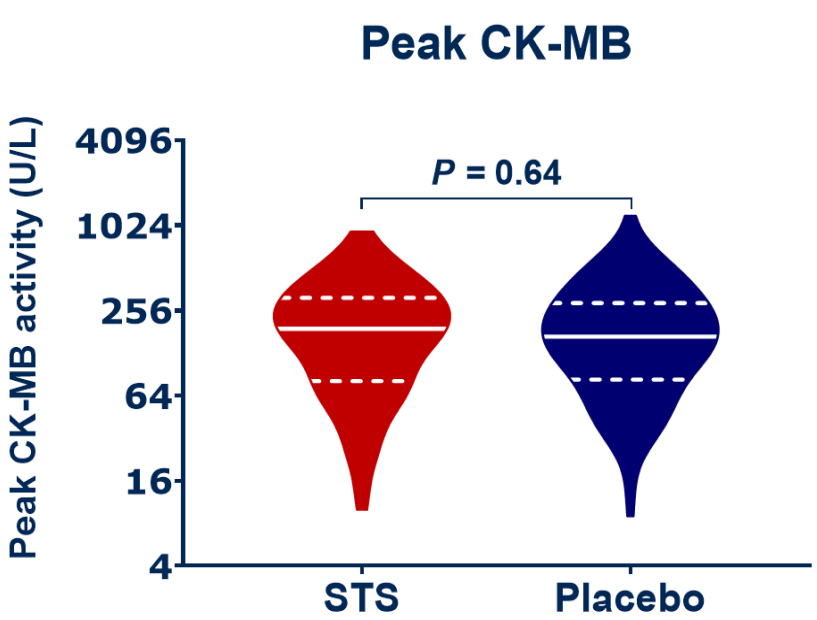
*analyzed with Beta Regression

Secondary outcomes



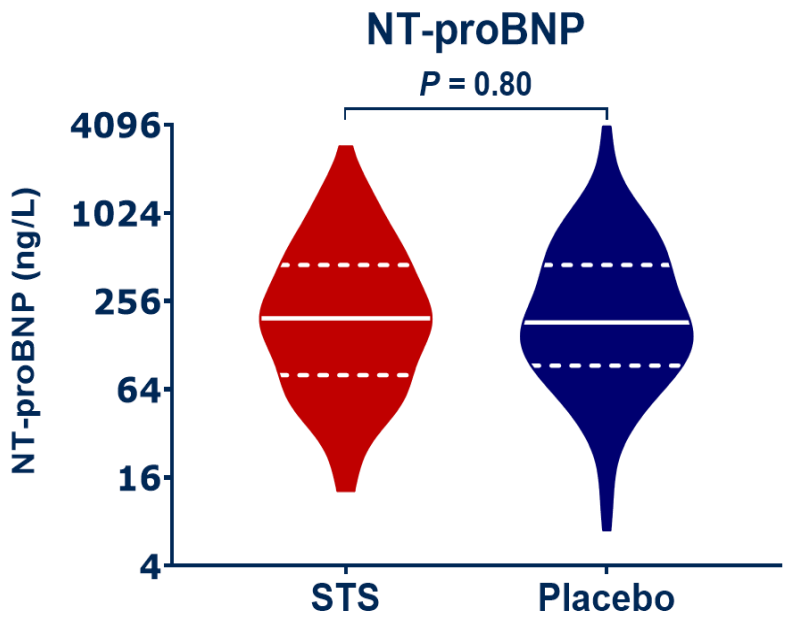
STS 56.1% (7.6)

Placebo 54.9% (8.7)



STS 191 (81, 315) U/L

Placebo 168 (84, 289) U/L



STS 195 (80, 452) ng/L

Placebo 183 (97, 445) ng/L

Clinical events

	STS (n=186)	Placebo (n=187)	*P*-value
Major adverse cardiovascular events	6	11	0.22
Cardiovascular mortality	1	2	0.57
Non-cardiovascular mortality	1	0	0.32
STEMI	2	6	0.16
NSTEMI	1	3	0.32
Unscheduled revascularization	4	5	0.74
Stent thrombosis	2	3	0.66
Stroke	1	0	0.32
Hospitalization for chest pain	6	3	0.31

