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Structural and Functional Insights into an Archaeal Lipid Synthase

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The role of cardiovascular magnetic resonance imaging and computed tomography angiography in suspected non–ST-elevation myocardial infarction patients: Design and rationale of the CARdiovascular Magnetic rEsoNance imaging and computed Tomography Angiography (CARMENTA) trial

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Background Although high-sensitivity cardiac troponin (hs-cTn) substantially improves the early detection of myocardial injury, it lacks specificity for acute myocardial infarction (MI). In suspected non–ST-elevation MI, invasive coronary angiography (ICA) remains necessary to distinguish between acute MI and noncoronary myocardial disease (eg, myocarditis), unnecessarily subjecting the latter to ICA and associated complications. This trial investigates whether implementing cardiovascular magnetic resonance (CMR) or computed tomography angiography (CTA) early in the diagnostic process may help to differentiate between coronary and noncoronary myocardial disease, thereby preventing unnecessary ICA.

Study Design In this prospective, single-center, randomized controlled clinical trial, 321 consecutive patients with acute chest pain, elevated hs-cTnT, and nondiagnostic electrocardiogram are randomized to 1 of 3 strategies: (1) CMR, or (2) CTA early in the diagnostic process, or (3) routine clinical management. In the 2 investigational arms of the study, results of CMR or CTA will guide further clinical management. It is expected that noncoronary myocardial disease is detected more frequently after early noninvasive imaging as compared with routine clinical management, and unnecessary ICA will be prevented. The primary end point is the total number of patients undergoing ICA during initial admission. Secondary end points are 30-day and 1-year clinical outcome (major adverse cardiac events and major procedure-related complications), time to final diagnosis, quality of life, and cost-effectiveness.

Conclusion The CARMENTA trial investigates whether implementing CTA or CMR early in the diagnostic process in suspected non–ST-elevation MI based on elevated hs-cTnT can prevent unnecessary ICA as compared with routine clinical management, with no detrimental effect on clinical outcome. (*Am Heart J* 2013;166:968-75.)

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As opposed to ST-elevation myocardial infarction (STEMI), electrocardiographic (ECG) changes are often nondiagnostic in non-ST-elevation MI (NSTEMI), and measuring cardiac troponin levels is an important diagnostic cornerstone.^{1,2} Despite being very sensitive and specific markers for myocardial injury, troponins are not specific for acute MI.^{3,4} The recently introduced high-sensitivity cardiac troponin (hs-cTn) assays have substantially improved the early diagnosis of acute MI in comparison with the conventional troponin (cTn) assays, but at the cost of a lower specificity.^{5,6} Therefore, it is often challenging to distinguish MI from other disorders that result in elevated troponin levels, such as myocarditis, pulmonary embolism (PE), or Takotsubo cardiomyopathy (ie, noncoronary myocardial disease).^{4,7}

An important component of the universal definition of acute MI is a typical rise and/or fall of cardiac troponin with at least 1 value above the 99th percentile of a reference population, but the magnitude of this rise and fall has not been defined.¹ Recent studies have shown that discriminating between acute MI and noncoronary myocardial disease can be improved by using algorithms that combine baseline hs-cTn values with absolute or relative changes over time. Limitations of these studies are that the final diagnosis of acute MI was adjudicated based on available clinical data, including the conventional troponin assay, and routine noninvasive imaging was not used. Furthermore, these studies were designed retrospectively.⁴

Invasive coronary angiography (ICA) remains necessary to distinguish between acute MI and noncoronary myocardial disease, predisposing the latter to unnecessary ICA, aggressive antithrombotic, and antiplatelet therapy. This potentially increases the length of hospitalization, number of complications, and health care costs. Noninvasive imaging techniques can be used to differentiate between coronary and noncoronary myocardial disease and direct patient management.⁸

Delayed-enhancement cardiovascular magnetic resonance imaging (DE-CMR) is a well-validated technique for the diagnosis of irreversible myocardial damage, both in ischemic and in nonischemic heart disease.^{9,10} An acute coronary syndrome can be accurately detected by using a CMR protocol comprising cine imaging, T_2 -weighted (T_2), myocardial perfusion, and DE imaging,^{11,12} and distinguished from noncoronary myocardial disease.^{13,14}

Computed tomography angiography (CTA) is a noninvasive imaging modality that rapidly determines the presence and extent of epicardial coronary artery disease (CAD). A normal CTA is associated with excellent prognosis.^{15,16} Furthermore, CTA is able to detect other life-threatening noncardiac causes of chest pain such as acute aortic dissection (AAS) and PE.¹⁷

Although CMR and CTA visualize different aspects of myocardial disease, each technique can uniquely be used

to distinguish between a coronary and noncoronary etiology of acute chest pain and hs-cTn rise. This study investigates whether implementing CTA or CMR early in the diagnostic process can prevent unnecessary ICA, by excluding significant CAD or establishing noncoronary myocardial disease.

