ESC European Society of Cardiology

European Heart Journal (2018) **39**, 934–941
doi:10.1093/eurheartj/ehx774

CLINICAL RESEARCH
Coronary artery disease

Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study

Iksung Cho[1,2,3], Subhi J. Al'Aref[1], Adam Berger[4], Bríain Ó Hartaigh[1], Heidi Gransar[5], Valentina Valenti[1], Fay Y. Lin[1], Stephan Achenbach[5], Daniel S. Berman[6], Matthew J. Budoff[7], Tracy Q. Callister[8], Mouaz H. Al-Mallah[9], Filippo Cademartiri[10], Kavitha Chinnaiyan[11], Benjamin J.W. Chow[12], Augustin DeLago[13], Todd C. Villines[14], Martin Hadamitzky[15], Joerg Hausleiter[16], Jonathon Leipsic[17], Leslee J. Shaw[4], Philipp A. Kaufmann[18], Gudrun Feuchtner[19], Yong-Jin Kim[20], Erica Maffei[10], Gilbert Raff[11], Gianluca Pontone[21], Daniele Andreini[21], Hugo Marques[22], Ronen Rubinshtein[23], Hyuk-Jae Chang[2], and James K. Min[1]*

[1]Department of Radiology, Dalio Institute of Cardiovascular Imaging, NewYork-Presbyterian Hospital, Weill Cornell Medical College, 413 East 69th Street, Suite 108, New York, NY 10021, USA; [2]Division of Cardiology, Severance Cardiovascular Hospital, Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [3]Division of Cardiology, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University, Seoul, South Korea; [4]Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA; [5]Department of Imaging, Cedars Sinai Medical Center, Los Angeles, CA, USA; [6]Department of Medicine, University of Erlangen, Erlangen, Germany; [7]Department of Medicine, Harbor UCLA Medical Center, Los Angeles, CA, USA; [8]Tennessee Heart and Vascular Institute, Hendersonville, TN, USA; [9]King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King AbdulAziz Cardiac Center, Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia; [10]Department of Radiology, Montreal Heart Institute, Montreal, Quebec, Canada; [11]William Beaumont Hospital, Royal Oaks, MI, USA; [12]Department of Medicine and Radiology, University of Ottawa, Ottawa, Ontario, Canada; [13]Capitol Cardiology Associates, Albany, NY, USA; [14]Department of Medicine, Walter Reed Medical Center, Washington, DC, USA; [15]Division of Cardiology, Deutsches Herzzentrum Munchen, Munich, Germany; [16]Medizinische Klinik I der Ludwig-Maximilians-Universität München, Munich, Germany; [17]Department of Medicine and Radiology, University of British Columbia, Vancouver, British Columbia, Canada; [18]University Hospital, Zurich, Switzerland; [19]Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria; [20]Seoul National University Hospital, Seoul, South Korea; [21]Department of Clinical Sciences and Community Health, University of Milan, Centro Cardiologico Monzino, IRCCS Milan, Milan, Italy; [22]UNICA, Cardiac CT and MRI Unit, Hospital da Luz, Lisbon, Portugal; and [23]Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Received 15 November 2016; revised 14 September 2017; editorial decision 14 December 2017; accepted 18 December 2017; online publish-ahead-of-print 20 January 2018

See page 942 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx801)

Aim The long-term prognostic benefit of coronary computed tomographic angiography (CCTA) findings of coronary artery disease (CAD) in asymptomatic populations is unknown.

Methods and results From the prospective multicentre international CONFIRM long-term study, we evaluated asymptomatic subjects without known CAD who underwent both coronary artery calcium scoring (CACS) and CCTA ($n = 1226$). Coronary computed tomographic angiography findings included the severity of coronary artery stenosis, plaque composition, and coronary segment location. Using the C-statistic and likelihood ratio tests, we evaluated the incremental prognostic utility of CCTA findings over a base model that included a panel of traditional risk factors (RFs) as well as CACS to predict long-term all-cause mortality. During a mean follow-up of 5.9 ± 1.2 years,

* Corresponding author. Tel: +1 646 962 6192, Fax: +1 646 962 0129, Email: jkm2001@med.cornell.edu

78 deaths occurred. Compared with the traditional RF alone (C-statistic 0.64), CCTA findings including coronary stenosis severity, plaque composition, and coronary segment location demonstrated improved incremental prognostic utility beyond traditional RF alone (C-statistics range 0.71–0.73, all $P < 0.05$; incremental χ^2 range 20.7–25.5, all $P < 0.001$). However, no added prognostic benefit was offered by CCTA findings when added to a base model containing both traditional RF and CACS (C-statistics $P > 0.05$, for all).

Conclusions Coronary computed tomographic angiography improved prognostication of 6-year all-cause mortality beyond a set of conventional RF alone, although, no further incremental value was offered by CCTA when CCTA findings were added to a model incorporating RF and CACS.

