



Rationale and Design of the Groningen Intervention Study for the Preservation of Cardiac Function with Sodium Thiosulfate after ST-segment Elevation Myocardial Infarction (GIPS-IV) trial

Marie-Sophie LY de Koning, MD^a, Paulien van Dorp, MD^a, Solmaz Assa, MD, PhD^a, Minke HT Hartman, MD, PhD^a, Michiel Voskuil, MD, PhD^b, Rutger L Anthonio, MD, PhD^c, Duco Veen, PhD^d, Gabija Pundziute-Do Prado, MD, PhD^a, Tim Leiner, MD, PhD^c, Harry van Goor, PhD^f, Peter van der Meer, MD, PhD^a, Dirk J van Veldhuisen, MD, PhD^a, Robin Nijveldt, MD, PhD^g, Erik Lipsic, MD, PhD^a, and Pim van der Harst, MD, PhD^{a,b}
Groningen, the Netherlands; Utrecht, the Netherlands; Emmen, the Netherlands; Nijmegen, the Netherlands

Background Ischemia and subsequent reperfusion cause myocardial injury in patients presenting with ST-segment elevation myocardial infarction (STEMI). Hydrogen sulfide (H₂S) reduces “ischemia-reperfusion injury” in various experimental animal models, but has not been evaluated in humans. This trial will examine the efficacy and safety of the H₂S-donor sodium thiosulfate (STS) in patients presenting with a STEMI.

Study design The Groningen Intervention study for the Preservation of cardiac function with STS after STEMI (GIPS-IV) trial (NCT02899364) is a double-blind, randomized, placebo-controlled, multicenter trial, which will enroll 380 patients with a first STEMI. Patients receive STS 12.5 grams intravenously or matching placebo in addition to standard care immediately at arrival at the catheterization laboratory after providing consent. A second dose is administered 6 hours later at the coronary care unit. The primary endpoint is myocardial infarct size as quantified by cardiac magnetic resonance imaging 4 months after randomization. Secondary endpoints include the effect of STS on peak CK-MB during admission and left ventricular ejection fraction and NT-proBNP levels at 4 months follow-up. Patients will be followed-up for 2 years to assess clinical endpoints.

Conclusions The GIPS-IV trial is the first study to determine the effect of a H₂S-donor on myocardial infarct size in patients presenting with STEMI. (Am Heart J 2022;243:167–176.)

Keywords: Acute coronary syndrome; Hydrogen sulfide; Thiosulfate; Ischemia-reperfusion injury; Cardioprotection

Acute myocardial infarction (MI) results in myocardial injury and increases the risk of future heart failure

From the ^aDepartment of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, ^bDepartment of Cardiology, Division of Heart & Lungs, University Medical Center Utrecht, Utrecht, the Netherlands, ^cDepartment of Cardiology, Treant hospital location Scheper, Emmen, the Netherlands, ^dDepartment of Methodology and Statistics, University Medical Center Utrecht, Utrecht, the Netherlands., ^eDepartment of Radiology, University Medical Center Utrecht, Utrecht, the Netherlands, ^fDepartment of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, ^gDepartment of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands

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Reprint requests: Marie-Sophie LY de Koning, MD, Department of Cardiology, Heart Center, University Medical Center Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB, Groningen, the Netherlands.

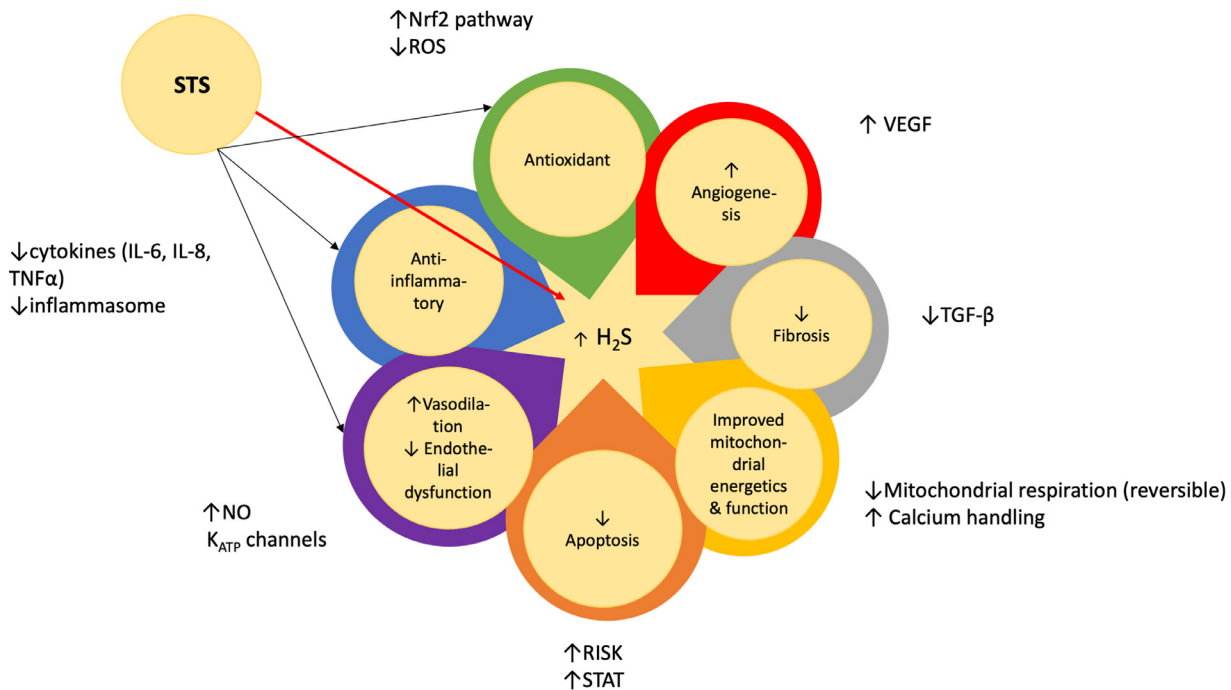
E-mail address: m.s.l.y.de.koning@umcg.nl.

