Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study

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ABSTRACT

Aims - This study assessed whether a diagnostic strategy supplemented by early CCTA improves clinical effectiveness compared with contemporary SOC.

Methods - In a prospective, open-label, multicenter, randomized trial, we enrolled patients presenting with symptoms suggestive of an ACS at the ED of 5 community and 2 university hospitals in the Netherlands. Exclusion criteria included the need for urgent cardiac catheterization and history of ACS or coronary revascularization. The primary endpoint was the number of patients identified with significant coronary artery disease requiring revascularization within 30 days.

Results - The study population consisted of 500 patients, of whom 236 (47%) were women (mean age 5410 years). There was no difference in the primary endpoint (22 [9%] patients underwent coronary revascularization within 30 days in the CCTA group and 17 [7%] in the SOC group [$p = 0.40$]). Discharge from the ED was not more frequent after CCTA (65% vs. 59%, $p = 0.16$), and length of stay was similar (6.3 h in both groups; $p = 0.80$). The CCTA group had lower direct medical costs (€337 vs. €511, $p < 0.01$) and less outpatient testing after the index ED visit (10 [4%] vs. 26 [10%], $p < 0.01$). There was no difference in incidence of undetected ACS.

Conclusion - CCTA, applied early in the work-up of suspected ACS, is safe and associated with less outpatient testing and lower costs. However, in the era of hs-troponins, CCTA does not identify more patients with significant CAD requiring coronary revascularization, shorten hospital stay, or allow for more direct discharge from the ED. (Better Evaluation of Acute Chest Pain with Computed Tomography Angiography [BEACON]; NCT01413282)

INTRODUCTION

Acute chest pain can herald severe cardiovascular conditions, such as an acute coronary syndrome (ACS) (1). However, the differential diagnosis of acute chest pain is broad, and the consequences of misdiagnosis can be detrimental (2–4). Physicians confront this diagnostic dilemma daily. Coronary computed tomography angiography (CCTA) allows noninvasive visualization of the coronary arteries (5). Because of its high accuracy in ruling out coronary artery disease (CAD), CCTA has been proposed for better decision making in the emergency department (ED), allowing for rapid discharge of patients without important CAD and, possibly, more appropriate referral for coronary revascularization (6,7). Early CCTA as a diagnostic strategy in low- to intermediate-risk patients suspected of ACS is considered safe and may provide logistic and economic benefits (8–10). Meanwhile, high-sensitivity troponin assays (hs-troponins) have become standard practice in many institutions, allowing for more accurate and faster rule-out of ACS (11,12). Whether hs-troponins will erode the potential clinical, logistic, and economic benefits of CCTA has not yet been investigated. The BEACON (Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography) trial is a European randomized trial comparing a diagnostic strategy supplemented by early CCTA with standard optimal care (SOC) for patients suspected of ACS in the era of hs-troponins.

METHODS

STUDY DESIGN

The BEACON study is a prospective, open-label, multicenter, randomized trial. Patients were enrolled at 2 university and 5 community hospitals in the Netherlands. Enrollment was performed during working hours, except at the Erasmus Medical Center University Medical Centre, where patients were included around the clock. The study complied with the CONSORT 2010 Statement and Declaration of Helsinki, and was approved by the institutional ethics committees of each participating center. All patients provided written informed consent.

PARTICIPANTS

Patients with acute chest pain or symptoms suggestive of ACS warranting further diagnostic evaluation, as determined by the treating physician, were eligible for inclusion. We included patients 30 years of age and older, with a maximum age of 75 years for men and 80 years for women. Patients were excluded if symptoms were clearly of noncardiac origin or a coexisting condition already necessitated hospital admission. Exclusion criteria also included a history of known CAD, clinical need for urgent invasive coronary

angiography (ICA), clinical instability, serum troponin levels above 3 times the upper limit of the 99th percentile of the local assay, impaired renal function (estimated glomerular filtration rate <60% of age-corrected normal values), pregnancy, known allergy to an iodinated contrast agent, severe arrhythmias, and body mass index >40 kg/m2.

RANDOMIZATION

Trial participants were randomly assigned to a CCTA-based diagnostic strategy or SOC (1:1). For allocation, a computer-generated block randomization sequence was used, stratified by participating center. An independent physician at the coordinating center extracted the randomization schedule from an electronic randomization tool and codes were sent in sealed, sequentially numbered, opaque envelopes to the participating centers.