Keywords Coronary artery calcium scoring • Coronary CT angiography • Prognosis • Coronary artery disease • Computed tomography • Atherosclerosis

Introduction

In asymptomatic individuals, coronary athero-phenotyping using imaging modalities such as coronary artery calcium scoring (CACS) has been widely used and numerous studies have documented that CACS provides powerful prognostic information across various age groups, gender, baseline risk factors (RFs), and ethnicities.[1–3]

Considering coronary computed tomographic angiography (CCTA) could provide more detailed coronary atherosclerotic information [i.e. degree of luminal stenosis, plaque composition, and location of coronary segment location including non-calcified plaques (NCPs)], it has been proposed that CCTA might afford additional prognostic benefit over CACS, as well as traditional risk stratification system in asymptomatic populations. Despite this, recent data from a large multicentre international registry revealed that CCTA has negligible benefit for cardiovascular risk stratification in asymptomatic populations.[4] Yet, given the relatively short-term follow-up duration of the latter study, along with the lack of CCTA information such as plaque composition and plaque location, it remains to be clarified whether CCTA adds further prognostic value beyond CACS and traditional RFs, especially when considering more sophisticated plaque and degree of stenosis information across a more long-term follow-up study.

In light of the preceding discussion, we sought to evaluate whether comprehensive assessment of coronary atherosclerosis by CCTA that included degree of stenosis, plaque composition, and coronary segment location, would stratify future risk of all-cause mortality of asymptomatic individuals, and second, whether the addition of the aforementioned CCTA measures augmented prognostication of all-cause death beyond a set of traditional RF and CACS.

Methods

Design overview, setting, and participants

We previously described the initial study design and rationale of the initial CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry elsewhere.[5] In brief, the CONFIRM registry was designed to assess the capability of CCTA findings to predict all-cause mortality in patients referred for CCTA. Foremost, study follow-up has been extended and the CONFIRM long term follow-up registry completed, which included study sites that prolonged their follow-up duration of more than 3 years. Thus, overall, 17 181 patients who underwent CCTA at 17 centres in nine countries (e.g. Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and USA) were enrolled between February 2003 and May 2011 as part of the long-term follow-up registry. Inclusion criteria were age 18 years or older, an evaluation by CCTA scanner with 64-detector rows or greater, and the presence of interpretable CCTA. For the current study, we excluded patients according to the following exclusion criteria: the presence of chest pain or dyspnoea ($n = 13\,590$), the absence of CACS data ($n = 2133$) or CCTA stenosis information ($n = 6$), the absence of age or gender information ($n = 1$), or individuals with revascularization within index period from CCTA (< 90 days) or prior history of CAD ($n = 225$). Eleven patients with missing baseline Framingham risk scores (FRS) were analysed for baseline characteristics but not included in the predictive analysis. Hence, the analytic sample comprised 1226 subjects. All study participants provided written informed consent and each of the study sites' institutional review boards approved the study protocol.

Clinical data collection

Prior to scanning procedures, we prospectively collected information regarding the presence of traditional cardiac RFs in each study participant. We employed standardized data collection methods in each participating study site.[6] Systemic arterial hypertension was defined as a documented history of high blood pressure or treatment with anti-hypertensive medications. Diabetes mellitus was defined as known untreated diabetes and/or use of insulin or oral hypoglycaemic agents. We defined dyslipidaemia as known but untreated dyslipidaemia or current treatment with lipid-lowering medications. A positive current smoking history was defined as current smoking or cessation of smoking within 3 months of investigation. Family history of coronary artery disease (CAD) was determined by patient query. Symptom presentation was classified into asymptomatic and symptomatic and symptomatic individuals were further classified into typical chest pain, atypical chest pain, non-cardiac pain, or dyspnoea. From these data, we calculated FRS based on the calculation method by National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATP III).[7]

Image acquisition and analysis

Coronary computed tomographic angiography and CACS measures were uniformly acquired using multi-detector row computed tomography (CT) scanners consisting of 64-rows or greater. Coronary artery calcium scoring were measured using the scoring system (in units) developed by Agatston *et al.*,[8] and participants were categorized in 0, 1–100, 101–400, and >400. In the analysis, the absolute CACS was

incorporated on top of traditional RFs utilized in the calculation of the FRS category, in order to be consistent with previously developed predictive models that use absolute clinical variables values in a model that already incorporates age and gender as separate variables.

