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An exploratory analysis of the utility of maximum degree of stenosis on computed tomography coronary angiography for predicting major adverse cardiac events

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Abstract

Introduction The strength of CT coronary angiography (CTCA) is ruling out significant coronary artery disease (CAD) in symptomatic intermediate risk patients. CTCA is gaining attention as a tool for stratifying patients' risk of major adverse cardiac events (MACE). This study evaluated the ability of stenosis reporting on CTCA to predict MACE in patients undergoing investigation at Townsville University Hospital.

Methods and results One-thousand and three patients (1003) who underwent a CTCA between January 2015 and November 2023 were followed up until February 2024. For each patient, maximum degree of stenosis on CTCA, coronary artery calcium score (CACS) and cardiac risk factors were collected. Four-hundred and seventy-one (471) patients had no stenosis on CTCA, 181 had 1–49% stenosis, 237 had 50–69% stenosis and 114 had $\geq$ 70% stenosis. One hundred and sixteen (116) patients had invasive coronary angiography (ICA) performed of which 29 had a subsequent percutaneous coronary intervention (PCI) and 9 had a coronary artery bypass graft (CABG). In patients with 70% or more stenosis on CTCA, the hazard ratio for suffering a three-point definition of MACE (all-cause mortality, myocardial infarction and stroke or TIA) was 3.74 compared to the 0% stenosis group. ROC curve analysis revealed similar performance of CTCA between subsets of the population. There was no statistically significant difference in the ability of CTCA to predict MACE between women and men, and between Aboriginal and/or Torres Strait Islander patients and other Australians.

Conclusions Maximum degree of stenosis on CTCA can predict MACE. The apparent predictive value of CTCA for MACE largely depends on the features extracted from CTCA and the definition of MACE used.

Keywords CT coronary angiography, Coronary artery calcium score, Major adverse cardiac events, Invasive coronary angiography, Percutaneous coronary intervention and coronary artery bypass graft

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Introduction

Coronary artery disease (CAD) refers to the build-up of atherosclerotic plaque in the coronary arteries. CAD restricts blood supply to the heart and may lead to stable angina or acute coronary syndrome [1]. Australian government statistics show that in 2017 approximately 580,000 Australians aged 18 and over had CAD. Total allocated expenditure on CAD was over $2.5 billion AUD in 2020 [2]. In Australia, CT coronary angiography (CTCA) is performed at the request of specialists or consulting physicians for patients with stable or acute symptoms consistent with coronary ischemia who are at low to intermediate risk of an acute coronary event (e.g. having no significant cardiac biomarker elevation and no electrocardiogram changes indicating acute ischemia) [3, 4]. CTCA provides an estimate of the extent of coronary artery stenosis and plaque calcification which can inform decisions about whether to investigate further for CAD (e.g. via functional imaging and/or invasive coronary angiography).

The value of utilising CTCA for prediction of major adverse cardiac events (MACE) in clinical practice remains unclear due to inconsistent definitions of outcome [5]. Many studies use all-cause mortality as a primary outcome. All-cause mortality has a plethora of different causes and is largely a product of age. It would be more appropriate to use cardiovascular specific outcomes closely linked to the state of the coronary arteries- such as myocardial infarction- when assessing the ability of CTCA to achieve improvements in the prediction of cardiac events [6, 7]. Other limitations of existing studies are inconsistent variables extracted from CTCA. The ability of CTCA to predict events largely depends on the variables extracted in the CTCA report which are constantly evolving and highly variable between sites and studies. For example, perivascular fat attenuation index and fractional flow reserve estimates are useful for prediction of MACE but are not routinely reported in current clinical practice [8, 9]. This study therefore focussed on maximum degree of stenosis which is routinely reported by all imagers, sites and studies. Finally, other studies fail to consider the impact of interventions performed after CTCA on prognosis [10, 11]. PCIs or CABGs performed on the basis of CTCA results may successfully defer events from occurring. This is not a failure of CTCA to predict MACE, but rather a success of CTCA in guiding early intervention. Thus any analysis of how well CTCA improves risk prediction must evaluate how CTCA leads to changes in patient management and thereby patient outcomes.

Another key limitation of existing studies is failure to analyse the ability of CTCA to predict MACE in subsets of the population [10]. The predictive performance of risk stratification tools is significantly different between subsets of the population meaning there may be subgroups in which using CTCA for prognostication of MACE is relatively more helpful than in others. For example, traditional risk stratification tools such as the Framingham Risk Score strongly underestimate risk in Aboriginal and/or Torres Strait Islander patients [12]. For this reason, coronary artery calcium scoring (CACS) is already recommended in low-risk asymptomatic Aboriginal and/or Torres Strait Islander patients over 40 years old to improve risk prediction in this cohort in Australia [13]. Whether maximum degree of stenosis on CTCA can lead to further improvements in risk prediction over CACS in Aboriginal and Torres Strait Islander patients is a novel area requiring further exploration. This is especially true given the paucity of research on the use of CTCA in Aboriginal and/or Torres Strait Islander patients [14, 15]. Similarly, several studies have found that the ability of CTCA to predict MACE is higher in asymptomatic diabetics than asymptomatic patients without diabetes suggesting CTCA may be relatively more useful for prediction of MACE in diabetic patients [16–22]. Ultimately, the utility of CTCA for predicting MACE in subsets of the population including women, patients with diabetes and Aboriginal and/or Torres Strait Islander patients needs validation [14, 23] and potential differences in the predictive value of the test across subsets should be explored.

This study aimed to address the current gap in knowledge by evaluating the ability of maximum luminal stenosis on CTCA to predict MACE- defined as a composite of all-cause mortality, myocardial infarction and stroke or TIA- at 5-years follow-up in all patients, then in subgroups of women, patients with diabetes and Aboriginal and/or Torres Strait Islander patients. Using CTCA for risk stratification and not just exclusion of CAD could maximise the utility of the test. Exploring differences in the ability of CTCA to predict events between subsets of the population could lead to identification of populations who receive greater benefit from the test.

