Comprehensive Cardiac CT versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT II Trial)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON40120

Source
ToetsingOnline

Brief title
CRESCENT II

Condition

- Coronary artery disorders

Synonym
Coronary disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw - doelmatigheid

Intervention

Keyword: computed tomography, coronary artery disease, diagnostic testing, exercise testing, myocardial perfusion imaging

Outcome measures

Primary outcome

Rate of negative invasive catheterization procedures (superiority)

Proportion of invasive angiograms without relevant coronary artery disease. A positive invasive angiogram is defined as: CAD with a class I indication for myocardial revascularization, in accordance with clinical guidelines [Wijns].

This indication will be assessed independently, in a blinded fashion, regardless of the clinical decision made by the treating physician:

* Left main coronary stenosis >50% with objective ischemia.

* Proximal LAD stenosis >50% with objective ischemia.

* Two or three vessel disease with impaired LV function and objective ischemia.

* Proven large area of ischemia (>10% LV)

* Any stenosis >50% with limiting anginal symptoms unresponsive to optimal medical treatment.

Secondary outcome

* Number of patients with class I coronary artery disease on invasive angiography

* Positive yield of invasive coronary angiography: proportion angiograms with class I CAD.

* Number of diagnostic procedures and related expenses per patient (at 6

months).

* Therapeutical expenses (medication, revascularizations) per patient (at 6 months).

* Overall medical expenses (at 6 months).

* Time until (final) diagnosis and treatment decision.

* Chest pain symptoms and quality of life (at six months).

* Composite major adverse event rate: cardiac death, non-fatal acute coronary syndrome, cerebro-vascular events.

* Cost-effectiveness (incremental cost-effectiveness ratio, net health benefit)

* Proportion of tests with diagnostic results

* Cumulative radiation exposure

* Diagnostic complications: allergic reactions, bleeding, arrhythmia, renal dysfunction.

Study description

Background summary

BACKGROUND
Angina pectoris is a clinical syndrome characterized by discomfort of the chest, provoked by exertion or emotional stress and relieved by rest or nitroglycerin, typically a symptom of oxygen deprivation of the heart muscle due to atherosclerotic obstruction of the coronary arteries. However, chest pain is a very common complaint, and may also be caused by numerous other cardiac and non-cardiac conditions. While the risk of severe complications appears relatively low for the group as a whole, subgroups with severely obstructive CAD with a 10-fold higher event rate can be distinguished. It is important to identify these high-risk individuals as clinical outcome can be improved through surgical or PCI myocardial revascularization [Yusuf].

USUAL DIAGNOSTIC CARE OF STABLE ANGINA
Patients with chest complaints, referred by their general practitioner, will

undergo a tiered diagnostic workup at the cardiology clinic [Fox]:
1)History, physical exam, ECG, risk profile, blood analysis.
2)Stress test: exercise ECG (X-ECG), and/or stress imaging by myocardial perfusion scintigraphy (SPECT) or dobutamine stress echocardiography (DSE).
3)Invasive catheter angiography (ICA): selectively used in case of severe ischemia, refractory complaints or non-conclusive stress test result.

HEALTH CARE EFFICIENCY PROBLEMS
1)Performance of the current diagnostic work-up is insufficient. Many patients are unable to exercise, and the sensitivity of X-ECG is only 50% (specificity 90%) in unselected populations [Gibbons]. As second option, stress imaging is more sensitive (84%), but with lower specificity (73%) and it is more expensive [Jaarsma].
2)Uncertainty about stress tests leads to invasive angiography. A recent US registry reported that only 37% of ICAs resulted in (mechanical) treatment, which illustrates how the noninvasive work-up fails as a gatekeeper to ICA [Patel]. Invasive angiography has a small risk of severe complications, as well as a more frequent occurrence of less serious complications and discomfort.
3)Since COURAGE [Boden] and FAME [Tonino, DeBruyne] there is growing consensus that (surgical) revascularization does not benefit every patient with angiographic CAD, but should be reserved for those with objective myocardial ischemia. Invasive angiography, without proper ischemia testing, leads to over-treatment.
4)Persistent symptoms, uncertainty about test results, layered testing, delayed or inaccurate diagnoses and under-/overtreatment, all have a negative effect on patient well-being. In addition, inefficient patient care is costly, in terms of health care related expenses and productivity losses.