For CCTA, we examined all identified coronary lesions by maximum-intensity-projection and multiplanar reconstruction methods along multiple longitudinal axes and in the transverse plane. We utilized a modified American Heart Association (AHA) 16-segment coronary artery model for analyses.[9] We defined the coronary plaque as any tissue structures larger than 1 mm^2, which were identified in two more planes and located either within the lumen of the coronary artery or adjacent to the coronary artery lumen that were able to be distinguished from adjacent epicardial fat, pericardial tissue, or the artery lumen. In each coronary artery segment, we visually classified plaques as non-calcified, mixed, or calcified. The presence of coronary calcification was determined visually in the contrast-enhanced dataset and calcified plaque was defined as a coronary plaque only containing calcification. Non-calcified plaque was defined as a coronary plaque with a density below the contrast-enhanced blood pool without calcification component. Coronary plaques showing both calcified areas of any extent and NCP were classified as mixed plaques. Further classification of NCP into lipid-rich or fibrous tissue was not undertaken due to limited accuracy and reproducibility of such a measurement with the generation of CT scans used during the enrolment period and the dependability of such a measurement on technical aspects such as the concentration of intraluminal contrast.

We defined coronary artery luminal stenosis as the presence of any plaque resulting in diameter reduction. We categorized coronary artery luminal stenosis: non-obstructive stenosis was defined as coronary artery segments displaying plaque with a luminal diameter stenosis 1–49%. Obstructive stenosis was defined as coronary artery plaques imparting luminal diameter stenosis ≥50%. We defined coronary segment location according to Society of Cardiovascular Computed Tomography (SCCT) guidelines.[10] The total mean dose length product for CCTA and coronary artery calcium scans was 598 ± 324 mGy × cm.

Statistical analysis

Continuous and categorical variables are expressed as mean ± standard deviation and absolute counts with percentages, respectively. Differences between continuous and categorical variables were analysed by the Student's *t*-test and the χ^2 test, or the Fisher's exact test, as appropriate. The primary endpoint of this study was all-cause mortality. Cumulative event rates as a function of time and CACS or CCTA parameters were calculated by use of the Kaplan–Meier survival estimates and compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) for the association of CACS and the various measures of CCTA with all-cause mortality were calculated by use of unadjusted and adjusted Cox proportional hazard regression models. In this study, the adjusted model controlled for covariates employed for the FRS.

Next, we assessed the incremental benefit of CACS and CCTA for improving prognostic utility by evaluating the statistical significance of the contribution of each added variable by use of the likelihood ratio test[11] and model discrimination with calculation of C-statistics.[12,13] Initially, a base model according to traditional RF only was employed, and included categories of the published FRS: low (<10%), intermediate (10–20%), and high (>20%). Subsequently, CACS, expressed as four categories (e.g. 0, 1–100, 101–400, >400), was added to determine its predictive value beyond the traditional RF. Last, we added the following CCTA diagnosed parameters to the model that included traditional RF model and both CACS and FRS model: (i) coronary luminal stenosis severity assessment models including number of segments with any stenosis (e.g. none, one, and ≥two segments), number of segments with obstructive (≥50%) stenosis (e.g. none, one, and ≥two segments), number of obstructive (≥50% stenosis) vessel disease [e.g. none, non-obstructive, obstructive one-vessel disease (VD), obstructive two-VD, and obstructive three-VD or left main disease]; (ii) coronary plaque composition assessment models including number of segments with non-calcified or mixed plaques (e.g. none, one, and ≥two segments), number of segments with calcified plaques (e.g. none, one, and ≥two segments); and (iii) coronary luminal stenosis location assessment models including number of proximal segments with any stenosis (e.g. none, one, and ≥two segments), number of proximal segments with obstructive stenosis (e.g. none, one, and ≥two segments). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA), and a statistical value of *P*-value <0.05 was considered significant.

Results

Baseline characteristics

Overall, the study population consisted of 1226 asymptomatic subjects: mean age was 58 ± 12 years and 66% were male. As reported in *Table 1*, among the study population, 639 (52%) subjects had coronary artery luminal stenosis and 587 (48%) subjects had no coronary atherosclerosis by CCTA. Patients with any coronary atherosclerosis tended to be older, male, and had a higher prevalence of hypertension, diabetes, current smokers, dyslipidaemia, and a higher body mass index (all $P < 0.01$).

Clinical outcomes and risk prediction models of FRS and coronary artery calcium scoring

During a mean follow-up of 5.9 ± 1.2 years, 78 deaths occurred. In Cox regression analysis, compared with individuals with low risk (FRS <10%), individuals with intermediate risk (FRS 10–20%) had an increased risk of all-cause death (HR 2.05, 95% CI 1.19–3.51; $P = 0.009$). As described in *Table 2*, individuals with high risk (FRS >20%) had a more pronounced risk of all-cause death (HR 3.87, 95% CI 2.21–6.78; $P < 0.001$). Increasing categories of CACS was also associated with a higher risk of mortality. That is, when compared with individuals with CACS 0, those with CACS 1–100 (HR 3.68, 95% CI 1.92–7.05; $P < 0.001$), CACS 101–400 (HR 3.04, 95% CI 1.45–6.40; $P < 0.003$), and CACS >400 (HR 7.88, 95% CI 4.19–14.83; $P < 0.001$) had a higher risk of death.