Methods

Ethics

Ethics approval was obtained from Townsville Hospital and Health Service Human Research Ethics Committee (HREC) on the 21st of June 2023 (HREC/2023/QTHS/94942). Public Health Act approval was granted by Queensland Health on the 18th of September 2023. Site specific approval was obtained from Townsville Hospital and Health Service on the 12th of October 2023. The project was authorised under the Umbrella Low and Negligible Risk (LNR) / Low Resource Research Collaboration Agreement between Townsville Hospital and Health Service and James Cook University.

Study participants

The study was a single-centre retrospective cohort study of patients who underwent a CTCA at Townsville University Hospital between January 1 2015 and November 1 2023. Patients were followed-up to February 1, 2024. Therefore all patients had at least 3 months follow-up after CTCA. To be eligible for inclusion in the current study, patients had to be aged over 18 years and have had both maximum degree of stenosis in any of the coronary arteries and CACS reported. Patients who were undergoing a follow-up CTCA were excluded from this analysis. Patients who had experienced a previous MACE were also excluded.

Participant data

Collected data for each patient included age, sex, past or present smoking status and history of diabetes, hypertension and dyslipidaemia. For the purpose of the current study, hypertension was defined as systolic blood pressure above 140mmHg [24], or prescription of antihypertensives. Tobacco use was defined as never or previous/current smoking status. Further details on the definitions of "hypertensive" and "dyslipidaemia" are provided in supplementary figure S1. Information on whether patients identified as an Aboriginal and/or Torres Strait Islander (self-reported), and an estimate of rurality of residence based on the Modified Monash Model, were also collected.

The primary outcome was major adverse cardiac events (defined as a composite of myocardial infarction (ICD I21), all-cause mortality, and stroke (ICD I63.9 and I61.2) or TIA (ICD G45.9)). Other outcomes of interest were ICA performed with CTCA as the indication, revascularisation (percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)), and commencement of aspirin or statin following the CTCA. Data was provided to the investigators by the Townsville Hospital Research Data Laboratory and the Queensland Cardiac Outcomes Registry. This study is reported in accordance with the STROBE guidelines.

Calcium score and maximum degree of stenosis reported on CTCA

Calcium scores were obtained using a gated non contrast cardiac CT. CTCAs were cardiac gated contrast enhanced prospective scans with multi planar reformats as per standard protocol. Patients were premedicated with beta-blockers and glyceryl trinitrate.

CT assessment of the left main, left anterior descending, left circumflex, right coronary artery, obtuse marginals, diagonal branches and ramus intermedius was performed by imagers as part of standard care according to institutional protocols. Data detailing the maximum degree of coronary artery stenosis and coronary artery calcium score were extracted from the CTCA reports by a single investigator (TF). An algorithm was written to extract these variables from each CTCA report and validated in 100 of the 1003 patients. A description of how the algorithm was developed by the primary investigator is provided in supplementary figure S2. Patients were grouped according to the maximum degree of arterial stenosis (normal: 0%, minimal: <25%, mild: 25–49%, moderate: 50–69%, severe: $\geq$ 70%) according to Society of Cardiovascular Computed Tomography (SCCT) guidelines [25]. CTCA were performed using institution specific protocols using a Toshiba Aquillon One CT scanner (320-slices).

Coronary artery calcium score (CACS) was collected and categorised as CACS 0, 1-100, 101–400, or over 400 by Cardiac Society of Australia and New Zealand guidelines [26].

For patients who proceeded to have an invasive coronary angiography performed with CTCA as an indication, invasive coronary angiography (ICA) reports were collected from the Queensland Cardiac Outcomes Registry. The maximum degree of stenosis in any of the coronary arteries and whether a PCI or CABG was performed was extracted from the ICA reports. The maximum luminal stenosis on CTCA was compared to the maximum luminal stenosis on ICA to determine if CTCA underestimated, correctly estimated or overestimated CAD disease severity compared to the gold-standard invasive coronary angiography [27].

Statistical analysis

The Shapiro-Wilks test demonstrated that continuous variables were not normally distributed and they were therefore reported as median and inter-quartile range (IQR) [28]. Continuous variables were compared between patient groups using the Wilcoxon rank sum test [29]. Categorical and ordinal variables were presented as frequencies and proportions and were compared between groups using the chi-squared test, or Fisher's exact test [30]. Cohort characteristics were presented in a table using the gtsummary package in R [31].

For the primary aim, the association of CT-estimated coronary stenosis with subsequent MACE was assessed using Kaplan-Meier curves (compared using the Log-rank test) in the survival package [32]. Violin plots testing the association between maximum degree of stenosis on CTCA and CACS (quantitatively assessed using the Kruskal-Wallis test) were generated using the ggplot2 package [33]. Cox proportional hazards regression models adjusted for potential confounders (age as a stratification variable, sex, diabetes, hypertension, dyslipidaemia and intervention with PCI or CABG) were generated using the survival package [32]. Patients were censored at the time of first event, or until lost to follow-up.

Given that smoking status was not recorded for 52% of patients, sensitivity analysis was performed in the 48% of patients (486 patients) for whom smoking status was available. For this subgroup analysis, patients were classified as either non-smokers or past or current smokers. Given the small sample size, a simplified model only incorporating covariates shown to be significantly associated with MACE risk in the whole population analysis was used. Calcium scores of 101–400 and over 400 were also grouped in this simplified model due to observations of similar hazards ratios for these parameters in models fit to the full cohort.

For the secondary aim, the potential for CTCA to predict MACE in specific subsets of the population (male and female, diabetic and non-diabetic and Aboriginal and/or Torres Strait Islander and other Australians) was further investigated using receiver operating characteristic (ROC) curves with ordinal variables. Area under the curve (AUC) on ROC analysis was used to quantitatively assess the predictive performance of CTCA. The discriminative model performance was assessed using the method of DeLong et al. in the pROC package [34]. Two-tailed p-values of $p < 0.05$ was considered to indicate statistical significance. All statistical analysis was performed in R (version 2023.06.1 + 524).