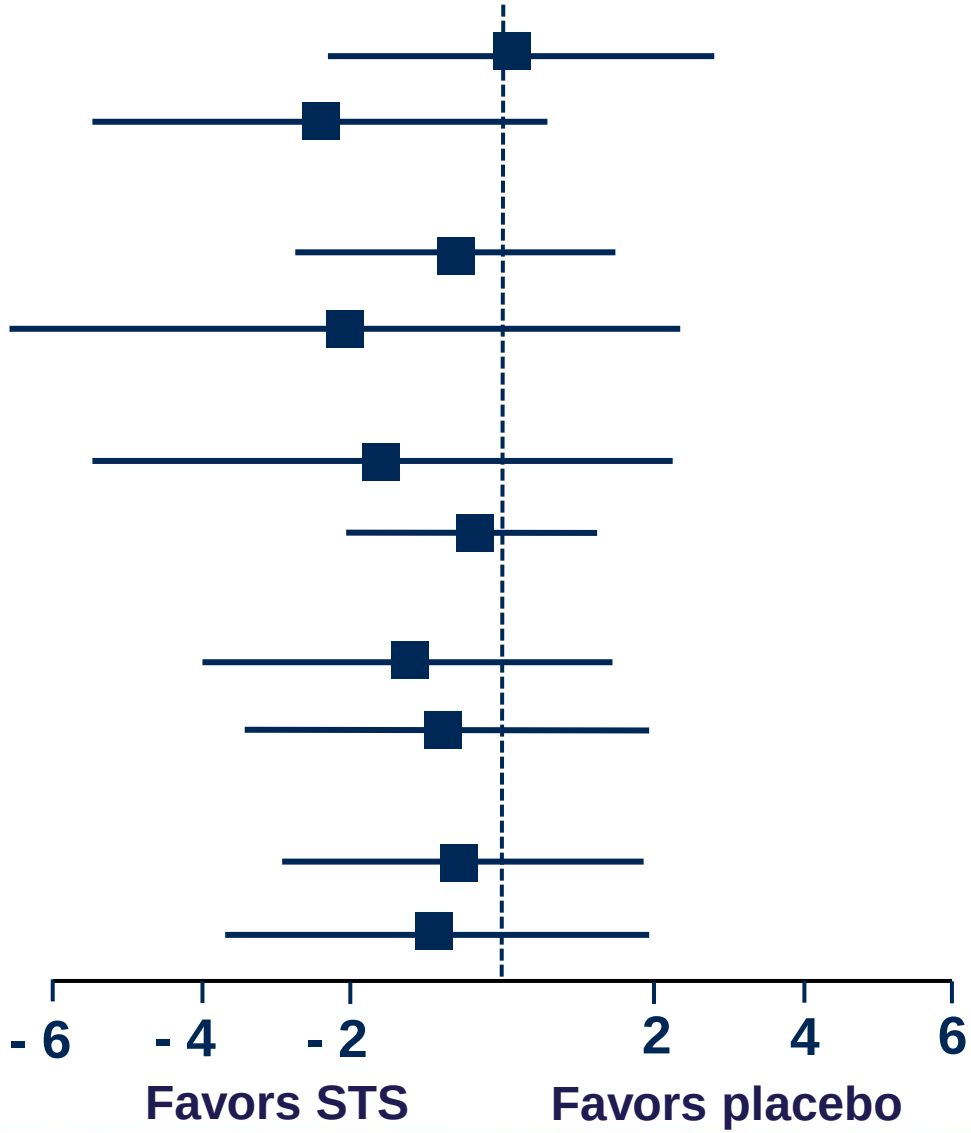
Safety

	STS (n=186)	Placebo (n=187)	*P*-value
Serious adverse events, total number	**18**	**18**	**0.99**
New-onset nausea*	**22%**	**6%**	**<0.001**
New-onset nausea without antiemetics	33%	12%	0.002
New-onset nausea with antiemetics	14%	3%	0.002
New-onset vomiting*	**14%**	**2%**	**<0.001**
New-onset vomiting without antiemetics	17%	3%	0.005
New-onset vomiting with antiemetics	11%	2%	0.004

*data shown for first dose

Subgroup analysis

Age ≤ median	58	66
Age > median	58	44
Male sex	91	94
Female sex	25	16
Anterior MI	44	43
Non-anterior MI	72	67
Ischemic time ≤ median	61	53
Ischemic time > median	52	54
TIMI flow pre-PCI 0/1	76	79
TIMI flow pre-PCI 2/3	40	31



Conclusions

Sodium thiosulfate at reperfusion:

- ➢ is safe to administer in patients presenting with STEMI
- ➢ does not reduce infarct size

Our results do not exclude H_2S as potential cardioprotective therapy

Targeting I/R-injury in humans remains challenging

Investigators & Committees

Participating sites & Principal investigator

University Medical Center Groningen
- P. van der Harst

University Medical Center Utrecht
- M. Voskuil

Treant Hospital, location Scheper
- R.L. Anthonio

Steering committee
P. van der Harst
E. Lipšic
S. Assa
R.J. Renken
D. Veen
M.L.Y. de Koning

DSMB
J.M. ten Berg
E. Kedhi
K.C.B. Roes
H. Boersma

EAC
V.E. Hagens
T.N.E. Vossenberg
M.A.H. van Leeuwen

Core laboratory
R. Nijveldt

Statistics
D. Veen

Monitoring
Schutjens Clinical Research Company