Risk prediction models of coronary computed tomographic angiography

The risk of death was classified using the degree and extent of luminal stenosis by CCTA with unadjusted and adjusted for traditional RF (*Figure 1*). Individuals with any stenosis in one segment had a 3.9-fold (95% CI 1.84–8.28; $P < 0.001$) higher risk of death, and those with stenosis in ≥two segments had 4.1-fold (95% CI 2.14–7.76; $P < 0.001$) higher risk of death than those without luminal stenosis after adjustment of traditional RF. In addition, the number of segments with obstructive luminal stenosis strongly predicted risk of death. Notably, individuals with one segment and more than two segments with obstructive stenosis experienced a 2.6-fold (95% CI 1.39–4.87; $P = 0.003$) and 3.5-fold (95% CI 1.95–6.32; $P < 0.001$) higher risk of death, respectively. Further, compared with individuals without

Table 1 Baseline characteristics according to presence or absence of coronary artery luminal stenosis by coronary computed tomographic angiography

Variables	Total (*n* = 1226)	No stenosis (*n* = 587)	Any stenosis (*n* = 639)	*P*-value
Age (years)	58.0 ± 12.4	53.1 ± 12.0	62.6 ± 10.8	<0.001
Gender (male)	813 (66.3)	339 (57.8)	474 (74.2)	<0.001
Hypertension	709 (58.3)	276 (47.4)	433 (68.3)	<0.001
Diabetes	123 (10.1)	42 (7.2)	81 (12.8)	0.001
Current smoking	196 (16.1)	78 (13.4)	118 (18.6)	0.010
BMI (kg/m^2)	26.8 ± 4.6	26.4 ± 4.5	27.3 ± 4.6	<0.001
Dyslipidaemia	674 (55.3)	240 (41.2)	434 (68.1)	<0.001
Aspirin use (%)	344 (31.7)	101 (19.8)	243 (42.3)	<0.001
Beta-blocker use (%)	290 (26.8)	143 (28.1)	147 (25.6)	0.357
Statin use (%)	376 (34.4)	94 (18.3)	282 (48.6)	<0.001

Continuous values are mean + SD and categorical values are number and percentage (%).
BMI, body mass index.

Table 2 Risk of all-cause mortality according to Framingham risk score and coronary artery calcium score categories

Model	No. of deaths/ subjects	HR (95% CI)	*P*-value
Framingham risk score			
Low (<10%)	26/681	1.00	NA
Intermediate (10–20%)	27/363	2.05 (1.19–3.51)	0.009
High (>20%)	25/171	3.87 (2.21–6.78)	<0.001
CACS			
0	15/602	1.00	NA
1–100	23/276	3.68 (1.92–7.05)	<0.001
101–400	13/188	3.04 (1.45–6.40)	0.003
>400	27/160	7.88 (4.19–14.83)	<0.001

CACS, coronary artery calcium scoring; CI, confidence interval; HR, hazard ratio; NA, not applicable.

luminal stenosis, the adjusted hazards for all-cause death increased proportionally on the background of CAD extent for any non-obstructive (1–49% stenosis) stenosis (HR 3.16; 95% CI 1.64–6.12; $P < 0.001$), obstructive (≥50% stenosis) one-vessel stenosis (HR 5.78, 95% CI 2.73–12.23; $P < 0.001$), obstructive two-vessel stenosis (HR 6.65, 95% CI 2.31–19.16; $P < 0.001$), and obstructive three-vessel stenosis or left main stenosis (HR 8.48, 95% CI 3.28–21.92; $P < 0.001$).

Moreover, coronary plaque composition assessment models including the presence of non-calcified or mixed plaque, as well as calcified plaque, heightened the risk of all-cause death in both unadjusted and adjusted models. For instance, the presence of non-calcified or mixed plaque in a single segment (HR 2.34, 95% CI 1.23–4.48; $P = 0.010$) and multi-segments (HR 2.50, 95% CI 1.48–4.21; $P = 0.001$) were shown to increase the risk of all-cause death as compared with individuals without any plaque, even after adjustment of traditional RF. Further, the presence of calcified plaque in multiple segments increased risk of death after adjustment of baseline RFs (HR 2.21, 95% CI 1.32–3.69; $P = 0.003$).