Sample size calculation

The study was powered to test the association of CTCA with the primary outcome (MACE). Presented Cox regression models were adjusted for the 8 covariates of age, sex, diabetes status, hypertensive status, dyslipidaemia status, CACS, CTCA stenosis and intervention (PCI or CABG). Given that multivariable models require 10 outcome events per covariate, and that 108 MACE were reported for the cohort, the study was adequately powered to test this hypothesis [35].

Results

Cohort characteristics

Figure 1 summarises the flow of patients through each stage of the screening process. Between 1/1/2015 to 1/2/2024, 1326 CTCAs were performed at Townsville University Hospital. Of these, 1304 were first-time CTCAs. Twenty had less than 3 months follow-up leaving 1284. After excluding patients with unavailable CTCA reports ($n = 141$), patients who had a MACE before their first CTCA ($n = 22$), patients who did not have coronary artery calcium score performed ($n = 104$) and patients who did not have maximum degree of stenosis reported ($n = 14$), data from 1003 patients were included in the current analysis. Of these, 471 had no coronary artery

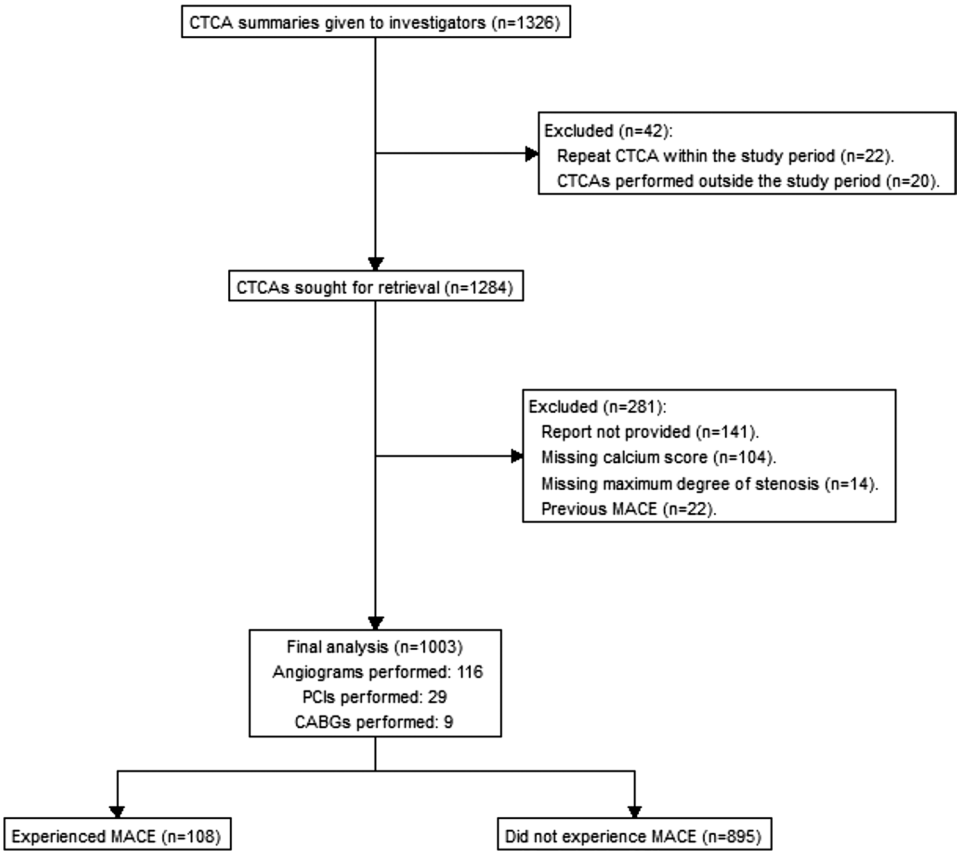

Fig. 1 CONSORT diagram

stenosis on CTCA, 181 had 1–49% stenosis recorded, 237 had 50–69% stenosis and 114 had $\geq$ 70% stenosis. One-hundred-and-sixteen (116) patients underwent an invasive coronary angiography after CTCA of which 37 had a coronary revascularisation. One patient had both a PCI and CABG so there was a total of 38 revascularisations.

The patient cohort was followed for a median of 52 (IQR 28–74) months, and 108 participants experienced a MACE. 54 MACE events were all-cause mortality, 47 were myocardial infarction, 4 were stroke and 3 were transient ischaemic attack. Patients who experienced a MACE were more likely to be older (median 59 years vs. median 53 years), male (58% vs. 46%), hypertensive (37% vs. 23%) and have dyslipidaemia (30% vs. 11%) than those who did not experience a MACE (p-value < 0.05 for each, Table 1). As anticipated, patients who experienced a MACE had a higher prevalence of severe ($\geq$ 70%) CAD (20.7% vs. 10.3%) and more pronounced coronary artery calcification (median CACS score of 110 vs. 0). Median time to first MACE was 23 months (IQR 4–49 months) in patients who experienced a MACE, whereas median follow-up for those who did not experience MACE was 56 months (IQR 32–77 months).