PROCEDURES

The initial standard clinical work-up at the ED included a 12-lead electrocardiogram (ECG) and blood analysis. If the initial clinical work-up did not reveal either an evident ACS or an evident noncardiac cause, eligible and consenting patients were randomized between a CCTA-guided strategy and SOC. In the intervention group, CCTA was performed after the initial clinical work-up at the ED. In both groups, hs-troponins were available (supplemental table 1). Image acquisition was performed on 64-slice or a more advanced computed tomography (CT) system, using ECG-synchronized axial or spiral scan protocols combined with radiation minimizing measures, depending on local practices, available technology, and patient characteristics. Results of CCTA were reported by certified radiologists with a minimum of 2 years of experience reading CCTA. Treating physicians were informed directly at the point of care regarding the result of CCTA and imaging-based recommendations were issued. Final medical management decisions were, however, left to the treating physicians (Figure 1). In the SOC group, the attending physicians made clinical decisions regarding further testing, including repeated cardiac marker assessment, hospital admission, noninvasive tests, and referral to ICA, according to current guidelines (13,14). Participants from both groups who were discharged from the ED, without prolonged observation (<8 h) were asked to return to the outpatient clinic after 48 to 72 hours for repeated measurement of cardiac biomarkers and a 12-lead ECG. All participants were followed-up at the outpatient clinic or contacted by telephone after 30 days.

OUTCOME MEASURES

The pre-defined primary endpoint of the study was the number of patients identified with significant CAD requiring coronary revascularization, as interpreted by the clinical operators, within the follow-up period of 30 days. This outcome parameter was chosen on the basis of the hypothesis that a CCTA-driven strategy would identify more

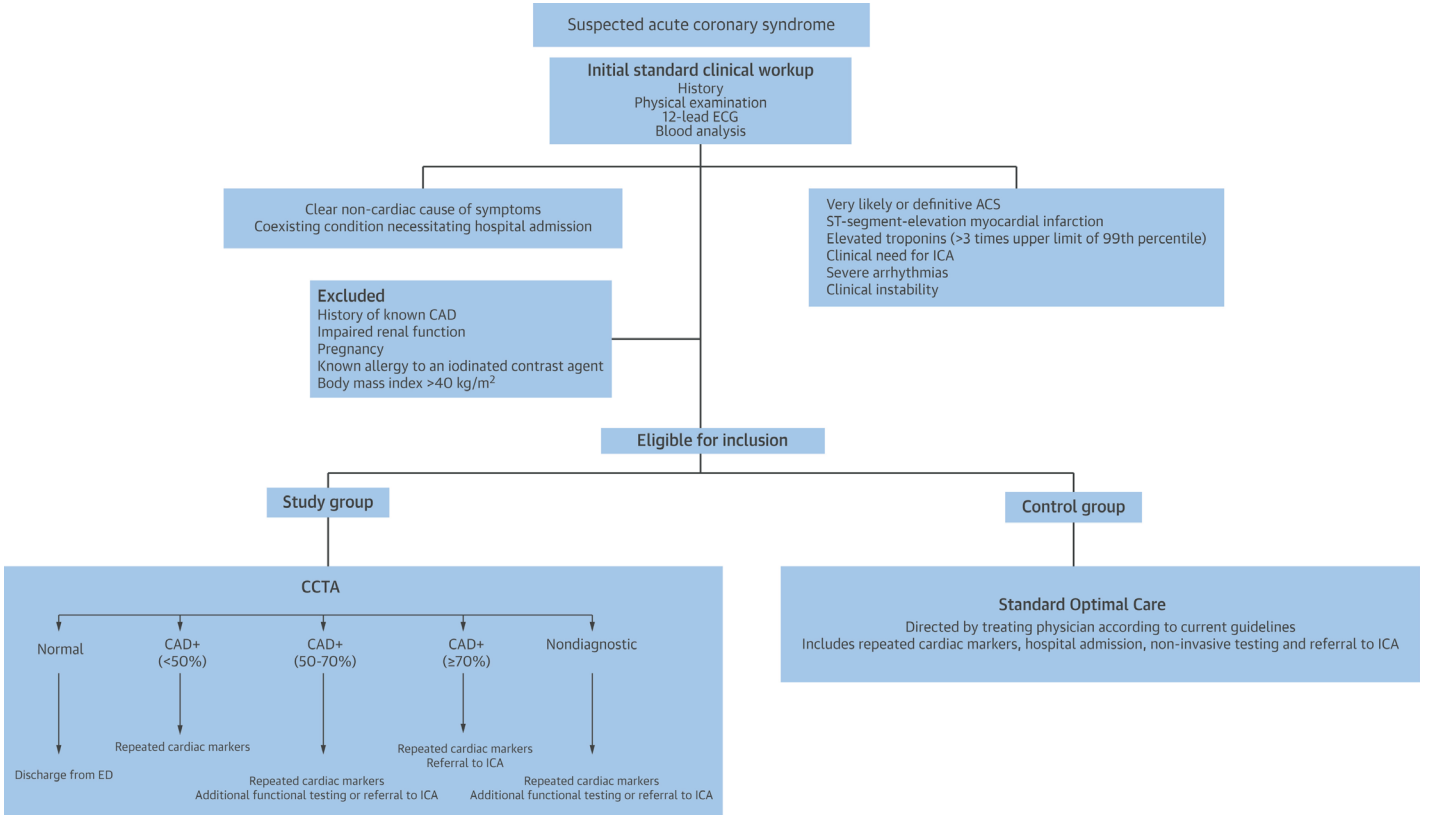

Figure 1. Trial profile.
In the study group, CCTA results were reported at the point of care, with imaging-based recommendations as displayed. However, the final decision regarding clinical work-up was left to the discretion of the treating physicians. Impaired renal function was classified as an estimated glomerular filtration rate <60% of the age-corrected normal values. ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography.