Incremental value of coronary computed tomographic angiography for prediction of all-cause death

As reported in *Table 3*, adding CACS over a traditional risk stratification model that used FRS significantly improved prediction of all-cause mortality (e.g. incremental χ^2 20.4, $P < 0.001$). Inclusion of CCTA information including the degree of luminal stenosis and plaque composition also improved prediction of all-cause death beyond the traditional RF model (all, *P* for incremental χ^2 <0.001). However, compared with the model that included both traditional RF and CACS, addition of CCTA information did not lead to a significant increase in prediction for all-cause mortality (all $P > 0.05$), with the exception of number of vessels with stenosis ≥50% (χ^2 9.69, $P = 0.046$), which provided only a modest significant increase.

The incremental benefit of CCTA was also evaluated using the C-statistic as described in *Table 4*. The added benefit of CCTA information including degree of luminal stenosis and plaque composition was significant when compared with the traditional RF model. However, no incremental benefit of any of the CCTA variables over traditional RFs and CACS (all $P > 0.05$) for prognostication was observed.

Discussion

In this international multi-centre study with long-term follow-up duration, we set out to determine whether comprehensive CAD assessment by CCTA improved risk prediction for future mortality over a traditional RF model and also when CACS was considered in asymptomatic population. The principle finding was that the incremental risk-predictive benefit of comprehensive CAD information by CCTA, including degree and extent of plaque, coronary segment location, and plaque composition, over traditional RFs and CACS model was negligible in asymptomatic population across a long-term follow-up. Such a finding is in agreement with the 2013 European

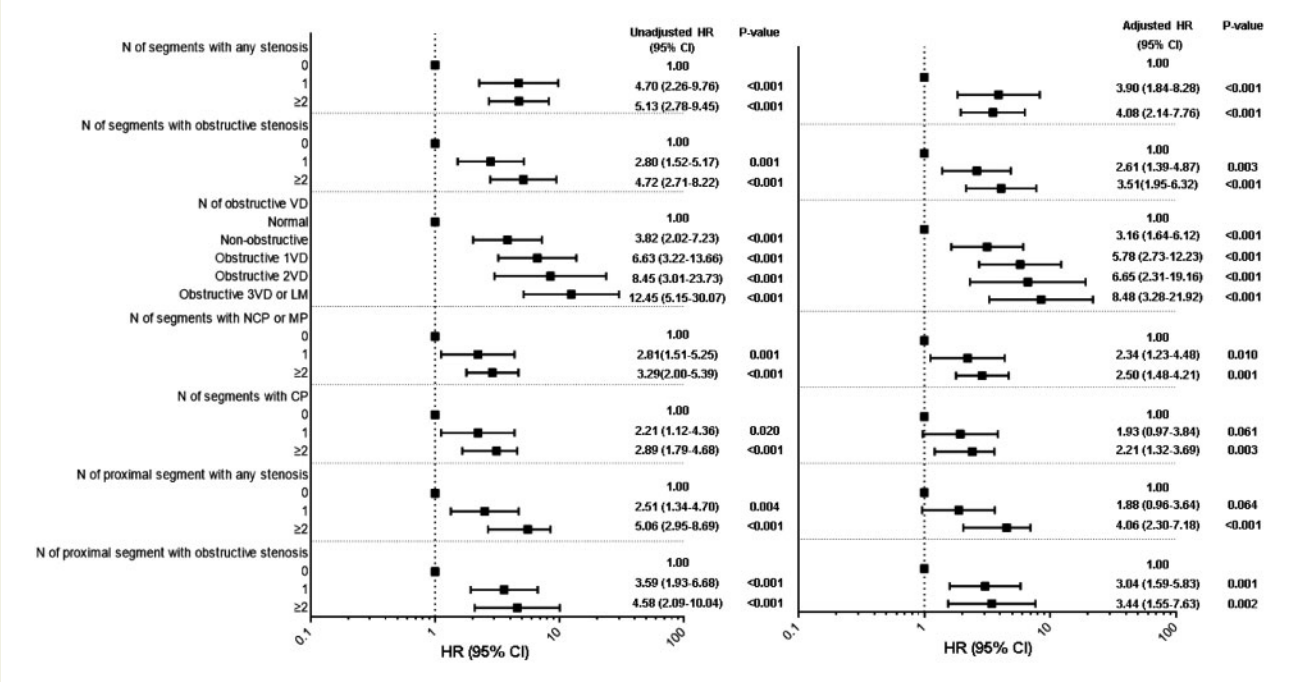

Figure 1 Risk of all-cause mortality according coronary computed tomographic angiography findings using unadjusted model and adjusted models for traditional risk factors. CI, confidence interval; CP, calcified plaque; HR, hazard ratio; N, number; NCP, non calcified plaque; MP, mixed plaque; VD, vessel disease.