Table 1 Cohort characteristics

Characteristic	Overall (N = 1003)[1]	No MACE (N = 895)[1]	MACE (N = 108)[1]	p-value[2]
Age (Median (IQR))	54 (45, 63)	53 (45, 62)	59 (49, 67)	< 0.001
Sex				0.012
Female	532 (53%)	487 (54%)	45 (42%)	
Male	471 (47%)	408 (46%)	63 (58%)	
Type 2 Diabetes	171 (17%)	138 (15%)	33 (31%)	< 0.001
Aboriginal or Torres Strait Islander	143 (14%)	123 (14%)	20 (19%)	0.2
Hypertension	246 (25%)	206 (23%)	40 (37%)	0.001
Dyslipidaemia	130 (13%)	98 (11%)	32 (30%)	< 0.001
Current or Former Smoker				0.9
No	343 (34%)	308 (34%)	35 (32%)	
Yes	143 (14%)	126 (14%)	17 (16%)	
Unknown	517 (52%)	461 (52%)	56 (52%)	
Duration of Follow-up (Months) (Median (IQR))	52 (28, 74)	56 (32, 77)	23 (4, 49)	< 0.001
Modified Monash Model Score				0.2
1–2	752 (75%)	676 (76%)	76 (70%)	
3–7	236 (24%)	207 (23%)	29 (27%)	
Unknown	15 (1.5%)	12 (1.3%)	3 (2.8%)	
Maximum Luminal Stenosis (%)				< 0.001
0%	471 (47%)	440 (49%)	31 (29%)	
1–49%	181 (18%)	169 (19%)	12 (11%)	
50–69%	237 (24%)	194 (22%)	43 (40%)	
70%+ Stenosis, Intervention	26 (2.6%)	22 (2.5%)	4 (3.7%)	
70%+ Stenosis, No Intervention	88 (8.8%)	70 (7.8%)	18 (17%)	
Coronary Artery Calcium Score (CACS)	0 (0, 79)	0 (0, 56)	110 (0, 350)	< 0.001
CACS Category				< 0.001
0	531 (53%)	502 (56%)	29 (27%)	
1–100	241 (24%)	218 (24%)	23 (21%)	
101–400	135 (13%)	104 (12%)	31 (29%)	
401+	96 (9.6%)	71 (7.9%)	25 (23%)	
PCI or CABG	37 (3.7%)	29 (3.2%)	8 (7.4%)	0.051

1. Median (IQR); n(%)

2. Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Five hundred and thirty-one (531) of the 1003 patients had calcium scores of zero, representing 52.9% of the study cohort. 421 of these patients had no coronary artery disease, 76 had minimal to mild disease, 25 had moderate disease and 9 had severe disease by CTCA.

Primary aim: the ability of CTCA and CACS to stratify 5-year risk of MACE

The risk of experiencing a MACE during follow-up significantly increased in parallel with the severity of coronary calcification or stenosis (Fig. 2A and C). Five-year freedom from MACE was 92.3% in patients with no stenosis compared to 76.6% in those with $\geq$ 70% stenosis (p-value < 0.0001, supplementary figure S3). Freedom from MACE was higher in patients with $\geq$ 70% coronary stenosis who underwent revascularisation than those who did not, however this was not statistically significant (p-value 0.54, Fig. 2B). Five-year freedom from events was 93.3% in patients with CACS of 0 and 70.8% in patients with CACS above 400 (p-value < 0.0001, supplementary figure S3). A statistically significant increase in CACS was observed as maximum luminal stenosis increased (Fig. 2E).

Unadjusted Cox regression revealed that the risk of experiencing a MACE increased as both the extent of calcification and stenosis increased (Table 2). Patients with 1–49% stenosis were not at statistically significant risk of MACE compared to patients with 0% stenosis. Similar hazard ratios were generated for patients with 50–69% and $\geq$ 70% stenosis (HR 3.305 and 3.737 respectively). As demonstrated in Fig. 2D, there was no statistically significant difference in the 5-year survival probability between patients with 70% or more stenosis who had a revascularisation and those who did not. Importantly, calcium scores above 400 were associated with significantly increased risk of MACE (HR 5.363 95% CI 3.139–9.162) compared to patients with CACS of 0.

The ability of CTCA to predict MACE largely depended on the definition of MACE used (Table 3). When acute myocardial infarction (AMI) was included as the only outcome, moderate stenosis on CTCA offered incremental benefit beyond CACS and clinical risk factors for