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and early mortality.¹ Timely reperfusion by percutaneous coronary intervention (PCI) is an effective treatment to improve outcomes. However, reperfusion has also been hypothesized to contribute to myocardial injury.^{2–4} It has been estimated that the contribution of this “ischemia-reperfusion (I/R) injury” can be as much as 50% of myocardial infarct size.² The underlying mechanisms that have been associated with I/R injury include intracellular pH changes, calcium overload, cardiomyocyte hypercontracture, myocardial inflammation, oxidative stress generation, and mitochondrial permeability transition pore opening.^{2,4} Apart from cardiomyocyte cell death, also the coronary microcirculation undergoes irreversible injury from I/R.⁵ Intervening in the I/R injury mechanisms may potentially reduce myocardial infarct size, decrease adverse cardiac remodeling, improve cardiac function, and eventually clinical outcomes.⁶ However, to date,

Figure 1.



Schematic overview of cardioprotection by sodium thiosulfate and hydrogen sulfide

Simplified overview of the mechanisms of STS and H₂S-mediated cardioprotection and important underlying signaling pathways. H₂S, hydrogen sulphide; IL, interleukin; K_{ATP} channel, ATP-sensitive potassium channel; NO, Nitric Oxide; Nrf2, Nuclear factor erythroid 2-related factor 2; RISK, reperfusion injury salvage kinase; ROS, Reactive oxygen species; STAT, signal transducer and activator of transcription; STS, sodium thiosulfate; TGF-β, Transforming growth factor beta; TNFα, Tumour Necrosis Factor alpha; VEGF, Vascular endothelial growth factor.

effective therapies targeting I/R injury in humans are lacking.

Hydrogen sulfide (H₂S), an endogenous gaseous signaling molecule, protects from I/R injury in cellular and various cardiac and non-cardiac animal models.⁷⁻⁹ H₂S is synthesized endogenously and is involved as a physiological mediator in several organ and tissue processes.⁷ In rodent and porcine animal models of MI, H₂S has been shown to reduce infarct size and improve cardiac function.^{10,11} The mechanisms underlying these cardioprotective effects include inhibition of leukocyte endothelial cell interactions, mitochondrial preservation, neutralization of reactive oxygen species (ROS), and the reduction of inflammation and apoptotic signaling (Figure 1).¹²⁻¹⁷ Accordingly, a compound that provides H₂S may be a promising new treatment strategy to reduce I/R injury in patients presenting with acute MI. A H₂S-donor with known safety and efficacy profile in humans for other diseases, including calciphylaxis and cyanide poisoning, is sodium thiosulfate (STS).¹⁸⁻²⁰ Moreover, in patients presenting with acute coronary syndrome a phase 1 study was conducted, showing that STS was well tolerated, even with concomitant use of blood pressure lowering drugs.²⁰

Although STS would seem an interesting drug in acute MI, no studies have been conducted so far to determine the efficacy of a H₂S-donor in the reduction of I/R injury. The GIPS-IV trial is the first trial in humans designed to test the hypothesis that STS provides protection against I/R injury in patients presenting with ST-segment elevation myocardial infarction (STEMI).

Methods

Study design and population

The GIPS-IV trial is a double-blind, randomized, placebo-controlled, multicenter clinical trial enrolling 380 patients presenting with STEMI. The primary objective of the GIPS-IV trial is to evaluate the efficacy of STS compared to placebo treatment to reduce myocardial infarct size as quantified by cardiac magnetic resonance (CMR) imaging 4 months after STEMI. Full in- and exclusion criteria are presented in (Table 1). In brief, all patients, ≥ 18 years old, presenting with a first STEMI within 12 hours after onset of chest pain with persistent symptoms and/or ST-elevation at arrival in the catheterization laboratory will be considered for enrollment. Main exclusion criteria are the presence of

Table 1. In- and exclusion criteria

Inclusion criteria

- Age \geq 18 years;
- The diagnosis STEMI defined by (1.) chest pain suggestive for myocardial ischemia for at least 30 minutes, the time from onset of the symptoms less than 12 hours before catheterization laboratory admission, and (2.) an ECG recording with ST-segment elevation of more than 0.1 mV in 2 or more contiguous leads or presence of new left bundle branch block;
- Symptoms and/or ST-segment deviation should be present (persisting) at time of arrival in the cath-lab;
- Primary PCI is being considered as treatment;
- Patient is willing to cooperate with follow-up during 2 years.

Exclusion criteria

- Prior MI (STEMI/non-STEMI/ACS), unless maximum troponin T < 50ng/L;
- Prior CABG;
- Prior PCI, complicated by periprocedural infarction, unless maximum troponin T < 50 ng/L;
- Known cardiomyopathy;
- Previous hospitalization for heart failure;
- Active malignancy (requiring chemotherapy, radiation or surgery at the time of randomization), except for adequately treated non-melanoma skin cancer or other noninvasive or in situ neoplasm (e.g., cervical cancer in situ);
- History of chemotherapy;
- History of radiotherapy in chest region;
- Relieve of symptoms and complete ST-segment resolution prior to arrival at the cath-lab;
- Known permanent atrial fibrillation;
- Presentation with cardiogenic shock (systolic blood pressure <90 mmHg);
- Severe hypertension (systolic blood pressure >220 mmHg);
- Sedated and/or intubated patients;
- The existence of a condition with a life expectancy of less than 1 year;
- Contraindication for 3 Tesla (T) CMR-imaging (e.g. body weight > 150 kg; known claustrophobia; 3T CMR incompatible ferromagnetic objects in the body, end-stage renal disease);
- Pregnancy or breastfeeding women; women of childbearing potential with clinical suspicion of possible pregnancy;
- A condition which, according to the clinical judgment of the investigator and/or treating physician, does not allow the patient to successfully participate in the study;
- Contra-indication for metoclopramide (e.g. Parkinson; epilepsy).