Study objective

The overall aim of the study is to demonstrate that a comprehensive cardiac CT examination improves the diagnostic workup of stable chest pain in terms of accuracy, efficiency and costs. In concrete terms, the purpose of this randomized controlled trial is to answer the following questions:
1) Does a comprehensive cardiac CT exam reduce the number of negative catheter angiograms? The unnecessary performance of an invasive examination represents failure of the non-invasive workup.
2) Does the comprehensive cardiac CT lead to a faster (correct) diagnosis?
3) How does the comprehensive cardiac CT approach affect symptoms and quality of life?
4) How does the cardiac CT approach affect overall costs, and is this new approach cost-effective?

Study design

Randomized multi-center diagnostic intervention study, with 6-months clinical

follow-up:
a) Comprehensive cardiac CT examination
b) Standard care according to international guidelines

Intervention

COMPREHENSIVE CARDIAC CT (INTERVENTION), to be completed depending on the results:
[1] CORONARY CALCIUM SCAN (CT-CALCIUM)
[2] CT CORONARY ANGIOGRAPHY (CT-ANGIO)
[3] CT MYOCARDIAL PERFUSION IMAGING (CT-MPI)

Study burden and risks

Roentgen exposure
The currently standard approach to stable chest pain complaints includes several investigations involving potentially harmful ionizing radiation, which is considered acceptable to reach the diagnostic goals of identifying ischemic heart disease. Also in the investigational arm there is exposure to radiation by the CT examination.
In the standard care arm a proportion of patients will undergo SPECT (effective dose 10-12 mSv) and/or invasive angiography (5-10 mSv).
In the investigational arm most patients will undergo calcium scanning (<1 mSv), approximately 60% will undergo CT angiography (3-4 mSv), and approximately 20% will undergo CT-MPI (8-10 mSv). Also a proportion (which is hopefully smaller) will undergo conventional angiography as well. We expect the overall exposure will not be substantially larger in the investigational group. Nevertheless, advanced techniques (prospectively triggered sequential mode and high-pitch spiral mode) and other precautions (low-mA/kV protocols, narrow longitudinal ranges, etc) will be used to minimize the roentgen exposure for each examination, including the CT scan.
For comparison, the yearly exposure to natural background radiation is 3.6 mSv.
In conclusion, the study protocol is unlikely to substantially increase the accumulated radiation exposure during the diagnostic workup.

CT contrast medium
Visualization of the coronary lumen and myocardium can only be accomplished by injection of iodine-containing contrast medium. Based on our registry data approximately 60% of the patients in the CT arm will undergo contrast-enhanced CT. Also in the standard of care group, approximately 20% of patients will be exposed to contrast during the time of cardiac catheterization. The dose required for 64-128 slice CT is approximately 80 ml, with 50 ml added if CT-MPI is performed, which is still less than conventional coronary angiography.
Allergic reactions to iodinated contrast media infrequently occur and may cause skin reactions or in very rare occasions result in breathing difficulty and hypotension (shock). Renal impairment (estimated creatinine clearance less than

70% of normal) or an established allergy to contrast media will be considered a contra-indication for study participation. The CT suite and personnel is equipped and trained to deal with unexpected allergic reactions to contrast media.