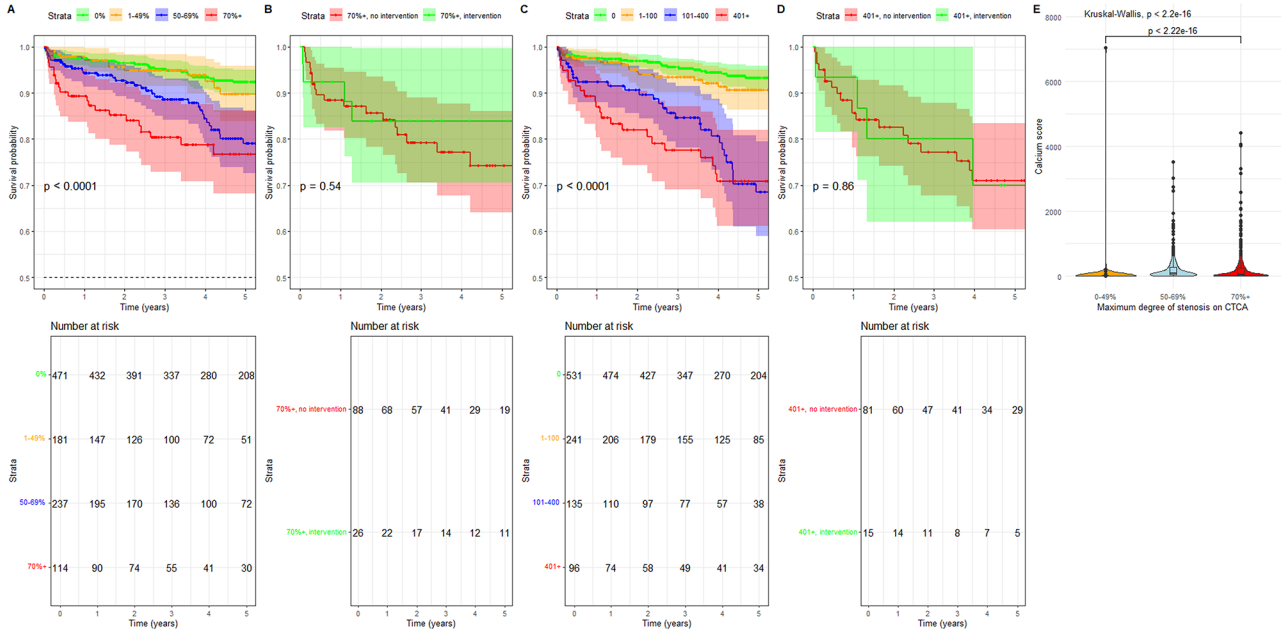

Fig. 2 Kaplan-meier survival curves. (**A**) 5-year MACE free survival in patients grouped by the maximum degree of stenosis on CTCA of 0%, 1–49%, 50–69% and 70%+. (**B**) 5-year MACE free survival in patients with 70%+ stenosis split into intervention and no intervention groups. (**C**) 5-year MACE free survival in patients grouped by calcium score of 0, 1-100, 101–400 and 401+. (**D**) 5-year MACE free survival in patients with calcium scores above 400 and calcium scores less than or equal to 400. (**E**) Violin plot evaluating the relationship between maximum luminal stenosis on CTCA and coronary artery calcium score

Table 2 Unadjusted Cox regression analysis

		Hazard ratio (95% CI)	*p*-value
Maximum percentage stenosis on CTCA	0%	Reference	NA
	1–49%	1.228 (0.630–2.393)	0.546
	50–69%	3.305 (2.080–5.249)	< 0.001
	70%+	3.737 (2.161–6.465)	< 0.001
	70%+, no revascularisation	4.141 (2.312–7.416)	< 0.001
	70%+, revascularisation	2.601 (0.917–7.376)	0.0723
Coronary artery calcium score	0	Reference	NA
	1-100	1.800 (1.041–3.115)	0.035
	101–400	4.714 (2.840–7.823)	< 0.001
	401+	5.363 (3.139–9.162)	< 0.001

predicting MACE. In contrast when a 3-point outcome was used comprising AMI, all-cause mortality and stroke or TIA, CTCA did not offer incremental benefit beyond CACS in our patient cohort for MACE prediction (see Table 3).

Adjusted cox regression in the subset of the population who had smoking status recorded confirmed the incremental benefit of calcium scoring over clinical risk factors for the prediction of MACE (supplement S4).

Secondary aim: the ability of CTCA and CACS to stratify 5-year risk of MACE in patients with diabetes and non-diabetics, in Aboriginal and/or Torres Strait Islander patients and other Australians, and in women and men

ROC curves for how well CTCA predicted MACE in subsets of the population (with patients who had a PCI or CABG removed to eliminate the protective effect of revascularisations on prognosis, and 0% stenosis grouped with 1–49% stenosis) are provided in Fig. 3. The ROC curves demonstrate that the performance of CTCA was relatively higher in women than men and Aboriginal and/or Torres Strait Islander patients than other Australians although the differences were not statistically significant. Performance was similar between patients with diabetes and patients without diabetes.

Comparisons in demographic profiles between subsets of the population are provided in supplements S5 to S9 and Table 4. Importantly, Aboriginal and/or Torres Strait Islander patients were statistically younger and had a higher burden of type 2 diabetes and were more likely to be female (supplements S5, S6 and S7). Of the 84 Aboriginal and/or Torres Strait Islander patients with coronary artery calcium scores of zero, 65 had no CAD, 13 had minimal or mild CAD, 5 had moderate CAD and 1 had severe CAD.

As demonstrated in supplement S8, women in this study were statistically more likely to be of Aboriginal and/or Torres Strait Islander descent, have lesser

Table 3 Adjusted Cox regression as part of the sensitivity analysis

AMI only (1003 patients, 47 events) - Chi-square *p*-value: 0.67		
	Hazard ratio (95% CI)	***p*-value**
0–49% stenosis	Reference	NA
50—69% stenosis	2.874 (1.009–8.182)	0.048*
70%+ stenosis	1.743 (0.492–6.177)	0.389
Calcium score 0	Reference	NA
Calcium score 1-100	0.888 (0.266–2.964)	0.846
Calcium score 101–400	2.304 (0.630–8.423)	0.207
Calcium score 401+	3.214 (0.789–13.099)	0.103
Male sex	1.093 (0.529–2.257)	0.810
Type 2 diabetic	1.348 (0.645–2.817)	0.427
Hypertensive	1.397 (0.667–2.927)	0.375
Dyslipidaemia	6.409 (2.839–14.469)	< 0.001*
Intervention (PCI or CABG)	2.447 (0.739–8.097)	0.143
AMI, all-cause mortality and stroke/TIA (1003 patients, 108 events) - Chi-square *p*-value: 0.55		
	Hazard ratio (95% CI)	***p*-value**
0–49% stenosis	Reference	NA
50—69% stenosis	1.667 (0.897–3.099)	0.106
70%+ stenosis	1.167 (0.524–2.599)	0.706
Calcium score 0	Reference	NA
Calcium score 1-100	1.161 (0.572–2.354)	0.679
Calcium score 101–400	3.259 (1.552–6.844)	0.002*
Calcium score 401+	3.867 (1.616–9.255)	0.002*
Male sex	1.156 (0.735–1.819)	0.531
Type 2 diabetic	1.228 (0.747–2.019)	0.418
Hypertensive	1.596 (1.002–2.543)	0.049*
Dyslipidaemia	3.235 (1.908–5.485)	< 0.001*
Intervention (PCI or CABG)	0.921 (0.373–2.270)	0.857

Calculated hazards ratios for categorical covariates compare patients with the risk factor to those who do not

maximum degree of stenosis on CTCA, have lower CACS, and were less likely to receive a PCI than men. They had a lower incidence of MACE than men. Of the 333 women with calcium scores of zero, 260 had no CAD, 50 had minimal or mild CAD, 17 had moderate CAD and 6 had severe CAD.