It is expected that in patients with suspected NSTEMI, noncoronary myocardial disease is more frequently diagnosed when CTA or CMR is performed early in the diagnostic process as compared with routine clinical management, thereby preventing unnecessary ICA. The primary objective of the CARMENTA trial is to investigate whether this approach reduces the total number of patients undergoing ICA during initial hospitalization. A secondary objective is to compare 30-day and 1-year clinical outcome to determine safety, time to final diagnosis, cost-effectiveness, and quality of life of each strategy.

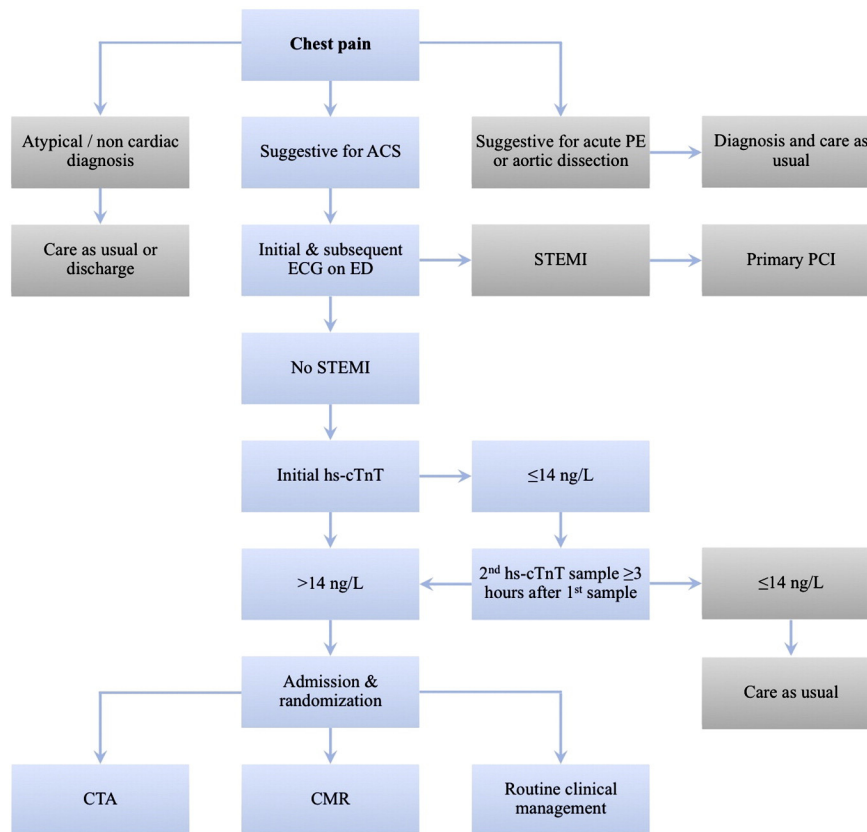
Methods

Study design and population

The CARMENTA trial (NCT01559467) is designed as a prospective, open-label, single-center randomized controlled clinical trial. The trial enrolls patients consecutively who present on the emergency department (ED) with acute chest pain, elevated serum hs-cTnT levels (>14 ng/L), and a nondiagnostic ECG. Enrollment will continue until 288 patients have completed the study protocol. Patients are randomized immediately after ED evaluation (comprising a detailed medical history, physical examination, serial ECGs, and serum hs-cTnT measurements) to 1) CMR (early in the diagnostic process), or 2) CTA (early in the diagnostic process), or 3) routine clinical management (without early CMR or CTA imaging). The CARMENTA trial is a comparative effectiveness trial evaluating the effectiveness of alternative clinical management strategies (CMR or CTA arm) in comparison with routine clinical care.¹⁸ Besides evaluating the prespecified end points, that is, the number of patients undergoing ICA during initial hospitalization, the trial design allows evaluating the overall clinical effects of implementing noninvasive imaging early in the diagnostic strategy in suspected NSTEMI.