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

prior cardiac conditions which might obscure CMR measurements (prior MI, CABG, known cardiomyopathy or a malignancy treated with chemo- and/or chest radiotherapy). This study was approved by the local Medical Research Ethics Committee (Ref. 2016.381, Groningen, the Netherlands). All study procedures will be in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. The trial has been registered in a clinical trial registry under number NCT02899364 (www.clinicaltrials.gov).

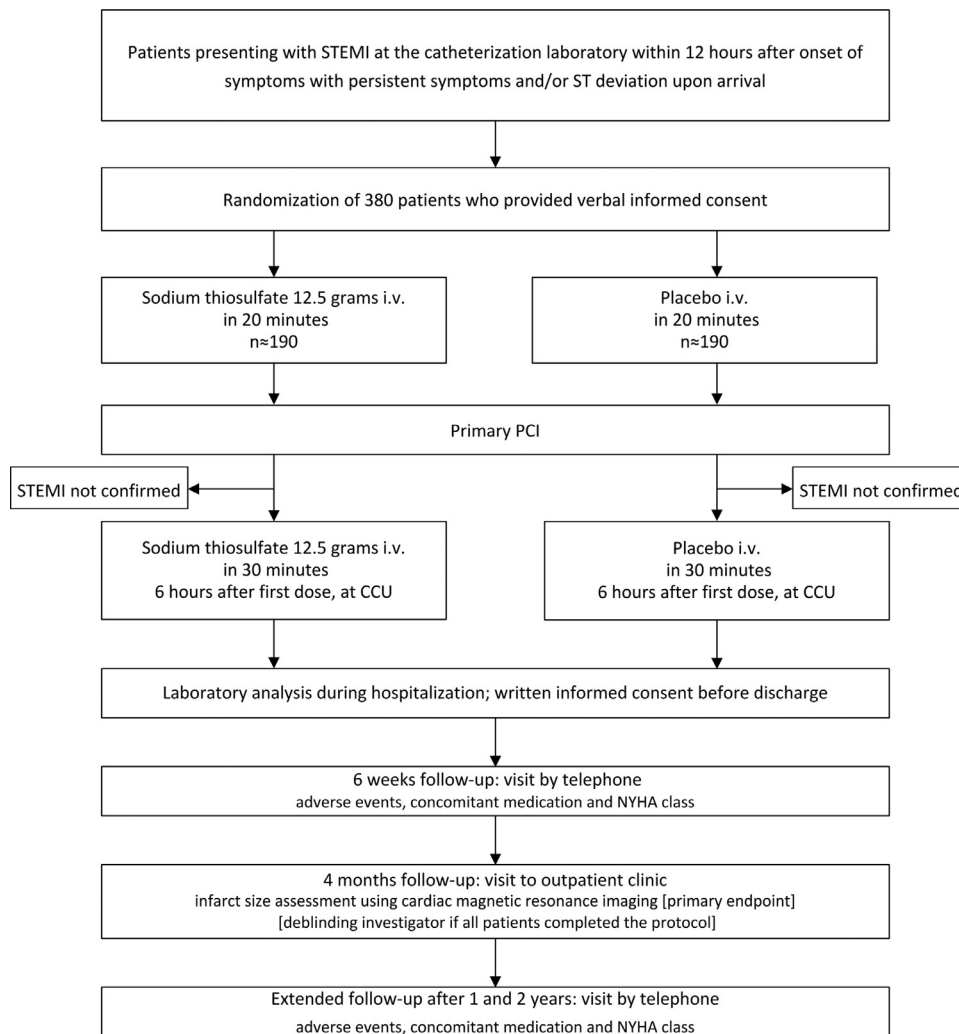
Study procedures

Study procedures of the GIPS-IV trial are summarized in (Figure 2). All patients will receive standard care for STEMI according to the guidelines of the European Society of Cardiology.²¹ At admission, baseline characteristics and vital signs will be assessed. Directly after arrival at the catheterization laboratory, after confirmation of eligibility and obtaining witnessed verbal consent by the interventional cardiologist, patients will receive their first dose of study medication. Coronary angiography and PCI will not be delayed and performed using standard techniques. The patient, interventional cardiologist, caregivers and data collectors are all blinded to the treatment allocation. The pharmacy of the University Medical

Center Groningen (UMCG) will keep the randomization code.

Study medication

Study medication, STS and matching placebo, was produced, labeled and randomized according to Good Manufacturing Practices (GMP) by A15 Pharmacy (Gorinchem, the Netherlands). STS, formulated as a sterile, colorless liquid, will be supplied in 5 vials of each 2.5 grams STS. Study medication will be packaged in numbered kits, one kit for each dose. Study medication will be randomized in permuted blocks of 4 with stratification by recruiting site and for anterior versus non-anterior MI, the latter to ensure balance of treatments across patients at high risk for a large infarcted area of the left ventricle and subsequent development of heart failure. Study medication will be dissolved in 250mL of normal saline and administered intravenously (i.v.) in 20 - 30 minutes at the catheterization laboratory. Six hours after the first dose, a second dose of study medication (12.5 grams STS or matching placebo dissolved in 250mL of normal saline) will be administered at the coronary care unit. The main known side effects of STS include nausea, vomiting and hypotension.²² This will be specifically surveyed before and after study medication. The timing and dosage of study medication was based on experimental data in the set-