The patients with diabetes in this study were more likely to be older, be of Aboriginal and/or Torres Strait Islander descent, have hypertension, have dyslipidaemia, have more severe coronary artery disease, have higher CACS and have a CABG performed. They had a higher incidence of MACE than patients without diabetes (supplement S9). Of the 58 patients with diabetes and calcium scores of 0, 41 had no CAD, 9 had minimal to mild CAD, 6 had moderate CAD, and 2 had severe CAD.

The association of CT-estimated coronary stenosis with revascularisation

CT-estimated coronary stenosis was strongly associated with decision to perform a downstream invasive coronary angiography (see supplementary figure S10). Only 4 of the 471 patients with 0% stenosis on CTCA went on to have an ICA, none of which had a PCI or CABG. In contrast, 62 of the 114 patients with at least 70% stenosis on CTCA had an invasive coronary angiography, of which 26 had a PCI and/or CABG.

There was a general tendency of stenosis reporting on CTCA to overestimate the maximum degree of stenosis by invasive coronary angiography (see supplementary figures S10 and S11). Of the 62 patients who had $\geq$ 70% stenosis reported on CTCA and had an invasive coronary angiogram performed, 38 (61.2%) had less than 70% stenosis reported at the time of ICA.

CT-estimated coronary stenosis was also associated with subsequent commencement of statins and/or aspirin. Only 16 of the 471 patients with 0% stenosis on CTCA (3.4%) were commenced on a statin, aspirin or both compared to 28 of 114 patients (24.6%) with 70% or more stenosis (see supplementary figure S12).

Discussion

The primary aim of this study was to evaluate the ability of maximum degree of stenosis on CTCA to predict 5-year risk of MACE in a symptomatic cohort. The rationale for the study was that CTCA can detect non-calcified plaque, plaque location and multivessel disease and so may lead to improved prognostication for MACE beyond CACS (an already validated tool for assessing overall atherosclerotic plaque burden) [36–39]. This study found that the risk of MACE increases with both maximum degree of stenosis on CTCA and coronary artery calcium score.

CTCA offered incremental benefit beyond CACS for predicting the outcome of acute myocardial infarctions (AMI) but not the 3-point definition of MACE including all-cause mortality. The stronger association between CTCA results and AMI than between CTCA results and MACE may reflect that AMI is a cardiovascular specific outcome closely linked to the state of the coronary arteries whilst all-cause mortality is a broad outcome involving processes outside the coronary vasculature. Other leading causes of all-cause mortality include dementia including Alzheimer's disease, COVID-19, lung cancer and cerebrovascular disease [40]. Ultimately, using a definition of MACE where the majority of events were all-cause mortality could under-estimate the ability of CTCA to predict "cardiac events". This emphasises the need for a consistent definition of MACE between studies, especially given that all-cause mortality is one of the most common MACE components in existing literature [1, 7]. These insights are consistent with the results of the CONFIRM study. The CONFIRM study found CTCA was independently predictive of future death, but the addition of CTCA to a model with Framingham risk

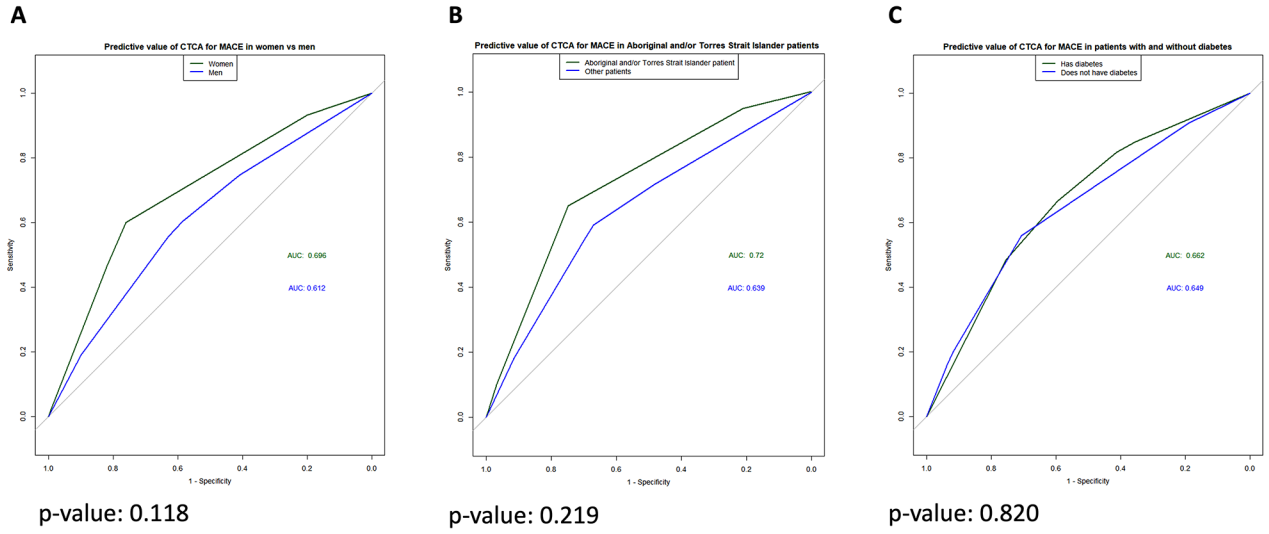

Fig. 3 Comparison of performance of CTCA for predicting MACE in subsets of the population. (**A**) ROC curve comparing the predictive value of maximum degree of stenosis on CTCA for MACE in men and women. (**B**) ROC curve comparing the predictive value of maximum degree of stenosis on CTCA for MACE in Aboriginal and/or Torres Strait Islander patients and other Australians. (**C**) ROC curve comparing the predictive value of maximum degree of stenosis on CTCA for MACE in patients with diabetes and patients without diabetes