Before the start of the trial, physicians and nurses were profoundly familiarized with the trial purpose and design to ensure consistency in management. After CMR or CTA is performed, a diagnosis of "coronary," "noncoronary myocardial disease," or "normal/equivocal" is reported in the hospital's electronic patient record. Additional management (ECG monitoring, biomarker testing, medical therapy, downstream testing, other clinically indicated interventions) is left at the discretion of the attending cardiologist and is in accordance with current (institutional/European Society of Cardiology/American Heart Association) NSTEMI guidelines. The study is conducted according to the principles of the Declaration of Helsinki and has been approved by the local medical ethical committee of Maastricht University Hospital and Maastricht University. [Figure 1](#) illustrates the patient selection process and the randomization strata of the CARMENTA trial.

Figure 1



Study design—flowchart patient selection. PCI, percutaneous coronary intervention.

Study end points and definitions

The primary end point of the CARMETA trial is the total number of patients with at least one ICA during initial admission in each arm. Secondary end points are 30-day and 1-year clinical outcome (a composite of major adverse cardiac events [MACEs] and major procedure-related complications), time to final diagnosis, cost-effectiveness, and quality of life. After 1 year, an independent clinical end point committee (including an interventional cardiologist, clinical cardiologist, and radiologist [both with >5 years' experience in CMR and CTA]), blinded for the allocated strategy, adjudicates a final diagnosis to each patient using all available clinical and imaging data.

Clinical outcome (MACE and major procedure-related complications) is defined as a composite of all-cause mortality or cardiac mortality, recurrent MI, revascularization (percutaneous coronary intervention and/or coronary artery bypass grafting) not planned after the index event or congestive heart failure requiring hospitalization, significant bleeding (fatal, intracranial, or resulting in hemodynamic compromise; need for blood transfusion or overt bleeding plus hemoglobin drop: minor bleeding ≥ 2.0 mmol/L or ≥ 3 g/dL) or major bleeding ≥ 3.0 mmol/L [≥ 5 g/dL)],¹⁹ renal failure (need for temporary or permanent hemodialysis), contrast-induced nephropathy ($\geq 25\%$ or $\geq 44\mu\text{mol/L}$ increase in serum creatinine from baseline),

nephrogenic systemic fibrosis, allergic reaction requiring urgent therapy, dissection/perforation/rupture after puncture of a vessel, stroke (ischemic or hemorrhagic), or transient ischemic attack diagnosed by a neurologist (preferably supported by imaging techniques). MACE and major procedure-related complications are scored during admission, and 1-month and 1-year follow up.

The definitions of recurrent MI and/or reinfarction are adapted from the universal definition of MI.¹

Costs will be assessed from a health care perspective. Implementing CMR or CTA early in the diagnostic process is expected to prevent unnecessary ICA and reduce the length of hospitalization in patients with noncoronary myocardial disease. Health care costs will be retrieved for all patients using hospital databases and patient records. Unit costs will be based on standard prices using the Dutch manual for cost research.²⁰

The economic evaluation will be a cost-effectiveness analysis, with quality-adjusted life years as an effectiveness measure. For this purpose, health state utilities will be derived using the EuroQol (baseline on admission and 1, 6, and 12 months after admission).²¹ To investigate the cost-effectiveness of the 3 strategies, incremental cost-effectiveness ratios will be calculated. Uncertainty surrounding the costs and effects will be examined using nonparametric bootstrap analyses with 1,000 replications. Cost-effectiveness acceptability curves will be derived to show

Table. Eligibility criteria

Inclusion criteria

- Prolonged symptoms suspected of cardiac origin (angina pectoris or angina equivalent), and presentation on the cardiac ED <24 h after symptom onset
- Increased levels of hs-cTnT (>14 ng/L; initial blood sample at presentation or a second sample ≥3 h after presentation)
- Age 18-85 y
- Willing and capable to give written informed consent
- Written informed consent