Figure 2.**Trial flowchart**

Schematic representation of the GIPS-IV trial design. CCU, coronary care unit; i.v. intravenously; PCI, percutaneous coronary intervention, NYHA, New York Heart Association classification; STEMI, ST-segment elevation myocardial infarction.

ting of ischemia-reperfusion injury,²³ clinical data on STS use,^{22,24} safety data from the SAFE-ACS pilot study,²⁰ the elimination time of STS,²² logistical reasons, and prior knowledge of the pathophysiological process of reperfusion injury.²⁵

Hospitalization

During hospitalization, vital signs, quality of life questionnaires (EQ-5D-5L and PANAS) and enzymatic infarct size will be collected.^{26,27} Enzymatic infarct size was defined as peak CK-MB and based on protocolized collection of blood samples taken at presentation and 3, 6, 9, 12 and 18 hours thereafter, unless enzymatic peak size

has been reached earlier or patients have been transferred to another hospital. Additional blood samples for biobanking will be drawn at presentation with STEMI and 9 hours after administration of the first dose. After treatment at the catheterization laboratory, written consent will be obtained at the coronary care unit or on the ward.

Follow-up

After discharge, subjects will be contacted by telephone at 6 weeks, 12 months and 24 months after randomization for the assessment of adverse events, NYHA class and medication use. Four months after randomiza-

tion, a period in which the infarct healing of the heart is expected to be completed,^{28,29} participants will be scheduled for a hospital visit. During this visit CMR, electrocardiography and non-mandatory echocardiographic assessment (of diastolic function) will be performed. Furthermore, vital signs, NYHA class, adverse events, quality of life questionnaires (EQ-5D-5L and PANAS), NT-proBNP and medication use will be assessed.^{26,27} In case a participant declines CMR, patients will be followed-up by telephone at 4 months after randomization to assess medication use, NYHA class and adverse events. Study procedures will take place at the UMCG, Groningen, University Medical Center Utrecht (UMCU), Utrecht, and Treant hospital, Emmen, all high-volume PCI centers with ample experience in STEMI care and research.

Study endpoints

The primary efficacy parameter of the GIPS-IV trial is infarct size, expressed as percentage of the LV mass, measured by CMR, at 4 months after randomization. CMR measured infarct size has been recommended as the most feasible and reliable primary endpoint for clinical cardioprotection trials.³⁰ Infarct size can be accurately measured with high reproducibility using late gadolinium enhancement (LGE) CMR, which is considered the gold standard. Infarct size is the major determinant of prognosis after MI and the preferred surrogate endpoint for clinical events.^{31,32}

Secondary efficacy parameters include the effect of STS on enzymatic infarct size as assessed by peak CK-MB during initial hospitalization for STEMI. CK-MB can be easily obtained in all patients and also serves as a (very early) safety parameter for the Data and Safety Monitoring Board (DSMB).³³ Furthermore, effects of STS on Left Ventricular Ejection Fraction (LVEF) as determined by CMR at 4 months follow-up and NT-proBNP levels after 4 months follow-up will be assessed. Both reduced LVEF and increased NT-proBNP have also been associated with increased risk of future clinical events,^{34,35} but these parameters are more subjected to (baseline) heterogeneity than infarct size. Laboratory secondary endpoints (CK-MB and NT-proBNP) were determined with Roche Cobas assays for UMCG and Treant and Siemens Atellica assays for UMCU. Clinical secondary endpoints include all-cause mortality and the combined incidence of Major Adverse Cardiovascular Events (MACE) defined as cardiovascular death, re-infarction and re-intervention (both re-PCI and coronary bypass grafting [except for scheduled revascularization based on the index coronary angiogram]) at 4 months follow-up and up to 2 years after randomization. Furthermore, the effects of STS on stroke, stent thrombosis, Implantable Cardioverter Defibrillator (ICD) implantation and hospitalization for heart failure or chest pain will be assessed at 4 months and up to 2 years follow-up.

Cardiac magnetic resonance imaging

Patients are studied with a 3 Tesla Siemens scanner (Magnetom Prisma, Erlangen, Germany) at the MRI facility of the Cognitive Neuroscience Center (University of Groningen, Groningen, The Netherlands) (Supplementary Material D) or a 3 Tesla Philips scanner (Best, The Netherlands) at the MRI facility of the UMCU. Electrocardiogram-gated balanced steady-state free precession cine images acquired during repeated breath holds in the standard long-axis views (4-, 3-, and 2-chamber view) and contiguous short-axis slices covering the entire left ventricle are used to assess global and regional ventricular function and to calculate LVEF (secondary endpoint). Using identical slice locations, LGE images are acquired 10 minutes after intravenous administration of a gadolinium-based contrast agent (0.2 mmol/kg) with an inversion-recovery gradient-echo pulse sequence to identify the location and extent of infarcted myocardium. The inversion time will be set to null the signal of viable myocardium for every individual patient. CMR data will be sent to an independent core lab, blinded for randomization status (Supplementary Material D). CMR data will be analyzed using a dedicated software package (QMass, Medis Suite 3.2.28.0, Leiden, the Netherlands). Infarct size will be expressed as a percentage of the total left ventricular mass, as most commonly used,³⁶ and quantified using an automated method (full width at half maximum) with manual correction.^{37,38}

Echocardiography

2D echocardiography is not a mandatory study procedure. Nevertheless, when performed as part of routine clinical practice, data will be collected. Tissue Doppler (TD) imaging of the early mitral valve flow velocity/early TD lengthening velocity (E/E'), the ratio of the early (E) to late (A) mitral valve flow velocity, the deceleration time, the left atrial volume index (LAVI), and the difference between the duration of reverse pulmonary vein atrial systole flow (Ard) and mitral valve atrial wave flow (Ad) at 4 months will be used to determine and classify diastolic function.