clinically important CAD, as suggested by the results of our single-center pilot study, which could effectuate a prognostic benefit (15). The use of fractional flow reserve for ischemia-proven coronary revascularization was encouraged, but not mandatory. This study was set up as a pragmatic clinical trial focusing on initial ED management without protocol-mandated medical management during the remaining clinical course. Secondary endpoints included expedited discharge rate from the ED, length of hospital stay, undetected ACS, cumulative radiation exposure, direct medical costs, and repeat visits to the ED or re-hospitalization for recurrent chest pain within 30 days of follow-up. We defined expedited discharge as discharge within 8 h from the ED, and length of stay as the time from presentation in the ED until hospital discharge. The treating physician made the decision to discharge. ACS was defined as either unstable angina pectoris or myocardial infarction, according to current guidelines (16). The diagnosis of ACS was not on the basis of the CCTA results. The occurrence of undetected ACS was assessed at both the safety follow-up within 72 hours and the general follow-up at 30 days. Cumulative radiation exposure was expressed in millisieverts (mSv) and defined as radiation exposure from all tests and interventions undergone within the first 30 days, including CCTA, single-photon emission computed tomography (SPECT) myocardial perfusion imaging, and ICA. Effective radiation dose was derived by multiplying the dose-length product by a conversion factor of 0.014 for CCTA, 0.0085 mSv/mBq for SPECT and 0.22 mSv/Gycm2 for ICA. To estimate the radiation dose of procedures without reported exposure data, the median radiation dose per procedure was used. Direct medical costs during the index visit and within the follow-up period of 30 days were assessed using reports from the Erasmus MC University Medical Centre cost-accounting system in 2013 in Euros. Finally, we compared the occurrence of total major adverse cardiac events within 30 days, defined as death, ACS, and coronary revascularization. Information on clinical events, repeat visits to the ED, re-hospitalization for recurrent chest pain, diagnostic testing, or interventions was verified by medical records. An adjudication committee consisting of 2 certified, independent cardiologists reviewed medical records of patients with clinically relevant events and a random 10% sample of patients without a diagnosis of cardiac disease.

STATISTICAL ANALYSIS

Statistical analyses were performed on the basis of an intention-to-treat analysis. Continuous data are presented as mean SD or medians with interquartile ranges. Independent samples Student t test or Mann-Whitney U test were used for between-group comparisons for continuous variables, and chi-square or Fisher exact test was used for categorical variables. A 2-sided p value <0.05 was considered to indicate statistical significance. For statistical analyses, we used SPSS version 20.0.

Figure 2. Enrollment, Randomization, and Follow-up of Study Participants
CT = computed tomography; Other abbreviations as in Figure 1.

Table 1. Baseline Characteristics

	CCTA (n = 250)	SOC (n = 250)	p-value
Age, yrs*	55 ± 10	53 ± 9	0.07
Sex, female	123 (49)	113 (45)	0.37
Medication			
Statin	65 (26)	51 (20)	0.14
Aspirin	48 (19)	35 (14)	0.12
Beta-blocker	41 (16)	40 (16)	0.90
ACE inhibitor	29 (12)	29 (12)	1.00
Angiotensin-receptor blocker	18 (7)	17 (7)	0.86
Calcium-channel blocker	18 (7)	19 (8)	0.86
Diuretic agent	36 (14)	23 (9)	0.07
Oral antidiabetic agent	22 (9)	24 (10)	0.76
Insulin	6 (2)	3 (1)	0.31
Cardiovascular risk factors			
Diabetes mellitus	31 (12)	33 (13)	0.79
Hypertension			0.95
>150 mm Hg systolic or >90 mm Hg diastolic	43 (17)	43 (17)	
Treated	66 (26)	69 (28)	
Hypercholesterolemia			0.31
Total cholesterol >5 mmol/l	25 (10)	35 (14)	
Treated	65 (26)	52 (21)	
Smoking			0.26
Current	93 (37)	78 (31)	
Stopped >1 yr	25 (10)	22 (9)	
History of cardiovascular disease			0.95
Peripheral artery disease	8 (3)	7 (3)	
TIA/CVA	16 (7)	17 (7)	
Family history	112 (45)	98 (39)	0.21
Blood pressure (mm Hg)			
Systolic*	140 ± 19	141 ± 20	0.67
Diastolic*	82 ± 12	82 ± 11	0.63
Heart rate* (beats/min)	72 ± 14	72 ± 13	0.86
TIMI risk score (39)†	1 (0-2)	1 (0-2)	0.31
0	74	83	
1	84	91	
≥2	92	76	
Grace risk score (40)†	85 (70–100)	81 (67–98)	0.28
Low	211 (84)	208 (83)	0.20
Intermediate	31 (12)	39 (16)	

Table 1. Baseline Characteristics (continued)