Table 3 Comparison of performance of coronary computed tomographic angiography over traditional risk factors alone and traditional risk factor plus coronary artery calcium scoring in predicting long-term risk of all-cause mortality using likelihood ratio tests

Models	LR incremental χ^2			
	Compared with traditional RF alone	*P*-value	Compared with CACS + traditional RF	*P*-value
Baseline models				
Traditional RF	NA	NA	NA	NA
Traditional RF + CACS	20.40	<0.001	NA	NA
Adding degree of stenosis Information by CCTA				
No. of segments with any stenosis	26.05	<0.001	5.65	0.059
No. of segments with stenosis ≥50%	25.43	<0.001	5.03	0.080
No. of vessels with stenosis ≥50%	30.09	<0.001	9.69	0.046
Adding plaque characterization Information by CCTA				
No. of segments with calcified plaques	20.70	<0.001	0.30	0.860
No. of segments with NCP or mixed plaque	23.26	<0.001	2.86	0.240
Adding plaque location information by CCTA				
No. of proximal segment with any stenosis	25.52	<0.001	5.12	0.080
No. of proximal segment with stenosis ≥50%	25.50	<0.001	5.10	0.080

CACS, coronary artery calcium scoring; CCTA, coronary CT angiography; LR, likelihood ratio; NCP, non-calcified plaque; NA, not applicable; RF, risk factors (covariates in the Framingham risk score such as age, gender, smoking status, total cholesterol, high-density lipoprotein cholesterol, blood pressure and treatment for hypertension).

Table 4 C-Statistics for evaluation of added benefit of coronary computed tomographic angiography findings over traditional risk factors alone and combined model of traditional risk factors plus coronary artery calcium scoring in predicting long-term all-cause mortality

Model	C-statistics	*P* compared with traditional RF	*P* compared with traditional RF + CACS
Baseline models			
Traditional RF	0.641	NA	NA
Traditional RF + CACS	0.711	0.030	NA
Adding degree of stenosis Information by CCTA			
No. of segments with any stenosis	0.723	0.009	0.305
No. of segments with stenosis ≥50%	0.728	0.013	0.075
No. of vessels with stenosis ≥50%	0.734	0.008	0.117
Adding plaque characterization Information by CCTA			
No. of segments with calcified plaques	0.709	0.033	0.597
n of segments with NCP or mixed plaque	0.721	0.013	0.286
Adding plaque location information by CCTA			
No. of proximal segment with any stenosis	0.727	0.012	0.071
No. of proximal segment with stenosis≥50%	0.724	0.015	0.117

CACS, coronary artery calcium scoring; CCTA, coronary CT angiography; NCP, non-calcified plaque; NA, not applicable; RF, risk factors (detailed in footnote of *Table 3*).

guidelines on the management of stable CAD and the 2016 European guidelines on Cardiovascular Disease Prevention in Clinical Practice, which give CACS a Class IIb label (level of evidence B) for use as a risk modifier in the assessment of cardiovascular risk and a Class III label (level of evidence C) for CCTA for use as a screening test in asymptomatic individuals.[14,15]

We previously demonstrated that CCTA afforded little to no benefit for prediction of fatal outcomes over a traditional RF and CACS model in an asymptomatic population across a short-term follow-up duration.[4] Since, several studies have analysed the prognostic benefit of CCTA in other asymptomatic populations.[16,17] Rodriguez *et al.*[18] demonstrated that diabetes, cholesterol level, and systolic blood pressure were related to NCP burden by CCTA, which cannot be distinguished by CACS, in an asymptomatic population at low-to-moderate risk. Lee *et al.*[16] also reported that CCTA offered added prognostic benefit over exercise testing in another asymptomatic population. More recently, Plank *et al.*[17] reported that high prevalence of CAD in a high-risk asymptomatic population and CACS = 0 did not exclude significant non-calcified coronary atherosclerosis. However, none of these studied observed that CCTA provided incremental benefit above and beyond traditional RF and CACS in an asymptomatic population. Further, a recent prospective randomized trial reinforced the lack of evidence of CAD screening by CCTA in asymptotic populations.[19] In that trial, although the study sample represented an asymptomatic diabetic population considered being at high risk, a CAD screening strategy by CCTA failed to lower fatal and non-fatal outcomes.

The chief cause why CCTA appeared to lack additional prognostic utility over the base model that included CACS, most likely owes to the contention that CACS is a robust marker of global coronary atherosclerotic burden. Although recent studies using CCTA demonstrated that patients with high-risk features such as NCP or positive remodelling experienced higher incidence of acute coronary syndrome, the total atherosclerotic plaque burden was not accounted for as a confounder.[20] Further, these studies enrolled symptomatic cohorts while there has been no evidence to suggest that high-risk plaque features were prognostically important in asymptomatic population. The current study suggests that the added benefit of assessing plaque composition and location over total atherosclerotic burden detected by CACS was not clinically beneficial in asymptomatic individuals.