Sample size considerations

This trial is designed as a proof-of-concept study. We considered an absolute reduction of 3% (33% relative) relevant. In the previous GIPS-III trial, recruiting similar STEMI patients, the mean infarct size was $9.0\% \pm 7.9$.³⁹ With 125 evaluable patients in each study arm, the study has 85% power to detect a 3% difference in change in infarct size between active treatment and control, assuming a 2-sided α of 0.05 for the change in infarct size. Based on local experience and from previous studies, we assume that CMR analysis is not available in up to 33% of patients (due to contraindications e.g. ICD-implantation, claustrophobia or study withdrawal).³⁹⁻⁴² Therefore, we

aim to include 380 patients in order to achieve 250 patients with available data for primary endpoint analysis.

Statistical considerations

Baseline characteristics will be summarized as mean \pm standard deviation (SD) or median [interquartile range] depending on data distribution. Categorical variables will be displayed by count (percentages). Treatment effects will be evaluated based on a 2-sided significance level of 0.05, unless otherwise stated. No formal interim analysis will take place. Missing data will not be imputed.

Primary endpoint analyses

The primary endpoint, infarct size, will be analyzed according to an intention-to-treat (ITT) principle including all patients randomized with an adequate CMR at 4 months. Primary endpoint will be analyzed with Beta regression with treatment allocation (dummy coded) and the variables used for stratification in the randomization process (recruiting site and anterior myocardial infarction) added to the model as a fixed factors. Likewise, a per-protocol analysis will be performed, including all patients with an adequate CMR at 4 months follow-up, who received complete treatment with study medication, without major protocol deviations. Prespecified subgroup analyses will be performed using regression analyses with a test for interaction for age (below vs above the median), gender, TIMI-flow pre-PCI (≤ 1 vs > 1), anterior MI (LAD vs non-LAD culprit) and ischemic time (below vs above the median), single vs. multivessel disease and time between start of study medication and time of intervention (below vs above the median).

Secondary endpoint analyses

For analyses of secondary endpoints, when binary, treatment comparisons will be performed using Fisher exact probability tests or Chi-square analyses. For continuous outcomes, independent samples *t*-tests or Mann-Whitney U tests will be used, as appropriate. For clinical outcomes, including the incidence of MACE, Kaplan-Meier curves and Cox regression analyses will be used to evaluate the association between study treatment and the endpoints.

Study organization and monitoring

The development of the protocol and progress of the study will be under supervision of the trial steering committee (Supplementary Material D). The GIPS-IV trial data will be captured in a dedicated electronic database (eCRF) (Research Electronic Data Capture; REDCap). The eCRF will be independently monitored for completeness and accuracy according to a pre-specified monitoring plan by Schutjens Clinical Research Consultancy (Supplementary Material D). Trial data will be reviewed periodically by an independent DSMB. The DSMB consist of 4 independent members with expertise in trial

methodology, (interventional) cardiology and biostatistics (Supplementary Material D). The DSMB reviews accumulating data in a semi-blinded fashion (group A vs group B) to detect possible safety concerns that could result in their recommendation to modify the protocol or prematurely terminate the execution of the trial. Clinical endpoints will be adjudicated by a blinded Endpoint Adjudication Committee, consisting of 3 members with expertise in (interventional) cardiology (Supplementary Material D). For valorization purposes a users' committee will be installed (Supplementary Material D). Database lock and subsequent debinding for primary analyses will be performed when all participants have completed 4 months follow-up, infarct sizes have been determined by the core lab and clinical events up to 4 months have been adjudicated. This study is supported by the Netherlands Organization for Health Research and Development, Siemens healthcare GmbH and the University Medical Center Groningen. The subsidizers had no role in the design and conduct of the study, all study analyses, and drafting or editing of the paper, and its final contents.

Present status

GIPS-IV enrolled its first patient in July 2018 and completed enrollment after 380 patients in March 2021. (Table 2) summarizes baseline demographics and clinical characteristics of all randomized participants of the GIPS-IV trial, based on a non-final snapshot taken at completion of enrollment. Mean age of the cohort is 62 years old and 23% is female. Results of the primary endpoint are expected in Q1 2022.

Discussion

The GIPS-IV study is the first clinical trial to investigate the effect of the H₂S-donor STS on myocardial infarct size in patients presenting with acute MI.

In the last decade, several clinical trials that targeted I/R injury have failed to demonstrate benefit despite promising experimental data. To understand and possibly overcome this mismatch between experimental and clinical data, several important recommendations have been made for future clinical cardioprotection trials.⁴³ These include the selection of I/R treatments that target multiple pathways at once and demonstrate beneficial effects in both small and large animal models. Indeed, STS treatment is in line with these recommendations: A wide range of signaling changes are induced by H₂S release from STS, all providing cardioprotective effects (Figure 1).⁷ Preclinical data demonstrated that these infarct-sparing effects are independent of animal size and the type of H₂S-donor used.¹⁰ STS is promising and practical to study as a H₂S-donor. STS is a slow-releasing H₂S-donor and acts as a precursor for H₂S signaling because multiple enzymes facilitate the reaction of thiosulfate to