	CCTA (n = 250)	SOC (n = 250)	p-value
High	8 (3)	3 (1)	
Ischemic ECG abnormalities	60 (24)	44 (18)	0.08
Baseline troponins			
Elevated‡	11 (4)	13 (5)	0.67

Unless otherwise specified, data are numbers of patients, with percentages in parentheses. *Data are means ± SD. †Data are medians, with interquartile ranges in parentheses. Diabetes mellitus is defined as plasma glucose >11.0 mmol/l or treated with either diet regulation or medication. Ischemic ECG abnormalities defined as Q-wave or ST-T-segment alterations suggestive of ischemia. ‡Elevated within 3 times the upper limit of the 99th percentile. CCTA = coronary computed tomography angiography; CVA = cerebrovascular accident; SOC = standard optimal care; TIA = transient ischemic attack; TIMI = Thrombosis in Myocardial Infarction.

Table 2. Primary Outcome and Clinical Endpoints Within 30 Days After Index Visit

	CCTA	SOC	p-value
Invasive coronary angiography*	41 (17)	31 (13)	0.20
Invasive coronary angiography at index visit	34 (14)	25 (10)	0.21
Coronary revascularization*	22 (9)	17 (7)	0.40
Percutaneous coronary intervention	22 (9)	13 (5)	
Coronary artery bypass graft surgery	0	4 (2)	
Acute coronary syndrome at discharge	22 (9)	17 (7)	0.40
Unstable angina	8 (3)	3 (1)	0.64
Myocardial infarction	14 (6)	14 (6)	
Repeat emergency department visit	13 (5)	19 (8)	0.27
Repeat hospital admission	7 (3)	14 (6)	0.12
Undetected acute coronary syndrome	1 (0)	3 (1)	0.62
Major adverse cardiac event	25 (10)	21 (9)	0.54
All-cause mortality	1 (0)	0	1.0

Unless otherwise specified, data are numbers, with percentages in parentheses. Major cardiac adverse event includes all-cause mortality, myocardial infarction and coronary revascularization. Abbreviations as in **Table 1**. *Includes procedures at index visit.

On the basis of our previous observational data, we anticipated an absolute 9% increase in the number of coronary revascularizations if the results of CCTA were to be incorporated (15). Considering an $\alpha = 0.05$ and $\beta = 0.8$ with an intervention versus control group enrollment ratio of 1:1, and allowing a loss to follow-up of approximately 10%, we would require 500 participants to detect a difference in the number of patients requiring revascularization of relevant CAD.

RESULTS

Between July 11, 2011, and January 30, 2014, 573 eligible patients were approached for the study; 73 (13%) declined to participate (Figure 2). In total, 7 patients in the CCTA group did not have a CT scan, and 6 patients in the SOC group eventually under-went a CT examination to exclude either CAD or other vascular conditions. At 30 days, 5 patients in each group had withdrawn from the study, resulting in complete follow-up in 490 (98%) patients.

STUDY POPULATION

Table 1 shows patient demographics, clinical characteristics, and medical treatment at baseline. The mean age of the study population was 54 ± 10 years and 236 (47%) participants were women. Baseline characteristics and clinical status were similar between the 2 groups. In the intervention group, CCTA identified 106 (42%) patients with no detectable CAD. Among the patients with CAD on CCTA, 71 (28%) had atherosclerotic plaque with <50% luminal narrowing, 35 (14%) had 50% to 70% luminal narrowing in 1 or more coronary arteries, and 13 (5%) had >70% luminal narrowing in 1 or more coronary arteries. The scan was considered non-diagnostic in 18 patients (7%). The mean radiation dose in the CCTA group was 7.3 ± 6.6 mSv versus 2.6 ± 6.5 mSv in the SOC group.

PRIMARY OUTCOME AND CLINICAL ENDPOINTS

For the primary outcome, the number of patients requiring revascularization within 30 days, no difference was observed between the CCTA group and SOC, that is, 22 (9%) versus 17 (7%) ($p = 0.40$) (Table 2). Also, the total number of ICAs performed within 30 days was similar. At hospital discharge, 22 (9%) patients in the CCTA group and 17 (7%) in the SOC group were diagnosed with ACS($p = 0.40$). Repeat visits to the ED occurred in 13 (5%) patients in the CCTA group, compared with 19 (8%) in the SOC group ($p = 0.27$). At 30 days, a similar incidence of total major adverse cardiac events, that is, 25 (10%) in the CCTA group and 21 (9%) in the SOC group was observed ($p = 0.54$).