Indeed, CACS is well known to provide superior discrimination and reclassification beyond other useful markers, such as carotid intima-media thickness, brachial flow-mediated dilation, ankle-brachial index, or C-reactive protein.[21] Further still, the prognostic benefit of CACS has been validated in numerous large-scale prospective multicentre studies utilizing several heterogeneous populations who were followed long-term.[1–3] Recently, a novel risk equation system for predicting 10-year CAD, which integrated traditional RFs and CACS, has been developed using data belonging to the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.[22] The purpose of this convenient scoring system is to facilitate the integrated use of CACS with traditional RF in clinical practice.

However, a major limitation of CACS is the lack of data for management or down-stream testing strategies according to CACS.[23] Although it is quite clear that a zero CACS warrantied very good prognosis in a long-term follow-up duration,[24] there is no consensus of treatment or downstream screening strategies for patients with CACS >0. More recently, we established that CCTA might induce some benefit over traditional RFs and CACS, specifically in those with intermediate CACS (i.e. between 100 and 400).[25] Most correctly reclassified subjects by CCTA were those with a non-event (e.g. 0.70 vs. 0.05 for non-event vs. event, respectively). To this end, CCTA should perhaps be considered for downstream study, particularly in patients presenting with intermediate CACS, in order to reclassify those with low risk for the purpose of avoiding unnecessary treatment or clinical decisions. Though clearly, forthcoming studies

are needed to test this notion. Furthermore, plaque characterization and quantification on CCTA, beyond obtaining a CACS, may become useful for determination of plaque progression or regression, which could ultimately influence clinical decision.[26]

This study had some limitations that bear mentioning. Our study sample were representative of a subgroup derived from the CONFIRM long-term follow-up registry who were referred for CCTA. As such, our patients do not truly reflect those in the general population, which might have led to potential selection bias. Though we may add, in order to minimize any potential for selection bias, we only employed experienced CCTA centres and prospectively used standardized data definitions. Although this study is considered to be the largest global multicentre CCTA registry to date, we cannot discount the possibility that the absence in incremental prognostic benefit associated with our CCTA measures might have been attributable to a small sample size, and consequently, low statistical power. Nevertheless, given the potential risk of radiation and intravenous contrast use, careful consideration of potential risks and benefits of the clinical investigation must be undertaken to perform prospective randomized studies to fully address these questions.

Inherent limitations of the CONFIRM study were such that baseline medication use was solely available without the recorded changes in medication intake after CCTA acquisition. Future studies investigating the impact of medication adjustment (e.g. aspirin, statin, and beta-blockers) on outcomes should be performed. Secondly, the FRS was used as the traditional RF assessment tool over contemporary and better-calibrated risk scores such as the ESC HEART SCORE, given the ability to compute such as score within the available clinical variables. Thirdly, the clinical endpoint examined was all-cause mortality, since major adverse cardiovascular events were not available for the entire cohort. Finally, there was no downstream functional testing performed in heavily calcified lesions when the degree of stenosis was questionable, which could have lead to misdiagnosis of luminal stenosis severity due to blooming and beam hardening artifacts. Previous studies have circumvented this issue through both anatomic and functional testing by integrating CT myocardial perfusion and fractional flow reserve -CT with CCTA.[27]

Conclusion

While CCTA demonstrated improved prognostic utility for prediction of long-term mortality over traditional RF alone, CCTA findings did not augment prognostication beyond traditional RFs when CACS was also taken into consideration. Until further proven, the clinical utility of CCTA should not be considered for future cardiovascular risk stratification in asymptomatic individuals.

Funding

This work is supported by the National Heart, Lung and Blood Institute under award number (R01HL115150 and R01HL118019) and also in part by a generous gift from the Dalio Institute of Cardiovascular Imaging (New York, NY) and the Michael Wolk Foundation. This study was also funded by an unrestricted educational grant from GE Healthcare.

Conflict of interest: J.K.M. serves on the scientific advisory board of Arineta, has ownership in MDDX, and has a research agreement with GE healthcare. All other authors have no disclosures to report.