Table 2. Characteristics of participants at presentation with STEMI

Characteristics	Randomized patients n = 373*
Demography	
Age (years), mean (SD)	62.2 (11.8)
Female gender, n (%)	85 (22.8%)
Body Mass Index (kg/m ²), mean (SD)	27.2 (4.3)
Caucasian Ethnicity, n (%)	363 (97.3%)
Medical history and cardiovascular risk factors, n (%)	
Hypertension	168 (45.0%)
Dyslipidemia	130 (34.9%)
Diabetes Mellitus	39 (10.5%)
Clinical characteristics	
Systolic blood pressure, mmHg, mean (SD)	140 (25)
Diastolic blood pressure, mmHg, mean (SD)	84 (16)
Heart rate, bpm, mean (SD)	74 (17)
Killip class I, n (%)	353 (97.0%)
PCI characteristics	
Time onset complaints to start study medication (min), median [IQR]	125 [85, 198]
Single vessel disease, n (%)	187 (50.1%)
Culprit territory, n (%)	
No clear culprit defined	10 (2.7%)
Left anterior descending	152 (40.8%)
Circumflex or marginal	56 (15.0%)
Right coronary artery	154 (41.3%)
Left main	1 (0.3%)
TIMI flow pre-PCI, n (%)	
0	226 (60.6%)
1	21 (5.6%)
2	47 (12.6%)
3	77 (20.6%)
Cannot be defined	2 (0.5%)
Initial intervention culprit lesion, n (%)	
PCI	355 (95.2%)
CABG	6 (1.6%)
Conservative	12 (3.2%)

* 7 patients fully withdrawn consent, therefore data were removed. Abbreviations: CABG, coronary artery bypass graft; IQR, interquartile range; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction.

H₂S.⁴⁴ Furthermore, STS is not only used in many pre-clinical studies¹⁸ but also has a proven safety and efficacy profile in humans. STS has been used since 1933 for the treatment of cyanide intoxication,⁴⁵ and since the 1980's for the treatment of calciphylaxis,⁴⁶ a rare complication of patients on haemodialysis. More recently, STS has been applied to prevent from ototoxicity due to cisplatin treatment in children.¹⁹ Also in patients with acute coronary syndromes, STS was well tolerated with concomitant use of vasodilators and blood pressure lowering drugs.²⁰

Another important aspect of the GIPS-IV trial design is the patient selection and timing of study medication. The GIPS-IV study required 'the presence of ongoing complaints and/or ST-elevation', thereby aiming to include patients with ongoing ischemia. Based on experiences in previous studies, the recommendation is to focus on patients with limited ischemic time (<2 - 3 hours), large area at risk and reduced coronary blood flow to increase the likelihood of amendable I/R injury.⁴³ The observed

ischemic time in the GIPS was median [IQR] 125 [85 - 198] minutes, which fits well with the recommendations. To reduce heterogeneity in area at risk between treatment arms, patients were stratified by anterior (associated with larger area at risk) vs non-anterior (associated with smaller area at risk) ST-segment elevation.⁴⁷ Furthermore, the administration of study medication was initiated *before* PCI/reperfusion, which might be important considering the hypothesis that I/R injury occurs already during the first moments after reperfusion.²⁵ However, the drawback of this approach is that we were uncertain of the coronary artery status before randomization and could not exclude patients with more than TIMI 1 flow.

The primary endpoint of the GIPS-IV trial is myocardial infarct size as determined by CMR. This parameter is considered the gold standard surrogate endpoint for clinical cardioprotection trials, since consistent evidence for associations with MACE is available.³⁰ Ideally, in cardioprotection trials also area at risk (AAR) should be taken

into account, since the final infarct size consists of both ischemic injury and amendable reperfusion injury.⁴⁸ Unfortunately, we were unable to quantify AAR or microvascular obstruction by CMR during hospitalization due to logistic reasons (limited scan time, COVID-19 restrictions, early transfer to other regional hospitals). The primary endpoint will be analyzed based on recommendations of the European Medicine Agency (EMA).⁴⁹ Beta regression will be used, since it is the preferred method of analysis for proportional data with a non-normal distribution.⁵⁰⁻⁵² Furthermore, it allows us to take stratification factors into account, in order to reduce heterogeneity and increase power.

In addition to primary analyses, we will perform exploratory analyses to study the effects of STS on secondary endpoints. Peak CK-MB was used as a very early safety marker for the DSMB, since it has been linked to final infarct size.³³ However, as secondary endpoint, it should be interpreted with caution because enzymatic infarct size reduction does not directly translate to final infarct size reduction, especially since different assays were used and release patterns might also be dependent on factors as TIMI flow pre-PCI or defibrillation.⁴⁸ In this study, we also perform an extensive follow-up for clinical events. However, it is important to note that our study is not powered to detect differences in clinical events. In case of superiority of STS (vs placebo) for the preservation of myocardial infarct size, further large-scale studies are warranted to confirm effects on clinical outcomes. Unfortunately, so far, positive phase II trials failed to demonstrate clinical benefit in subsequent phase III trials. A possible explanation is that not all patients benefit from cardioprotection, due to highly functional reperfusion techniques in developed countries, already resulting in small infarctions. Therefore, possible future trials should consider the investigation of STS in a population at high risk and in an all-comers registry separately.^{53,54} At last, next to primary endpoint and long-term follow-up, we will collect additional laboratory samples for biobanking, allowing further investigation on potential mechanisms involved in STS use in STEMI patients.

Conclusions

GIPS-IV is a double-blind, randomized, placebo-controlled, multicenter trial to determine whether STS treatment reduces infarct size in patients presenting with STEMI. Results of the primary endpoint analyses are expected in Q1 2022.

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care GmbH (Push project IPA No.10) and the University Medical Center Groningen.

Conflict of interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ahj.2021.08.012](#).