Table 4 Cox regression analysis on subsets of the population

Aboriginal And Or Torres Strait Islander Patients		**Hazard ratio (95% CI)**	***p*-value**
Maximum percentage stenosis on CTCA	0%	Reference	NA
	1–49%	0.470 (0.057–3.908)	0.485
	50–69%	4.344 (1.601 0 11.784)	0.004
	70%+	5.212 (1.046–25.963)	0.044
Coronary artery calcium score	0	Reference	NA
	1-100	2.774 (0.693–11.11)	0.146
	101–400	7.837 (2.209–27.8)	< 0.01
	401+	11.586 (3.264–41.13)	< 0.001
Women		**Hazard ratio (95% CI)**	***p*-value**
Maximum percentage stenosis on CTCA	0%	Reference	NA
	1–49%	0.673 (0.195–2.324)	0.531
	50–69%	4.551 (2.325–8.907)	< 0.001
	70%+	4.959 (2.009–12.243)	< 0.001
Coronary artery calcium score	0	Reference	NA
	1-100	2.880 (1.294–6.413)	0.010
	101–400	7.659 (3.437–17.067)	< 0.001
	401+	12.172 (5.124–28.912)	< 0.001
Patients With Diabetes		**Hazard ratio (95% CI)**	***p*-value**
Maximum percentage stenosis on CTCA	0%	Reference	NA
	1–49%	2.290 (0.662–7.925)	0.191
	50–69%	4.367 (1.595–11.959)	0.004
	70%+	2.687 (0.847–8.525)	0.093
Coronary artery calcium score	0	Reference	NA
	1-100	4.287 (0.890–20.65)	0.070
	101–400	14.864 (3.314–66.67)	0.0004
	401+	11.154 (2.491–49.94)	0.002

factors and CACS did not lead to a significant improvement in risk stratification for all-cause mortality. CTCA did, however, lead to a significant improvement for the composite outcome of death and non-fatal MI [41]. The varying performance of CTCA to predict events depends on the event definition used. Myocardial infarction is arguably the most specific and relevant endpoint for a tool that assesses the condition of the coronary arteries. Additionally, medications commenced based on CTCA results may have prevented MACE affecting the relationship between severe CAD and subsequent events.

Furthermore, the present study found no statistically significant difference in risk of MACE between patients with no CAD and patients with 1–49% maximum luminal stenosis. These results are consistent with a 2016 meta-analysis by Pizzi et al. [42] If patients had been followed up for a longer period of time, non-obstructive CAD may have progressed to obstructive CAD and caused MACE [43].

Previous studies assessing the prognostic value of traditional stenosis-based categories (e.g. non-obstructive and obstructive CAD) for future MACE found that stenosis reporting on CTCA does not offer incremental benefit beyond CACS [10, 41, 44]. In contrast, studies assessing the prognostic value of the CAD-RADS method for reporting CTCA- a method which includes more specific stenosis grading, plaque burden components and high-risk plaque features- have found that CTCA adds substantial prognostic value over CACS [10]. These contrasting conclusions emphasise how the method of reporting CTCA along with the primary outcome

used strongly impacts the predictive value of CTCA for MACE.

This study found that there was no statistically significant difference in 5-year survival between patients who had 70% or more stenosis who had an intervention and patients who did not. These results are consistent with the ISCHEMIA trial which demonstrated that revascularisation in stable coronary disease does not improve the endpoint of all-cause mortality over a median follow-up of 3.2 years [45].

The study reported similar event rates across stenosis categories to existing literature. A 2020 study found that the a 4.5% incidence of MACE in the CACS = 0 group at 6 years, where the definition of MACE included cardiovascular death as opposed to all-cause mortality [46]. A 2018 study by Sadeghpour et al. found that the MACE- free survival rates were 99.1%, 99.1%, and 87.7% at one, three, and five years, respectively for patients with CACS of 0, a higher rate of MACE in a shorter period of time than identified in our study [47].

The secondary aim of the present study was to determine whether the ability of CTCA to predict events differed between subsets of the population. The study found that there was no statistically significant difference in the association between CTCA results and MACE between women and men, and Aboriginal and/or Torres Strait Islander patients and other Australians. There was, however, a tendency of CTCA to be more effective in stratifying risk of MACE in women than men and Aboriginal and/or Torres Strait Islander populations than other Australians. Future studies with larger population sizes should explore whether there a statistically significant trend in the predictive value of CTCA for MACE emerges in these specific populations. This study validated the predictive value of CTCA in women, patients with diabetes and Aboriginal and/or Torres Strait Islander patients. Delayed presentation leading to events in these subsets may explain the relatively better performance of CTCA. Women are more likely to present with atypical chest pain leading to a delay in diagnosis and treatment [48, 49], whilst Aboriginal and/or Torres Strait Islander patients may present later with more severe disease for a wide range of reasons including access to health services [50] and comorbidity with diabetes leading to silent disease [51–53]. Recognising differences in the diagnostic performance of CTCA between subsets of the population could lead to more selective use of the test as a risk stratification tool in the future.

The study also assessed the association of CT-estimated coronary stenosis with revascularisation and other interventions. The relatively high rate of revascularisations in this study in patients with severe CAD may reflect that some patients in the study were undergoing CTCA for troponin negative chest pain that occurred at rest and not strictly stable coronary artery disease.

Some patients who had severe CAD on CTCA did not have an invasive angiogram. This could be because patients undergo functional imaging after a positive CTCA result under current chest pain guidelines; if they have a negative result they may not go on to have an ICA [54]. The study also demonstrated that not all patients with severe disease on CTCA have a PCI or CABG after angiogram, possibly because some patients with severe disease may have either comorbidities prohibiting ICA or multivessel disease that is not amenable to intervention [55]. The study also revealed that there is a tendency of CTCA to overestimate the degree of stenosis in the coronary arteries compared to ICA. This may be due to blooming artifact, where calcified plaque appears more stenotic than it is at the time of invasive angiography [56], and the fact that CTCA provides a multiplanar cross-sectional view of the coronary arteries whereas ICA provides a 2-dimensional projection [57]. The use of fractional flow reserve estimated by CTCA (FFR-CT) as an adjunct test alongside CTCA could improve the performance of CTCA as a gatekeeper for ICA and reduce the incidence of non-hemodynamically significant plaque at the time of ICA [58].

