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Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals

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ABSTRACT

Background: Coronary artery disease (CAD) diagnosis by coronary computed tomographic angiography (CCTA) is useful for identification of symptomatic diabetic individuals at heightened risk for death. Whether CCTA-detected CAD enables improved risk assessment of asymptomatic diabetic individuals beyond clinical risk factors and coronary artery calcium scoring (CACS) remains unexplored.
Methods: From a prospective 12-center international registry of 27,125 individuals undergoing CCTA, we identified 400 asymptomatic diabetic individuals without known CAD. Coronary stenosis by CCTA was graded as 0%, 1–49%, 50–69%, and ≥70%. CAD was judged on a per-patient, per-vessel and per-segment basis as maximal stenosis severity, number of vessels with ≥50% stenosis, and coronary segments weighted for stenosis severity (segment stenosis score), respectively. We assessed major adverse cardiovascular events (MACE) – inclusive of mortality, nonfatal myocardial infarction (MI), and late target vessel revascularization ≥90 days (REV) – and evaluated the incremental utility of CCTA for risk prediction, discrimination and reclassification.

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Results: Mean age was 60.4 ± 9.9 years; 65.0% were male. At a mean follow-up 2.4 ± 1.1 years, 33 MACE occurred (13 deaths, 8 MI, 12 REV) [8.25%; annualized rate 3.4%]. By univariate analysis, per-patient maximal stenosis [hazards ratio (HR) 2.24 per stenosis grade, 95% confidence interval (CI) 1.61–3.10, $p < 0.001$], increasing numbers of obstructive vessels (HR 2.30 per vessel, 95% CI 1.75–3.03, $p < 0.001$) and segment stenosis score (HR 1.14 per segment, 95% CI 1.09–1.19, $p < 0.001$) were associated with increased MACE. After adjustment for CAD risk factors and CACS, maximal stenosis (HR 1.80 per grade, 95% CI 1.18–2.75, $p = 0.006$), number of obstructive vessels (HR 1.85 per vessel, 95% CI 1.29–2.65, $p < 0.001$) and segment stenosis score (HR 1.11 per segment, 95% CI 1.05–1.18, $p < 0.001$) were associated with increased risk of MACE. Beyond age, gender and CACS (C-index 0.64), CCTA improved discrimination by maximal stenosis, number of obstructive vessels and segment stenosis score (C-index 0.77, 0.77 and 0.78, respectively). Similarly, CCTA findings improved risk reclassification by per-patient maximal stenosis [integrated discrimination improvement (IDI) index 0.03, $p = 0.03$] and number of obstructive vessels (IDI index 0.06, $p = 0.002$), and by trend for segment stenosis score (IDI 0.03, $p = 0.06$).
Conclusion: For asymptomatic diabetic individuals, CCTA measures of CAD severity confer incremental risk prediction, discrimination and reclassification on a per-patient, per-vessel and per-segment basis.

1. Introduction

The prevalence of diabetes mellitus is rapidly increasing worldwide, with a projected prevalence of more than 350 million individuals by 2030 [1]. While diabetics have been traditionally considered a coronary heart disease (CHD) equivalent [2], studies using coronary artery calcium scoring (CACS) have observed a high percentage of diabetic individuals to possess no coronary calcium, a finding associated with low future cardiovascular risk. These studies of CACS have also shown that this test augments prediction of CHD risk in asymptomatic diabetic individuals beyond consideration non-diabetes CHD risk factors. As an example, a high proportion of diabetics have a CAC score of 0, which is associated with an excellent prognosis. In contrast, for every increasing non-zero category of CACS, the risk is higher for a diabetic than a non-diabetic patient. Thus, current professional societal guidelines endorse the use of diagnostic testing for selected asymptomatic individuals by means of stress testing [3,4] or coronary artery calcium scoring (CACS) [5].

Coronary computed tomographic angiography (CCTA) is a non-invasive test that demonstrates high diagnostic performance for the detection and exclusion of any atherosclerosis as well as anatomically obstructive CAD [6–9]. In the general population of asymptomatic patients undergoing CCTA scanning, CCTA findings have not shown more effective risk stratification than CACS. However, whether CCTA represents a more effective method for risk assessment than CACS in selected higher risk asymptomatic patients – such as those with diabetes – is unknown.

From a consecutive cohort of individuals within a large prospective international multicenter observational cohort study, we evaluated whether CAD identified by CCTA would offer incremental risk assessment over CHD risk factors and CACS for asymptomatic diabetic individuals.

2. Methods

The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry is an open-label, international, multicenter observational dynamic registry designed to evaluate associations between patient characteristics, CCTA findings, and incident adverse clinical events. A total of 27,125 patients who underwent CCTA at 12 centers in 6 countries (United States, Canada, Germany, Switzerland, Italy, and South Korea) were enrolled into the registry between February 2003 and December 2009. Details of the registry and data collection have been previously been published [10]. For the present study, sites with data on all-cause mortality, non-fatal myocardial infarction, and late target vessel revascularization (REV) were included, resulting in a total of 17,218 patients. From this cohort, we identified 400 patients with an established diagnosis of diabetes; who were asymptomatic; and had no history of obstructive CAD, coronary revascularization, or myocardial infarction. All patients had a CACS performed as a routine part of the CCTA examination. Diabetes was defined by established guidelines [11] and included a known history of diabetes or the use of diabetic medications. All sites had approval of their respective institutional review boards, and were compliant with the Health Insurance Portability and Accountability Act where applicable.

2.1. Data acquisition and image analysis

All CCTA performance, data acquisition, image post-processing, and interpretation in the study cohort were consistent with site-specific policies and Society of Cardiovascular Computed Tomography guidelines [12]. All CCTA studies were performed using a scanner with at least 64 detector rows, and interpreted using a 16-segment coronary vascular model.

In each coronary artery, coronary atherosclerosis was defined as any tissue structures ≥ 1 mm^2 in size within or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. The luminal stenosis of coronary atherosclerotic lesions was determined by visual estimation in accordance with guidelines [12]. Maximal stenosis severity was categorized into a 4-point scale, defined as no CAD (no plaque), mild CAD (maximal stenosis 1–49%), moderate CAD (maximal stenosis 50–69%), and severe CAD ($\geq$70% stenosis). CAD was also assessed by the number of major epicardial vessels with obstructive ($\geq$50% stenosis) CAD, with obstructive left main artery disease considered 3-vessel CAD; and the segment stenosis score, which measures the extent and severity of plaque by assigning each of 16 segments a score of 0–3 for absent to severe stenosis up to a maximum score of 48 [13].

2.2. Patient follow-up

Patient outcomes were determined at each institution using a dedicated physician and/or research nurse by direct interview, telephone contact, and/or review of medical records using a standardized questionnaire, as we have previously described [10]. In the United States, all-cause mortality was additionally assessed by query of the Social Security Death Index.

2.3. Statistical analysis

Our primary endpoint was major adverse cardiovascular events (MACE), as defined by a composite of all-cause mortality, non-fatal