SAFETY ENDPOINTS

Undetected ACS occurred once (0.5%) in the CCTA group and 3 times (1%) in the SOC group within the 30-day follow-up period ($p = 0.62$). In the CCTA group, 1 patient had recurrent chest pain with ECG changes suggestive of myocardial ischemia at his safety visit. In the SOC group, 1 patient returned with recurrent complaints, and underwent coronary revascularization following an abnormal exercise electrocardiography (ExECG) result. Another patient reported intermittent chest pain at his safety visit within 72 hours and his laboratory tests showed elevated cardiac biomarkers. The third patient returned after 5 days with recurrent complaints and elevated cardiac biomarkers. One patient in

Table 3. Diagnostic Testing and Resource Utilization

	CCTA	SOC	p-value
Length of stay (h)*	6.3 (4.8–11.1)	6.3 (4.5–25.5)	0.80
Discharge status			0.16
Discharge from emergency department	159 (65)	144 (59)	
Admitted to hospital	86 (35)	101 (41)	
ExECG at index visit	23 (9)	130 (53)	<0.01
ExECG<30 days	32 (13)	143 (58)	<0.01
SPECT at index visit	2 (1)	7 (3)	0.18
SPECT <30 days	2 (1)	16 (7)	<0.01
CMR at index	1 (0)	1 (0)	1.0
CMR <30 days	1 (0)	3 (1)	0.62
CCTA after index visit	1 (0)	2 (1)	1.0
Outpatient diagnostic testing <30 days†	10 (4)	26 (11)	<0.01
Cost (€)*	337 (337–932)	511 (309–916)	<0.01

Unless otherwise specified, data are numbers of patients, with percentages in parentheses. *Data are medians, with interquartile ranges in parentheses. †Total of ExECG, SPECT, CMR, and CCTA in an outpatient setting after index ED visit. CMR = cardiac magnetic resonance imaging; ExECG = exercise electrocardiography; SPECT = *single-photon emission computed tomography* myocardial perfusion imaging. Other abbreviations as in **Table 1**.

the CCTA group died of a hemorrhagic stroke following emergency thrombolysis for occlusive peripheral artery disease 11 days after the index ED visit. Nine CCTA examinations (4%) had minor com-plications: 3 patients had self-limiting, transient increases in their creatinine levels, 4 patients experienced contrast medium extravasation without clinical consequences, and 2 had mild, medically treated allergic skin reactions. In the SOC group, 1 patient who was discharged early had a transient increase in the creatinine level at his safety visit.

DIAGNOSTIC TESTING AND RESOURCE UTILIZATION

More patients were discharged immediately from the ED after CCTA (159 [65%] vs. 144 [59%]), although this difference did not reach statistical significance (p = 0.16) (Table 3). The median length of stay was similar in both groups. ExECG was the most commonly performed alternative noninvasive diagnostic test. In the CCTA group, 32 (13%) patients underwent ExECG within 30 days: 3 (9%) were suspected of ischemia and 10 (31%) were non-diagnostic. In the SOC group, 143 (58%) patients underwent ExECG within 30 days: 9 (6%) were suspected of ischemia and 39 (27%) were non-diagnostic (supplemental table 2). Outpatient testing was less frequently performed in the CCTA group (10 [4%] vs. 26 [11%]; p < 0.01), and direct medical costs after 30 days were lower (€337 [€337 to €932] vs. €511 [€309 to €916]; p < 0.01).