Exclusion criteria

- Ongoing severe ischemia requiring immediate ICA (at discretion of cardiac ED physician/cardiologist)
- Shock (mean arterial pressure <60 mm Hg) or severe heart failure (Killip class ≥III)
- STEMI (ST elevation in 2 contiguous leads: ≥0.2 mV in men or ≥0.15 mV in women in leads V₂-V₃ and/or ≥0.1 mV in other leads or new left bundle-branch block)
- Chest pain highly suggestive of noncardiac origin (as judged by the cardiac ED physician/cardiologist)
 - Acute aortic dissection
 - Acute PE (high-risk patient defined as Wells score >6)
 - Musculoskeletal or gastrointestinal pain
 - Other (pneumothorax, pneumonia, rib fracture, etc)
- Previously known CAD, defined as follows:
 - Any noninvasive diagnostic imaging test positive for CAD (perfusion defects, and/or stress-induced wall motion abnormalities)
 - Coronary stenosis >50% on any previous ICA or CTA
 - Documented previous MI
 - Documented previous coronary artery revascularization (PCI and/or CABG)
- Known cardiomyopathy (dilated, hypertrophic, infiltrative, etc)
- Pregnancy
- Life-threatening arrhythmia on the cardiac ED or before presentation (sustained ventricular tachycardia, repetitive nonsustained ventricular tachycardia, ventricular fibrillation, sinoatrial or atrioventricular block)
- Atrial fibrillation
- Tachycardia (≥100 beats/min)
- Angina pectoris secondary to anemia (<5.6 mmol/L), untreated hyperthyroidism, aortic valve stenosis (AVA ≤1.5 cm²), or severe hypertension (>200/110 mm Hg)
- Life expectancy <1 y (malignancy, etc)
- Contraindications to CMR
 - Metallic implant (vascular clip, neurostimulator, Cochlear implant)
 - Pacemaker or implantable cardiac defibrillator
 - Claustrophobia
 - Body weight >130 kg
- Contraindication to CMR or CTA contrast agent (gadolinium or iodine)
 - Renal failure (estimated GFR ≤30 mL/min per 1.73 m²/chronic renal failure stages 4-5)
 - Known severe contrast allergy (a patient with mild allergy is eligible for inclusion when premedication according to hospital guidelines can be administered)
- Contraindication to adenosine
 - High-degree atrioventricular block (second or third degree)
 - Severe bronchial asthma
 - Chronic obstructive pulmonary disease Gold ≥III
 - Concomitant use of dipyridamole (Persantin)
 - Long-QT syndrome (congenital)

PCI, Percutaneous coronary intervention; CABG, coronary artery bypass grafting; AVA, aortic valve area; GFR, glomerular filtration rate.

the probability of each strategy being cost-effective, for a range of possible maximum values a decision maker is willing to pay for a quality-adjusted life year.²²

Eligibility criteria

The detailed inclusion and exclusion criteria are shown in Table. All consecutive patients are screened for eligibility on the ED by cardiologists in training and their supervisors, 24 hours a day, 7 days per week, whole year-round. Inclusion and randomization of eligible patients are performed on week days from 8:00 AM until 6:00 PM (office hours). Patients presenting on the ED with suspected NSTEMI (ie, prolonged angina pectoris or symptoms equivalent to angina, normal or nondiagnostic ECG, and increased levels of hs-cTnT [>14 ng/L on admission or 3 hours later]) are eligible. Patients with shock, ongoing severe ischemia requiring immediate ICA, or chest pain highly suggestive of noncardiac origin (eg, musculoskeletal and gastrointestinal) are excluded. In addition, patients with previously known CAD or cardiomyopathy and patients experiencing angina pectoris secondary to anemia, severe aortic valve stenosis, severe hypertension, or tachycardia (type II MI) are excluded.¹ A log of all patients screened for eligibility is kept, including all ineligible and eligible patients but who declined participation or dropped out.

The Netherlands Heart Foundation sponsors the CARMENTA trial. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript, and its final contents.