CT pre-medication
Betablockers are used by millions of patients and are generally considered safe. The side-effects and risks of incidental use of betablockers includes bradycardia (which is the reason for administration, to improve image quality), hypotension, and in rare occasions wheezing (bronchospasm) and dyspnea. Allergic reactions to beta-blocker are rare. Betablockers will only be considered in patients with a heart rate over 65 beats per minute, without clinical signs of heart failure, electrical conduction abnormalities, or a history of bronchial asthma.
Although several precautions are routinely taken, i.e. flushing, detection electrodes, extravasation of contrast occasionally occurs, which will require observation, and in very rare instances surgical intervention.
Also nitroglycerine, which is a vasodilator, is safely used by millions of patients. Side-effects include hypotension, flushing, palpitations and headache. It cannot be used in hypotensive patients, or those taking sildenafil, tadalafil en vardenafil (within 24-72 hours before the examination), as this may cause severe hypotension. Headache and sensations of flushing will subside within minutes after administration.
Ivabradin is a selective sinus node inhibitor known for its lack of side effects or severe bradycardia. It will be second choice to betablockers only for economic reasons.
The type of heart rate modulation will be chosen depending on the patient and potential contraindications. To put it in perspective, after close to 1000 CT examinations as part of the fast-track chest pain clinic no adverse events attributed to premedication have occurred.
Adenosine may precipitate bronchospasm, and should be avoided in asthmatic individuals, as well as patients with a 2nd or 3rd degree AV block or sinus node dysfunction (unless a pacemaker is implanted. Adenosine injection may be experienced as uncomfortable: flushing, palpitations, dizziness, chest pain, which resolves shortly after infusion.

Exercise electrocardiography
XECG is routinely performed at the department of cardiology and complications are rare. Death and MI occur in less than 1 in 2500 tests. The test will performed under careful supervision, with a physician present in the immediate vicinity. Patients with contra-indications will not perform XECG. During the test the ECG will be recorded and continuously displayed, with blood pressure measurements at 2-min intervals. Trained personnel and equipment is available in case of emergencies.

Pharmacological stress testing
Pharmacological stress test are generally safe with major complications

(including sustained ventricular arrhythmia) occurring 1/1500 tests with dipyridamole, and 1/300 tests with dobutamine. Trained personnel and equipment is available to act upon severe complication, should they occur.
Adenosine may precipitate bronchospasm, and should be avoided in asthmatic individuals, as well as patients with a 2nd or 3rd degree AV block or sinus node dysfunction (unless a pacemaker is implanted. Adenosine injection may be experienced as uncomfortable: flushing, palpitations, dizziness, chest pain, which resolves shortly after infusion. Dipyridamole has similar side-effects, and both should be avoided in asthmatic patients. Dobutamine infusion can also be uncomfortable, but generally to a lesser extent. It cannot be used in patients with a LV outflow obstruction.

Potential adverse events related to the study algorithm
Participation to the study will affect further management, depending on the diagnostic approach and subsequent findings. Although we consider it unlikely that long-term outcome will be (negatively) affected by participation to the study, patients will be asked to immediately report back any major adverse cardiovascular events (unplanned hospital visits and treatment in relation to cardiovascular disease). An excess of major adverse events in the investigational arm will result in early termination of the study.

Patient burden
Patient response to the fast-track chest pain clinic (which combined CT and XECG in all patients) as it exists now is very good. In general the CT examination is tolerated equally well or better than XECG or SPECT). Randomization to the CT arm will not prolong or otherwise burden the patient in time or effort. As a matter of fact we hope that implementation of CT will improve logistics and reduce the number of examinations and hospital visits. Patients participating in the study will be asked for detailed information concerning their well being and medical expenses at baseline and during follow-up (questionnaires). The time consumption for the patient is estimated to be less than 30 minutes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Stable chest pain, requiring evaluation of coronary artery disease

Exclusion criteria

History of CAD: prior myocardial infarction or revascularization procedure (CABG or PCI)
Contra-indication to radiation exposure (CT/SPECT): pregnancy
Contra-indication to iodine contrast media: renal failure, iodine allergy
Contra-indications to adenosine

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2013
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO Date:	29-05-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL42570.078.13