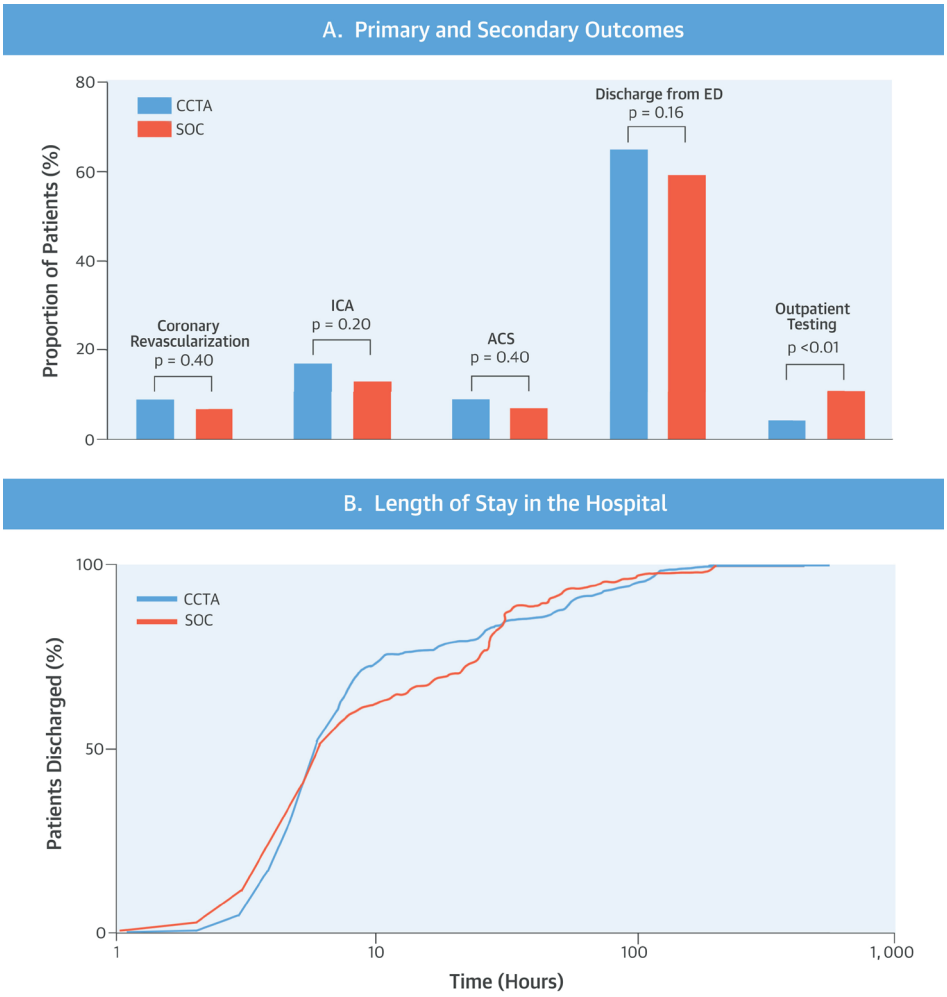

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Figure 3. Central illustration
A. Primary and secondary outcomes in the early CCTA group and SOC group.
B. Length of stay and proportion of patients discharged.
ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; ED = emergency department; ICA = invasive coronary angiography; SOC = standard optimal care.

DISCUSSION

In this prospective, open-label, multicenter, randomized trial, we compared a diagnostic strategy supplemented by early CCTA with contemporary SOC encompassing hs-troponins. In a European setting, early CCTA was safe, less expensive, with less sub-sequent outpatient testing than SOC alone. However, a diagnostic strategy supplemented

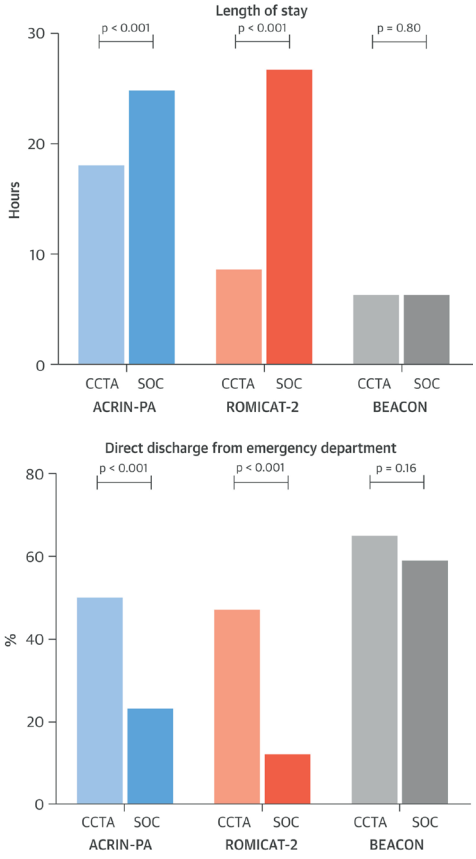

Figure 4. Length of Stay and Discharge Rate From the Emergency Department in the ACRIN-PA, ROMICAT-2, and BEACON trials
Reported data are medians. Abbreviations as in Figure 1.

by early CCTA did not identify more patients with significant CAD requiring coronary revascularization, reduce the length of stay, or allow more expedited discharge from the ED (Figure 3).

CCTA IN THE EMERGENCY DEPARTMENT

Initial observational studies showed that CCTA was feasible and could safely be performed in the ED (19,20). The ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) study, where 50% of patients with acute chest pain were free from any CAD, demonstrated high negative predictive value and underlined the potential of CCTA in this setting (6). Because CCTA identifies the presence of nonobstructive coronary atherosclerotic plaque, it also may provide the basis for preventive therapeutic medical measures, as opposed to SPECT or ExECG, which detect the presence of existing myocardial ischemia (21). In the current study, non-obstructive coronary atherosclerosis was found in 28% of patients, warranting preventive management, which would be overlooked with SOC.

Shortly after these initial studies, randomized controlled trials were initiated to examine whether a CCTA-based strategy would be more clinically effective than current practice. The CT-STAT trial compared CCTA with nuclear myocardial perfusion imaging as initial tests in the management of patients with acute chest pain (10). Investigators reported a 54% reduction in time to diagnosis and 38% lower costs of ED care with CCTA. In the ACRIN-PA (American College of Radiology Imaging Network-Pennsylvania) trial, investigators left decisions to perform diagnostic tests in the SOC group to the discretion of the treating physicians (9). The study demonstrated that low-risk patients could be safely discharged with early CCTA twice as often, and CAD was more likely to be diagnosed with CCTA. The ROMICAT-2 trial also included a cost analysis, demonstrating a reduction of the median length of hospital stay from 26.7 to 8.6 hours with early CCTA and a 4-fold higher discharge rate from the ED (47% vs. 12%) without increasing medical expenditure (8).