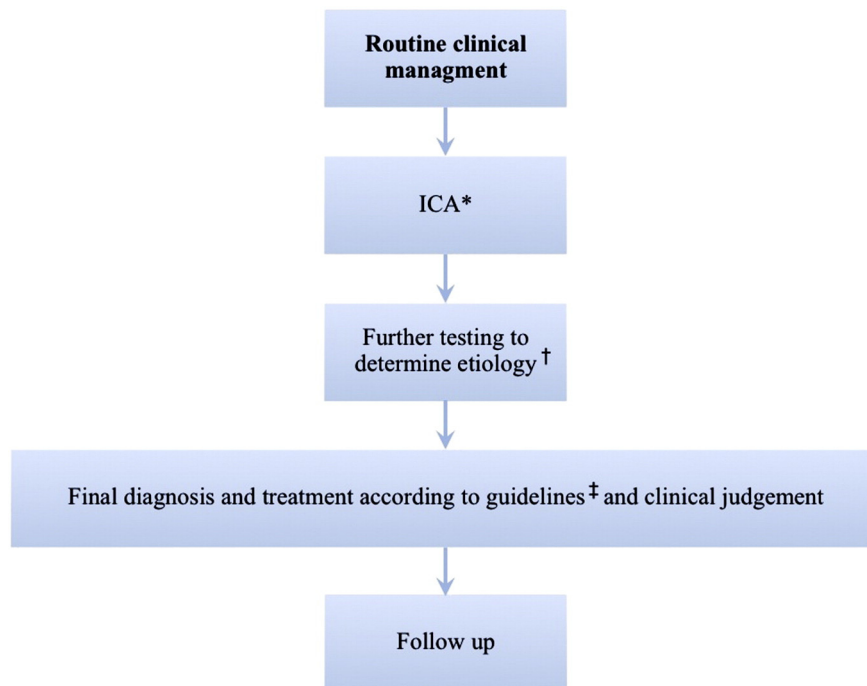
Randomization

Patients are randomized immediately after initial ED evaluation and after obtaining informed consent. Patients are randomized in a 1:1:1 fashion to one of the following strategies: (1) CMR, or (2) CTA early in the diagnostic process, or (3) routine clinical management without early noninvasive imaging. A stratified randomization method is used to equally distribute patients with an hs-cTnT concentration of 15 to 50 ng/L and patients with an hs-cTnT concentration of >50 ng/L (based on the highest hs-cTnT value of the first 2 blood samples) among 1 of the 3 strategies. Variable block randomization (3, 6, or 9 patients per block) is assembled to safeguard equal distribution of patients equally over time and to prevent prediction of allocation of patients.

Randomization is performed with TENALEA randomization software (FormsVision BV, Abcoude, The Netherlands) provided by the Clinical Trial Center Maastricht. The software is an Internet-based service supporting online patient registration and randomization. The online randomization module includes comprehensive reporting tools, audit tools, and tools for monitoring operational system components.

Patient care (treatment) in randomization arms

Randomization arm 1: routine clinical care. In the routine clinical management arm, patients are not

Figure 2

Recommendations to guide clinical management in clinical routine arm. *If appropriate according to clinical judgment and in the absence of regular contra-indications. †If coronary angiography results are ambiguous. ‡Current guidelines: European Society of Cardiology, American College of Cardiology, Netherlands Society of Cardiology and local hospital protocols.

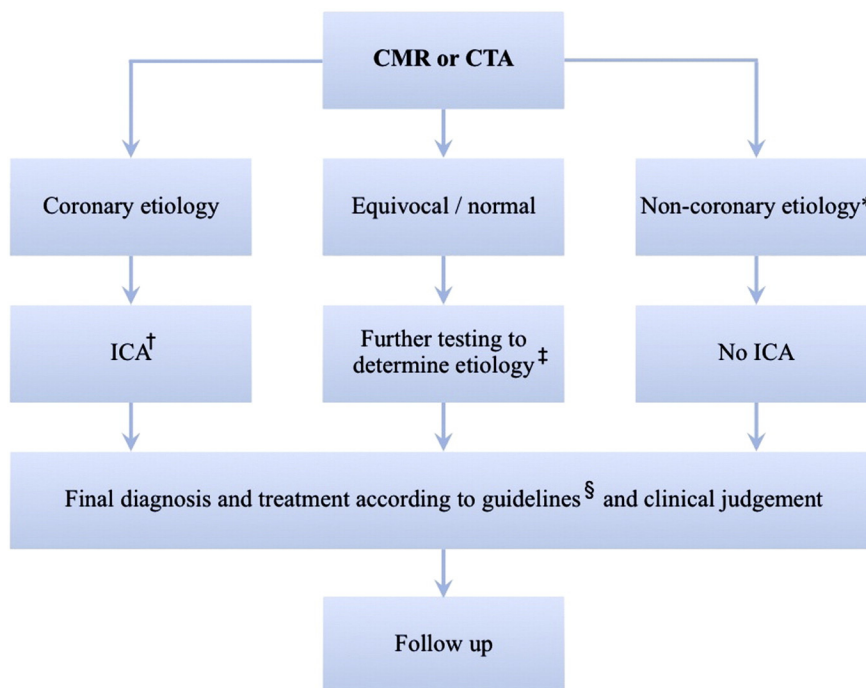
intended to undergo early CMR or CTA. Patients are admitted and treated according to current guidelines and clinical judgment. The decision to proceed to ICA, and additional downstream testing is made on clinical grounds and left at the discretion of the clinical cardiologist taking care of the patient. Recommendations are provided to prevent heterogeneity between attending cardiologists (Figure 2).