The relatively low rate of prescription of statins and antihypertensives as noted in supplementary figure S12 in this study could be explained by patients being commenced on preventative medications by a private cardiologist or general practitioner outside of hospital.

Ultimately, this study found that maximum degree of stenosis on CTCA can predict major adverse cardiac events. The study elucidated how features extracted from CTCA reports as well as the definition of the primary outcome affect the predictive performance of CTCA relative to calcium scoring. The study found the predictive value of maximum degree of stenosis on CTCA for MACE was higher in women than men and in Aboriginal and/or Torres Strait Islander patients than other Australians although these results were not statistically significant.

Strengths, limitations and future directions

A key strength of this study is that it was performed on a large Australian cohort with outcomes. The cohort included a large Aboriginal and/or Torres Strait Islander population (more than 10% of the overall cohort). There is little published on the utility of CTCA in Aboriginal and/or Torres Strait Islander patients, noting that Aboriginal and Torres Strait Islander Australians have three times the rate of major adverse cardiac events compared to non-Indigenous Australians and are 40% less likely to be investigated by invasive angiography when in hospital [59].

The results of this study must be considered in light of inherent limitations.

A limitation of this study is that smoking data was missing for 52% of patients. Smoking is one of the leading risk factors for CAD and major adverse cardiac events [60]. Additionally, it is well established that former smokers have better prognosis than active smokers so it would be preferrable to categorise active and former smokers differently when assessing the event rates in subsets of the population [61]. To overcome this limitation, sensitivity analysis was performed using a simplified model in the patients with available smoking data. A further limitation was that statins and antihypertensives had to be used as surrogate markers for dyslipidaemia and hypertension due to missing clinical measurements.

Additionally, radiologists may have had different thresholds for reporting "minimal", "mild", "moderate" and "severe" stenosis from the CTCA reports than the standard developed by the SCCT, especially for "minimal" and "mild" [25]. To overcome this, patients with 0% and 1–49% stenosis were grouped in the sensitivity analysis. In the future, a standardised method of reporting CTCA such as CAD-RADS 2.0 could lead to more consistency in reporting and predicting events [10, 62, 63], although the potential usefulness of CAD-RADS is limited by the fact that few clinicians report according to the CAD-RADS template in Australia and a combination of qualitative and quantitative assessment of luminal stenosis (as in the present study) is far more common [64]. Whilst high risk plaque features, fractional flow reserve estimates from CTCA and pericoronary fat attenuation index all have prognostic value for MACE, these features are not routinely reported on CTCA at present. Many of these features have already been demonstrated to independently predict MACE [65] but are not routinely used in clinical practice suggesting more information can be taken from CTCA than currently reported to maximise the utility of the test.

The results of this study do not necessarily translate to asymptomatic patients. Whilst calcium score is recommended for asymptomatic patients to guide preventative therapies, calcium score is reported alongside all CTCA reports because it a useful measure of overall atherosclerotic plaque burden in the coronary arteries. The predictive value of maximum degree of stenosis on CTCA was compared to the predictive value of CACS as the results of this study may carry forward to asymptomatic patients; the SCOT-HEART 1 study found that all patients (with both possible angina and nonanginal chest pain) derived similar benefit from CTCA [66]. Furthermore, nearly half of patients undergoing a CTCA have no CAD, suggesting that the patients in this study undergoing CTCA were not necessarily symptomatic with coronary artery disease. Thus the results of this study may be relevant to asymptomatic patients. The study also adds to limited existing literature validating the performance of CTCA in Aboriginal and/or Torres Strait Islander patients [14, 15], a population in whom traditional risk stratification tools such as the Framingham Risk Equation underperform [67].

Future investigators should conduct prospective, multicentre studies with comprehensive data collection, standardized reporting criteria (e.g. CAD-RADS 2.0), and detailed plaque characterization. A broad definition of MACE including all-cause mortality potentially obscures CTCA's cardiovascular-specific predictive utility. A more refined definition focussing on cardiovascular-specific events such as AMI, cardiovascular death and possibly PCI and CABG would better assess CTCA's predictive value for MACE.

Conclusion

Maximum luminal stenosis on CTCA is associated with 5-year incidence of MACE. This study found CTCA offered incremental benefit beyond CACS for predicting myocardial infarction but not a 3-point definition of outcome including all-cause mortality stressing the need for a consistent, cardiovascular-specific definition of MACE between studies. The study recognised that investigations and management after CTCA can interfere with event rates and the predictive value of the test. The study also provided important validation for the use of CTCA as a predictive tool for subsets of the population in whom traditional risk stratification tools have underperformed.

Abbreviations

CTCA	Computed tomography coronary angiography
CACS	Coronary artery calcium score
CAD	Coronary artery disease
ICA	Invasive coronary angiography
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft
MACE	Major adverse cardiac event. In this study, a three-point definition of MACE composed of non-fatal myocardial infarction, all-cause mortality and stroke or transient ischaemic attack was used [1].

Supplementary Information

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Supplementary Material 1

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Author contributions

T.F., J.M., S.P. and S.M. designed the research project.T.F. wrote the main manuscript text.T.F., J.M., S.P. and S.M. reviewed the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was obtained from Townsville Hospital and Health Service Human Research Ethics Committee (HREC) on 21st of June 2023 (HREC/2023/QTHS/94942). Public Health Act approval was granted by Queensland Health on the 18th of September 2023. Site specific approval was obtained from Townsville Hospital and Health Service on the 12th of October 2023. The project was authorised under the Umbrella Low and Negligible Risk (LNR) / Low Resource Research Collaboration Agreement between Townsville Hospital and Health Service and James Cook University.

Consent for publication
No individual person's data is presented in any form.

Competing interests
Joseph Moxon is an associate editor for BMC.

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