Since these trials were completed, the introduction of hs-troponin has changed SOC considerably. These new assays are more sensitive and reach negative predictive values of >97% for myocardial infarction within 3 h (11,12). Early observations indicated that hs-troponins would allow fast and accurate exclusion of ACS in a substantial proportion of low- to intermediate-risk patients, obviating the need for prolonged observation and in-hospital diagnostic testing in the absence of elevated high-sensitivity cardiac biomarkers or precarious ECG abnormalities (22–24).

CURRENT RESULTS IN PERSPECTIVE

The BEACON trial was designed to compare the clinical effectiveness of a diagnostic strategy supplemented by early CCTA with contemporary SOC encompassing hs-troponins. The current study included a population with a higher prevalence of obstructive CAD on CCTA (19%) compared with previous randomized trials. The majority of patients were referred by a general practitioner, deferring very low-risk patients or those with non-cardiac conditions from the ED. Furthermore, as mandated by the study protocol, only patients with acute chest pain or symptoms suggestive of an ACS warranting further diagnostic evaluation, as determined by the treating physician, were eligible for inclusion. Finally, the inclusion of patients with mildly elevated troponins probably led to an increased prevalence of CAD.

A diagnostic strategy supplemented by early CCTA was inclined to detect more patients with significant CAD requiring coronary revascularization in our study; however, this was not of statistical significance. The results of our logistic endpoints differ from previous trials, as early performance of CCTA did not shorten the length of stay, nor reduce the number of hospital admissions in our study. The length of stay with early CCTA in this study is com-parable or even lower than previously reported (Figure 4). However, the length of stay in our SOC group was substantially lower (median 6.3 hours), underlin-

ing the vigorous improvement of SOC after the introduction of hs-troponins, and also making it harder to achieve an improvement with early CCTA.

Similarly, as many as 59% of patients in the SOC group could be discharged from the ED, a proportion 2 to 4 times higher than reported in previous randomized trials with physician-directed standard care as a comparator. Differences in the Netherlands and U.S. health care systems may be responsible, to some extent, for the contrast between our observations and those from previously published studies from the United States. In the Netherlands, primary care physicians, who are easily accessible and fully covered by medical insurance, have an important gatekeeper role and can defer patients at very low risk or with probable non-cardiac etiology from the ED, which avoids overcrowding and likely increased the overall coronary disease prevalence in our population (25,26). Furthermore, coverage by Dutch insurance companies is comparable for elective and emergency care, and financial incentives that stimulate outpatient work-up and testing are in place (27,28). In the United States, delays in access to care, social differences, and insurance coverage problems in-crease the number of patients seeking care in the ED (29,30). In addition, although guidelines allow for outpatient testing in 48 to 72 hours after discharge from the ED, U.S. physicians are more inclined to achieve a conclusive work-up for the presence of CAD before discharge because of the availability of the testing, poor follow-up, and vulnerability to litigation (31–34). Testing is typically available only during working hours, leading to prolonged hospital stays. Nonetheless, we believe that the contrasting findings are largely explained by the profound effect of the introduction of hs-troponins in the work-up of suspected ACS (11,12,35).

An attractive consequence of early CCTA in our study was the reduced number of subsequent outpatient testing and lower medical costs at 30 days. Outpatient testing was mostly driven by the preference of the treating physician to assess the presence of CAD as the cause of symptoms, which was no longer necessary if CCTA had been performed at first presentation. Although direct comparison of absolute costs between studies is difficult, the shorter length of stay, more frequent use of exercise testing instead of nuclear imaging, and relatively lower cost of CCTA likely reduced general medical expenditure in this study (36). When comparing costs between the 2 groups in our study, some important aspects should be taken into account. According to the applied hospital cost-accounting system, CCTA was only slightly more expensive than ExECG. Nuclear myocardial imaging, which is substantially more costly than either CCTA or ExECG in the Netherlands, was more frequently performed in the SOC group. Finally, the higher costs in the SOC group can likely be attributed to the higher proportion of admitted patients. The median cost per patient in the SOC group was not affected by the unbalanced coronary artery bypass graft distribution.

CLINICAL IMPLICATIONS

There is growing evidence that patients with hs-troponin values below the 99th percentile of the upper reference limit have a very low likelihood of ACS. These patients have a very good prognosis and very often have a normal functional or CCTA test (37–39). However, those with levels above the 99th percentile might benefit from additional testing (i.e., CCTA or a functional test) where (especially in those with low clinical risk profile) a negative test would make the occurrence of cardiovascular events in the short term very unlikely and the need for immediate further testing unnecessary. In this light, it would be of interest for future studies to assess the value of a tiered approach, where application and timing of CCTA or test of choice is directly guided by risk profiles and biomarker results.