Randomization arm 2: CMR imaging. A comprehensive CMR study is performed on a clinical whole-body 3.0-T multitransmit magnetic resonance imaging scanner (Achieva; Philips Medical Systems, Best, The Netherlands) as soon as possible after admission (<72 hours). A bright blood sequence in the transversal plane covering the whole heart and large vessels is used to determine anatomy and extracardiac pathology. Cine-CMR in the short axis (multislice, covering the whole heart), left ventricular outflow tract, and horizontal and vertical long-axis view (single slice) is used to evaluate ventricular volumes, regional wall motion abnormalities, and overall function. T_2 -weighted CMR in short-axis view (multislice, covering the whole heart), horizontal and vertical long-axis view (single slice), and adenosine-stress-rest perfusion CMR (basal, mid, and apical slice) and DE-CMR in short axis (multislice, covering the whole heart) and

horizontal and vertical long axis (single slice) are used to detect edema, ischemia, and/or scar, respectively. All images are reviewed step by step during scanning. Additional nonstandardized images are obtained when observations during standardized views remain ambiguous. Gadolinium contrast infusion (Gadovist 0.2 mmol/kg body weight; Bayer Pharma AG, Berlin, Germany) is used for perfusion and DE-CMR imaging. A coronary etiology of chest pain is assumed in case of the following: subendocardial or transmural late enhancement on DE-CMR in the territory of a coronary artery with/without regional wall motion abnormalities on cine, with/without obvious increased signal intensity on T_2 -weighted-CMR, and/or a subendocardial or transmural perfusion defect corresponding to the distribution territory of a coronary artery during rest and/or stress perfusion.

Randomization arm 3: CTA. A comprehensive CT scanning investigation is performed using a second-generation dual-source CT scanner (Somatom Definition Flash; Siemens Medical Solutions, Forchheim, Germany) as soon as possible after admission (<72 hours). To achieve a stable heart rate of <65 beats/min, patients will be premedicated with beta blocking agents (if no contraindications, 50 mg metoprolol oral and up to 20 mg metoprolol intravenously before the scan).

Figure 3



Recommendations to guide clinical management in CMR or CTA arm. *Cardiomyopathy (Takotsubo, hypertrophic, dilated, infiltrative), myocarditis, pericarditis, aortic dissection, acute PE. †If appropriate according to clinical judgment and in the absence of contraindications. ‡Left at the discretion of caring cardiologist. §Current guidelines: European Society of Cardiology, American College of Cardiology, Netherlands Society of Cardiology and local hospital protocols.

Sublingual nitrates (if no contraindications) will ensure maximal vasodilatation to enhance coronary lumen visualization before scanning.

A nonenhanced scan is performed to determine the coronary calcium score, using the method of Agatston et al.²³ A testbolus is used to ensure optimal timing for CTA. Computed tomography angiography is performed using a dual-head injector contrast protocol (Ultravist 300; Bayer Pharma AG, Berlin, Germany) with a total amount of 120 mL to facilitate sufficient late-enhancement imaging. Every patient in the CTA arm will undergo a non-contrast baseline CT scan, coronary CTA, and, for experimental reasons, DE imaging.

In patients with a stable heart rate <65 beats/min, a prospectively triggered high-pitch spiral protocol is used. In patients with a heart rate ≥65 beats/min or in case of an irregular heart rhythm, a retrospectively gated helical protocol with dose modulation is used. Dual-energy DE images are acquired 6 minutes after contrast injection using a prospectively gated dual-energy scanning protocol. Images are reconstructed with thin slices, and field of view and reconstruction kernel are adapted to evaluate the coronary arteries, to assess the whole lung, pulmonary arteries, and the

aorta. Images are directly viewed and evaluated on a dedicated postprocessing workstation (MultiModality Workplace; Siemens Medical Solutions).

A coronary etiology of the chest pain syndrome is considered highly likely in case of the following: a significant stenosis (≥70% luminal narrowing) or total occlusion in a coronary artery. Also, an Agatston score of more than 1,000 will be considered as evidence of a coronary etiology, in the absence of AAS, PE, or alternative causes.