References

- Ezekowitz JA, Kaul P, Bakal JA, et al. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *J Am Coll Cardiol* 2009;53:13–20. doi:[10.1016/j.jacc.2008.08.067](#).
- Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med* 2007;357:1121–35. doi:[10.1056/NEJMra071667](#).
- Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? *J Clin Invest* 1985;76:1713–19. doi:[10.1172/JCI112160](#).
- Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol* 2020;17:773–89. doi:[10.1038/s41569-020-0403-y](#).
- Heusch G. Coronary microvascular obstruction: the new frontier in cardioprotection. *Basic Res Cardiol* 2019;114:45. doi:[10.1007/s00395-019-0756-8](#).
- Hausenloy DJ, Botker HE, Engstrom T, et al. Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and tribulations. *Eur Heart J* 2017;38:1477–86. doi:[10.1093/eurheartj/ehw145](#).
- Donnarumma E, Trivedi RK, Lefer DJ. Protective actions of H2S in acute myocardial infarction and heart failure. *Compr Physiol* 2017;7:583–602. doi:[10.1002/cphy.c160023](#).
- Liu Y-H, Lu M, Bian J-S. Hydrogen sulfide and renal ischemia. *Expert Rev Clin Pharmacol* 2011;4:49–61. doi:[10.1586/ecp.10.127](#).
- Pavoni V, Nicoletti P, Benemei S, et al. Effects of hydrogen sulfide (H2S) on mesenteric perfusion in experimental induced intestinal ischemia in a porcine model. *Heart Lung Vessel* 2015;7:231–7.
- Karwi QG, Bice JS, Baxter GF, et al. Pre- and postconditioning the heart with hydrogen sulfide (H2S) against ischemia/reperfusion injury in vivo: a systematic review and meta-analysis. *Basic Res Cardiol* 2017;113:6. doi:[10.1007/s00395-017-0664-8](#).
- Chen S, Yang C, Yang Z, et al. Hydrogen sulphide protects H9c2 cells against chemical hypoxia-induced injury. *Clin Exp Pharmacol Physiol* 2010;37:316–21. doi:[10.1111/j.1440-1681.2009.05289.x](#).
- Zanardo RCO, Brancaleone V, Distrutti E, et al. Hydrogen sulfide is an endogenous modulator of leukocyte-mediated inflammation. *FASEB J Off Publ Fed Am Soc Exp Biol* 2006;20:2118–20. doi:[10.1096/fj.06-6270fje](#).
- Elrod JW, Calvert JW, Morrison J, et al. Hydrogen sulfide attenuates myocardial ischemia-reperfusion injury by preservation of mitochondrial function. *Proc Natl Acad Sci U S A* 2007;104:15560–5. doi:[10.1073/pnas.0705891104](#).
- Simon F, Giudici R, Duy CN, et al. Hemodynamic and metabolic effects of hydrogen sulfide during porcine ischemia/reperfusion

- injury. *Shock* 2008;30:359–64. doi:10.1097/SHK.0b013e3181674185.
15. Sun W-H, Liu F, Chen Y, et al. Hydrogen sulfide decreases the levels of ROS by inhibiting mitochondrial complex IV and increasing SOD activities in cardiomyocytes under ischemia/reperfusion. *Biochem Biophys Res Commun* 2012;421:164–9. doi:10.1016/j.bbrc.2012.03.121.
 16. Sivarajah A, Collino M, Yasin M, et al. Anti-apoptotic and anti-inflammatory effects of hydrogen sulfide in a rat model of regional myocardial I/R. *Shock* 2009;31:267–74. doi:10.1097/SHK.0b013e318180ff89.
 17. Calvert JW, Jha S, Gundewar S, et al. Hydrogen sulfide mediates cardioprotection through Nrf2 signaling. *Circ Res* 2009;105:365–74. doi:10.1161/CIRCRESAHA.109.199919.
 18. Hayden MR, Goldsmith DJA. Sodium thiosulfate: new hope for the treatment of calciphylaxis. *Semin Dial* 2010;23:258–62. doi:10.1111/j.1525-139X.2010.00738.x.
 19. Brock PR, Maibach R, Childs M, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. *N Engl J Med* 2018;378:2376–85. doi:10.1056/NEJMoa1801109.
 20. de Koning MLY, Assa S, Maagdenberg CG, et al. Safety and tolerability of sodium thiosulfate in patients with an acute coronary syndrome undergoing coronary angiography: a dose-escalation safety pilot study (SAFE-ACS). *J Interv Cardiol* 2020;2020:6014915. doi:10.1155/2020/6014915.
 21. 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 Socie. *Eur Heart J* 2018;39:119–77. doi:10.1093/eurheartj/ehx393.
 22. U.S. Food and Drug administration. Summary of product characteristics sodium thiosulfate. Reference ID: 3087621. 2012.
 23. Ravindran S, Kurian GA, Ramachandran K, et al. Effect of sodium thiosulfate postconditioning on ischemia-reperfusion injury induced mitochondrial dysfunction in rat heart. *J Cardiovasc Transl Res* 2018;11:246–58. doi:10.1016/j.biochi.2018.01.004.
 24. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med* 2018;378:1704–14. doi:https://doi.org/10.1056/NEJMra1505292
 25. Vinten-Johansen J. Involvement of neutrophils in the pathogenesis of lethal myocardial reperfusion injury. *Cardiovasc Res* 2004;61:481–97. doi:10.1016/j.cardiores.2003.10.011.
 26. EuroQol group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208. doi:10.1016/0168-8510(90)90421-9.
 27. Tran V. Positive Affect Negative Affect Scale (PANAS). In: Gellman MD, Turner JR, editors. *Encycl Behav Med*; 2013. p. 1508–9.
 28. Sun Y, Weber KT. Infarct scar: a dynamic tissue. *Cardiovasc Res* 2000;46:250–6. doi:10.1016/s0008-6363(00)00032-8.
 29. Ganame J, Messalli G, Masci PG, et al. Time course of infarct healing and left ventricular remodelling in patients with reperfused ST segment elevation myocardial infarction using comprehensive magnetic resonance imaging. *Eur Radiol* 2011;21:693–701. doi:10.1007/s00330-010-1963-8.
 30. Ibanez B, Aletras A, Arai A, et al. Cardiac MRI endpoints in myocardial infarction experimental and clinical trials: jacc scientific expert panel. *J Am Coll Cardiol* 2019;74:238–56. doi:10.1016/j.jacc.2019.05.024.
 31. Roes SD, Kelle S, Kaandorp TAM, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. *Am J Cardiol* 2007;100:930–6. doi:10.1016/j.amjcard.2007.04.029.
 32. Kwon DH, Halley CM, Carrigan TP, et al. Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyperenhancement cardiac magnetic resonance study. *JACC Cardiovasc Imaging* 2009;2:34–44. doi:10.1016/j.jcmg.2008.09.010.
 33. Hartman MHT, Eppinga RN, Vlaar PJJ, et al. The contemporary value of peak creatine kinase-MB after ST-segment elevation myocardial infarction above other clinical and angiographic characteristics in predicting infarct size, left ventricular ejection fraction, and mortality. *Clin Cardiol* 2017;40:322–8. doi:10.1002/clc.22663.
 34. El Aidi H, Adams A, Moons KGM, et al. Cardiac magnetic resonance imaging findings and the risk of cardiovascular events in patients with recent myocardial infarction or suspected or known coronary artery disease: a systematic review of prognostic studies. *J Am Coll Cardiol* 2014;63:1031–45. doi:10.1016/j.jacc.2013.11.048.
 35. He P-C, Duan C-Y, Liu Y-H, et al. N-terminal pro-brain natriuretic peptide improves the C-ACS risk score prediction of clinical outcomes in patients with ST-elevation myocardial infarction. *BMC Cardiovasc Disord* 2016;16:255. doi:10.1186/s12872-016-0430-0.
 36. Bulluck H, Hammond-Haley M, Weinmann S, et al. Myocardial infarct size by cmr in clinical cardioprotection studies: insights from randomized controlled trials. *JACC Cardiovasc Imaging* 2017;10:230–40. doi:10.1016/j.jcmg.2017.01.008.
 37. Flett AS, Hasleton J, Cook C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2011;4:150–6. doi:10.1016/j.jcmg.2010.11.015.
 38. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update : society for cardiovascular magnetic resonance (SCMR): board of trustees task force on standardized post-processing. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 2020;22:19. doi:10.1186/s12968-020-00610-6.
 39. Lexis CPH, van der Horst ICC, Lipsic E, et al. Effect of metformin on left ventricular function after acute myocardial infarction in patients without diabetes: the GIPS-III randomized clinical trial. *JAMA* 2014;311:1526–35. doi:10.1001/jama.2014.3315.
 40. Siddiqi N, Neil C, Bruce M, et al. Intravenous sodium nitrite in acute ST-elevation myocardial infarction: a randomized controlled trial (NIAMI). *Eur Heart J* 2014;35:1255–62. doi:10.1093/eurheartj/ehu096.
 41. Lønborg J, Vejstrup N, Kelbæk H, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012;33:1491–9. doi:10.1093/eurheartj/ehr309.
 42. Le Corvoisier P, Gallet R, Lesault P-F, et al. Intra-coronary morphine vs placebo in the treatment of acute ST-segment elevation myocardial infarction: the MIAMI randomized controlled trial. *BMC Cardiovasc Disord* 2018;18:193. doi:10.1186/s12872-018-0936-8.