References

1. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;**358**:1336–1345.
2. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25, 253 patients. *J Am Coll Cardiol* 2007;**49**:1860–1870.
3. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Grönemeyer D, Seibel R, Kälsch H, Bröcker-Preuss M, Mann K, Siegrist J, Jöckel K-H; Heinz Nixdorf Recall Study Investigative Group. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol* 2010;**56**:1397–1406.
4. Cho I, Chang HJ, Sung JM, Pencina MJ, Lin FY, Dunning AM, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Callister TQ, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Maffei E, Cademartiri F, Kaufmann P, Shaw LJ, Raff GL, Chinnaiyan KM, Villines TC, Cheng V, Nasir K, Gomez M, Min JK; SCOT-HEART Investigators. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). *Circulation* 2012;**126**: 304–313.
5. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah MH, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan KM, Chow B, Delago A, Hadamitzky M, Hausleiter J, Karlsberg RP, Kaufmann P, Maffei E, Nasir K, Pencina MJ, Raff GL, Shaw LJ, Villines TC. Rationale and design of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) Registry. *J Cardiovasc Comput Tomogr* 2011;**5**:84–92.
6. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines T, Berman DS; CONFIRM Investigators. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23, 854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;**58**:849–860.
7. Cleeman JI, Grundy SM, Becker D, Clark LT, Cooper RS, Denke MA, Howard WJ, Hunninghake DB, Illingworth DR, Luepker RV, McBride P, McKenney JM, Pasternak RC, Stone NJ, Van Horn L, Brewer HB, Ernst ND, Gordon D, Levy D, Rifkind B, Rossouw JE, Savage P, Haffner SM, Orloff DG, Proschan MA, Schwartz JS, Sempos CT, Shero ST, Murray EZ; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–2497.
8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;**15**:827–832.
9. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;**51**:5–40.
10. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, Cheng V, DeFrance T, Hellinger JC, Karlsberg RP; Society of Cardiovascular Computed Tomography. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr* 2009;**3**: 122–136.
11. Vickers A, Cronin A, Begg C. One statistical test is sufficient for assessing new predictive markers. *BMC Med Res Methodol* 2011;**11**:13.
12. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004;**23**:2109–2123.
13. Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. *Clin Chem Lab Med* 2010;**48**:1703–1711.
14. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the

special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
15. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di MC, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der WEE, Vrints CJ, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**: 2949–3003.
16. Lee S-E, Cho I, Hong G-R, Chang H-J, Sung JM, Cho I-J, Shim CY, Choi BW, Chung N. Differential prognostic value of coronary computed tomography angiography in relation to exercise electrocardiography in asymptomatic subjects. *J Cardiovasc Ultrasound* 2015;**23**:244–252.
17. Plank F, Friedrich G, Dichtl W, Klauser A, Jaschke W, Franz W-M, Feuchtner G. The diagnostic and prognostic value of coronary CT angiography in asymptomatic high-risk patients: a cohort study. *Open Heart* 2014;**1**:e000096.
18. Rodriguez K, Kwan AC, Lai S, Lima JAC, Vigneault D, Sandfort V, Pattanayak P, Ahlman MA, Mallek M, Sibley CT, Bluemke DA. Coronary plaque burden at coronary CT angiography in asymptomatic men and women. *Radiology* 2015;**277**: 73–80.
19. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, Bluemke DA, Towner SR, Le V, Bair TL, Vavere AL, Anderson JL. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA* 2014;**312**:2234–2243.
20. Arbab-Zadeh A, Fuster V. The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J Am Coll Cardiol* 2015;**65**:846–855.
21. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;**308**:788–795.
22. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, Folsom AR, Khera A, Ayers C, Mahabadi AA, Lehmann N, Jockel KH, Moebus S, Carr JJ, Erbel R, Burke GL. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). *J Am Coll Cardiol* 2015;**66**:1643–1653.
23. Andersson C, Vasan RS. Is there a role for coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease?: Clinical risk scores are sufficient to define primary prevention treatment strategies among asymptomatic patients. *Circ Cardiovasc Imaging* 2014;**7**:390–397; discussion 397.
24. Valenti V, Ó Hartaigh B, Heo R, Cho I, Schulman-Marcus J, Gransar H, Truong QA, Shaw LJ, Knapper J, Kelkar AA, Sandesara P, Lin FY, Sciarretta S, Chang HJ, Callister TQ, Min JK. A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9, 715 individuals. *JACC Cardiovasc Imaging* 2015;**8**:900–909.
25. Cho I, Chang HJ, Ó Hartaigh B, Shin S, Sung JM, Lin FY, Achenbach S, Heo R, Berman DS, Budoff MJ, Callister TQ, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJ, Dunning AM, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Leipsic J, Shaw LJ, Kaufmann PA, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Min JK. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) study. *Eur Heart J* 2015;**36**:501–508.
26. Lee SE, Chang HJ, Rizvi A, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, Volpato V, Budoff MJ, Gottlieb I, Lee BK, Chun EJ, Cademartiri F, Maffei E, Marques H, Leipsic JA, Shin S, Choi JH, Chung N, Min JK. Rationale and design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: a comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. *Am Heart J* 2016;**182**:72–79.
27. Coenen A, Rossi A, Lubbers MM, Kurata A, Kono AK, Chelu RG, Segreto S, Dijkshoorn ML, Wragg A, van Geuns RM, Pugliese F, Nieman K. Integrating CT myocardial perfusion and CT-FFR in the work-up of coronary artery disease. *JACC Cardiovasc Imag* 2017;**10**:760–770.