Cardiovascular magnetic resonance and CTA analysis and recommendations

For both CMR and CTA, the following noncoronary myocardial disease diagnoses are made: (peri)myocarditis, stress cardiomyopathy, other cardiomyopathies (eg, amyloidosis and sarcoidosis), AAS, PE, and other (non-) cardiac (incidental) findings. A CMR or CTA investigation is “equivocal” when the images are nondiagnostic, owing to insufficient image quality (artifacts) or incomplete image acquisition, and when a final diagnosis cannot be made. A CMR or CTA study is interpreted as “normal” if the images are diagnostic and no (extra-)cardiac pathology is seen.

All CMR and CTA images are interpreted simultaneously and routinely by 2 experienced readers, a cardiologist and a radiologist, to come to a diagnosis including extracardiac diagnosis. During scanning, a step-by-step algorithm is followed, such that at each point, the scan can be interrupted after a diagnosis is made to minimize study scan duration and minimize hazard for the patient.

Immediately after the investigation, diagnostic information from CMR or CTA will be reported in the electronic hospital records (time stamped) and the responsible clinician notified. The final decision to perform additional diagnostic testing or intervention is left at the discretion of the attending cardiologist. Recommendations are provided to prevent heterogeneity between supervising cardiologists (Figure 3).

Patient safety

An independent statistician will perform an interim analysis after 50, 100, and 200 included patients, to reduce the risk of exposure of study participants to a possibly inferior strategy. The results of this interim analysis will be reported to the medical ethical committee. For patient safety, MACE rate (all-cause death, revascularization not planned during the initial admission, re-admission for heart failure, and recurrent MI between groups) will be compared. The CMR or CTA arm will be discontinued in case the interim analysis shows a significant ($P < .05$) increase in MACE in patients in either arm. No additional patients will be randomized to the inferior strategy, but the other 2 strategies (CMR or CTA vs routine clinical care) will be continued. The follow-up of included patients will continue even if the inclusion of new patients is stopped. After randomization, the cardiologist taking care of the patient can deviate from the study protocol at all times. If other urgent diagnostics or therapeutics than prescribed by the study protocol are necessary, this will receive priority. Protocol violations will be reported.

Sample size calculation

The primary end point of the present study is a reduction in total number of patients with at least 1 ICA during initial admission by the application of noninvasive diagnostic imaging techniques CMR or CTA early in the diagnostic process as compared with routine clinical management. The primary comparison groups in this randomized controlled trial are, therefore, CMR vs standard care and CTA vs standard care.

Based on clinical experience, approximately 75% of admitted patients with NSTEMI undergo ICA during initial hospitalization. This is supported by data from the CRUSADE and ACTION registry, reporting an overall rate of in-hospital ICA of 73% and 80%, respectively.^{24,25}

Trials such as the ICTUS, CRUSADE, FRISC II, PURSUIT, TIMI IIIB, GRACE, and MATE report that up to 7% to 25% of patients with clinically suspected MI have normal coronary arteries or insignificant disease at ICA and may ultimately be diagnosed as having noncoronary myocardial disease.²⁶ It is expected that these numbers will increase when using the new hs-cTn assays to detect myocardial injury. Early noninvasive imaging (either CMR or CTA) may filter out noncoronary myocardial disease, reducing the need for ICA to approximately 60% of patients. Ninety-six patients per treatment arm with completed study protocols will be sufficient to detect this difference in proportions with a power of 80% and α value of .05. Accounting for a dropout rate of 10%, it is assumed that in total, 321 patients have to be enrolled.

Data analysis

For all 3 groups, the relative risk of ICA will be calculated. To evaluate the primary objective, the total number of patients with at least one ICA during the initial admission will be compared between groups by χ^2 analysis. Comparison will be done between a CMR-guided approach vs standard care, a CTA-guided approach vs standard care, and a CMR vs a CTA-guided approach. Multivariable logistic regression models will be used to adjust for potential confounders.

To assess clinical outcome (a composite of MACEs and major procedure-related complications) over time, Kaplan-Meier plots will be constructed and groups will be compared by using a log-rank test. To assess clinical outcome, Cox regression models will be fitted to adjust for confounders. A prespecified secondary analysis will be performed on the effect of hs-cTnT level and patient age on the primary and secondary end points. Prespecified subgroups are the following: hs-cTnT (15-50 and >50 ng/L) and age (<60 and ≥ 60 years).