43. Bulluck H, Yellon DM, Hausenloy DJ. Reducing myocardial infarct size: challenges and future opportunities. *Heart* 2016;102:341–8. doi:10.1136/heartjnl-2015-307855.
44. Marutani E, Ichinose F. Emerging pharmacological tools to control hydrogen sulfide signaling in critical illness. *Intensive care Med Exp* 2020;8:5. doi:10.1186/s40635-020-0296-4.
45. Chen KK, Rose CL. Nitrite and thiosulfate therapy in cyanide poisoning. *J Am Med Assoc* 1952;149:113–19. doi:10.1001/jama.1952.02930190015004.
46. Kyriakopoulos G, Kontogianni K. Sodium thiosulfate treatment of tumoral calcinosis in patients with end-stage renal disease. *Ren Fail* 1990;12:213–19. doi:10.3109/08860229009060727.
47. Sörensson P, Saleh N, Bouvier F, et al. Effect of postconditioning on infarct size in patients with ST elevation myocardial infarction. *Heart* 2010;96:1710–15. doi:10.1136/hrt.2010.199430.
48. Bøtker HE, Hausenloy D, Andreadou I, et al. Practical guidelines for rigor and reproducibility in preclinical and clinical studies on cardioprotection. *Basic Res Cardiol* 2018;113:39. doi:10.1007/s00395-018-0696-8.
49. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on adjustment for baseline covariates in clinical trials. European Medicines Agency 2015:1–11 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf.
50. Chen K, Cheng Y, Berkout O, et al. Analyzing proportion scores as outcomes for prevention trials: a statistical primer. *Prev Sci* 2017;18:312–21. doi:10.1007/s11121-016-0643-6.
51. Swearingen CJ, Tilley BC, Adams RJ, et al. Application of beta regression to analyze ischemic stroke volume in NINDS rt-PA clinical trials. *Neuroepidemiology* 2011;37(2):73–82. doi:10.1159/000330375.
52. Kieschnick R, McCullough BD. Regression analysis of variates observed on (0, 1): percentages, proportions and fractions. *Stat Modelling* 2003;3:193–213. doi:10.1191/1471082X03st053oa.
53. Heusch G, Gersh BJ. Is cardioprotection salvageable? *Circulation* 2020;141:415–17. doi:10.1161/CIRCULATIONAHA.119.044176.
54. Heusch G. Critical issues for the translation of cardioprotection. *Circ Res* 2017;120:1477–86. doi:10.1161/CIRCRESAHA.117.310820.