STUDY LIMITATIONS

The majority of patients were enrolled during office hours, and round-the-clock implementation of CCTA in the ED poses practical challenges. In real-world clinical practice, SOC might prove more efficient than CCTA for 24-hours use. Extrapolation of our results may be affected by differences in CT technology, imaging expertise, local practices, and cost-accounting systems. The overall observed incidence of the primary endpoint was lower than anticipated on the basis of experiences from our observational study. Although speculative, we believe that the exceptional sensitivity of hs-troponins, allowing early and precise detection of ACS, reduced the incidence of the primary endpoint in both groups, resulting in an underpowered sample size. Earlier troponin elevations and expedited catheterization procedures rendered a proportion of high-risk patients ineligible for study inclusion. In addition, a substantial proportion of patients (50%) with obstructive CAD on CCTA were ultimately not referred for catheterization. Without elevated troponins, these lesions were probably considered stable, which would justify optimal medical treatment on the basis of large coronary revascularization outcome trials (40). Given the low incidence of undetected ACS, this strategy does not appear to have affected safety. Inherent to the nature of diagnostic trials, blinding of patients and treating physicians was not possible, although study participants were treated by physicians who aimed for optimal clinical care, and had no direct involvement in the design and realization of this study. The effect of an early CCTA strategy on long-term downstream testing, resource utilization, and clinical outcome has yet to be determined. Although the majority of patients were evaluated with hs-troponins, 21% entered the study when these assays were not yet available at a number of centers. Finally, an important and noteworthy disadvantage of CCTA is the exposure of patients to radiation. However, use of more innovative CT technology and dose-saving protocols resulted in lower radiation exposure compared with earlier trials (7.3 vs. 14.3 mSv).

CONCLUSION

CCTA, applied early in the work-up of suspected ACS, is safe and associated with less outpatient testing and lower costs. However, in the era of hs-troponins, CCTA does not identify more patients with significant CAD requiring coronary revascularization, nor does CCTA shorten hospital stay or allow for more immediate discharge from the ED.

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SUPPLEMENTAL MATERIAL

Direct medical costs

Based on the costs of the initial ED evaluation (including fee of physician, costs of laboratory tests and ECG), proportions of diagnostic tests, costs of hospital admission, and costs of repeat ED evaluation and readmission, an estimation of costs for the two arms can be compared for other settings and prices using the following formula:

Average cost per patient in the CCTA group = [cost of initial ED evaluation] + [cost CCTA] + 0.13 * [cost XECG] + 0.01 * [cost SPECT] + 0.004 * [cost CMR] + 0.17 * [cost ICA] + 0.09 [cost PCI] + 0 * [cost CABG] + 0.05 [cost repeat ED evaluation] + 0.03 [repeat hospital admission]

Average cost per patient in the SOC group = [cost of initial ED evaluation] + 0.58 * [cost XECG] + 0.07 * [cost SPECT] + 0.01 * [cost CMR] + 0.13 * [cost ICA] + 0.05 [cost PCI] + 0.02 * [cost CABG] + 0.08 [cost repeat ED evaluation] + 0.06 [repeat hospital admission]

Supplemental Table 1. Detailed information on the troponin assays used.

Assay	N (%)	Infarction threshold (ng/L)	Management	Interm. range (ng/L)	Level of detection (ng/L)	99th percentile (ng/L)	10% Coeff. of variation (ng/L)
hs-cTnT Roche Elecsys	39 (78)	50	Serial measurement (3h interval). Value above the pre-defined threshold or a significant rise is regarded as infarction	14-50	5	14	13
TnT Gen 4 Roche Elecsys	87 (17)	30	Serial measurement (6h interval). Value above the pre-defined threshold is regarded as infarction	10-30	10	10	30
cTnI Abbott ARCHITECT	13 (3)	50	Serial measurement (6h interval). Value above the pre-defined threshold is regarded as infarction	28-50	10	28	32
hs-cTnI Abbott ARCHITECT	4 (1)	34	Serial measurement (3h interval) Value above the pre-defined threshold or a significant rise is regarded as infarction	16-34	1.2	16	3
AccuTnI Gen 3 enhanced Beckman Coulter	4 (1)	60	Serial measurement (6h interval) Value above the pre-defined threshold is regarded as infarction	40-60	10	40	60

Supplemental Table 2. Clinical care in the SOC and CCTA group.

	Standard optimal care			Coronary CT angiography				
	TIMI 0 (83)	**TIMI 1 (91)**	**TIMI ≥2 (76)**	**No CAD (106)**	**<50% (71)**	**50-70% (35)**	**>70% (13)**	**Non-diagnostic (18)**
Exercise ECG	51 (61)	47 (52)	32 (42)	4 (4)	1 (1)	11 (31)	2 (15)	5 (28)
SPECT MPI	1 (1)	5 (5)	1 (1)	0	0	0	0	2 (7)
Invasive angiography	4 (5)	4 (4)	17 (22)	0	4 (6)	13 (37)	11 (85)	6 (33)
Revascularization	1 (1)	1 (1)	10 (13)	0	0	6 (17)	11 (85)	2 (7)

Numbers of patients are shown with percentages between parentheses. Tests performed within 30 days from initial presentation. Standard optimal care (SOC) arm sub-classified by Thrombolysis In Myocardial Infarction score (TIMI) (1). Coronary CT angiography (CCTA) arm, sub-classified by most severe obstructive lesion per patient. SPECT MPI = *single-photon emission computed tomography* myocardial perfusion imaging.

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