Differences between the 3 groups in quality of life will be reported descriptively. In addition, differences between the randomization groups in both generic and disease-specific quality of life will be tested using analysis of variance.

Summary

The CARMENTA trial investigates whether the implementation of CMR or CTA early in the diagnostic process in patients presenting with acute chest pain, nondiagnostic or normal ECG, and elevated hs-cTnT levels (ie, suspected NSTEMI) leads to an early alternative diagnosis than MI (eg, myocarditis, PE, etc) as compared with routine clinical management. Consequently, this could prevent unnecessary ICA and associated complications and reduce length of hospitalization and costs, without having a detrimental effect on clinical outcome. Especially in the current era of hs-cTn

assays that have very high sensitivity but lower specificity for acute MI than conventional (fourth generation) troponin assay, this trial may have important implications for the future diagnostic workup of patients with suspected but not yet proven NSTEMI.

References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126:2020-35.
2. Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003;349:2128-35.
3. Agewall S, Giannitsis E, Jernberg T, et al. Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J* 2011;32:404-11.
4. Haaf P, Drexler B, Reichlin T, et al. High-sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac noncoronary artery disease. *Circulation* 2012;126:31-40.
5. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361:858-67.
6. Keller T, Zeller T, Peetz D, et al. Sensitive troponin i assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;361:868-77.
7. Assomull RG, Lyne JC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. *Eur Heart J* 2007;28:1242-9.
8. Morrow DA. Clinical application of sensitive troponin assays. *N Engl J Med* 2009;361:913-5.
9. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of mri delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999;100:1992-2002.
10. Mahrholdt H, Wagner A, Judd RM, et al. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J* 2005;26:1461-74.
11. Kwong RY, Schussheim AE, Rekhraj S, et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. *Circulation* 2003;107:531-7.
12. Plein S, Greenwood JP, Ridgway JP, et al. Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging. *J Am Coll Cardiol* 2004;44:2173-81.
13. Laradogitia Zaldumbide E, Perez-David E, Larena JA, et al. The value of cardiac magnetic resonance in patients with acute coronary syndrome and normal coronary arteries. *Rev Esp Cardiol* 2009;62:976-83.
14. Leurent G, Langella B, Fougerou C, et al. Diagnostic contributions of cardiac magnetic resonance imaging in patients presenting with elevated troponin, acute chest pain syndrome and unobstructed coronary arteries. *Arch Cardiovasc Dis* 2011;104:161-70.
15. Meijboom WB, Mollet NR, Van Mieghem CA, et al. 64-Slice ct coronary angiography in patients with non-ST elevation acute coronary syndrome. *Heart* 2007;93:1386-92.
16. Vanhoenacker PK, Heijnenbroek-Kal MH, Van Heste R, et al. Diagnostic performance of multidetector ct angiography for assessment of coronary artery disease: meta-analysis. *Radiology* 2007;244:419-28.
17. Takakuwa KM, Halpern EJ. Evaluation of a "triple rule-out" coronary ct angiography protocol: use of 64-section ct in low-to-moderate risk emergency department patients suspected of having acute coronary syndrome. *Radiology* 2008;248:438-46.
18. Hlatky MA, Douglas PS, Cook NL, et al. Future directions for cardiovascular disease comparative effectiveness research: report of a workshop sponsored by the national heart, lung, and blood institute. *J Am Coll Cardiol* 2012;60:569-80.
19. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation* 2011;123:2736-47.
20. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM, et al. Handleiding voor kostenonderzoek. Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekering. Geactualiseerde versie 2010.
21. The EuroQol Group. Euroqol—a new facility for the measurement of health-related quality of life. The euroqol group. *Health Policy* 1990;16:199-208.
22. van Hout BA, Al MJ, Gordon GS, et al. Costs, effects and c/e-ratios alongside a clinical trial. *Health Econ* 1994;3:309-19.
23. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-32.
24. Ryan JW, Peterson ED, Chen AY, et al. Optimal timing of intervention in non-ST-segment elevation acute coronary syndromes: insights from the crusade (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) registry. *Circulation* 2005;112:3049-57.
25. Leonardi S, Chen AY, Gharacholou SM, et al. Limitations of using cardiac catheterization rates to assess the quality of care for patients with non-ST-segment elevation myocardial infarction. *Am Heart J* 2012;164:502-8.
26. Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. *J Am Coll Cardiol* 2009;55:1-16.