Prognostic value of myocardial perfusion imaging after first-line coronary computed tomography angiography

A multi-center cohort study

Winther, Simon; Andersen, Ina Trolle; Gormsen, Lars Christian; Steffensen, Flemming Hald; Nielsen, Lene Hüche; Grove, Erik Lerkevang; Diederichsen, Axel Cosmus Pyndt; Urbonaviciene, Grazina; Lambrechtsen, Jess; Zaremba, Tomas; Elpert, Frank Peter; Husain, Majed; Zelechowski, Marek Wojciech; Bøtker, Hans Erik; Bøttcher, Morten; The Western Denmark Cardiac CT Study Group

Published in:
Journal of Cardiovascular Computed Tomography

DOI (link to publication from Publisher):
10.1016/j.jcct.2021.08.001

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Journal of Cardiovascular Computed Tomography 16 (2022) 34–40

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.JournalofCardiovascularCT.com

Research paper

Prognostic value of myocardial perfusion imaging after first-line coronary computed tomography angiography: A multi-center cohort study

Simon Winther [a,b,*], Ina Trolle Andersen [c], Lars Christian Gormsen [d], Flemming Hald Steffensen [e], Lene Hüche Nielsen [e], Erik Lerkevang Grove [b,f], Axel Cosmus Pyndt Diederichsen [g], Grazina Urbonaviciene [h], Jess Lambrechtsen [i], Tomas Zaremba [j], Frank-Peter Elpert [k], Majed Husain [l], Marek Wojciech Zelechowski [m], Hans Erik Bøtker [b,f], Morten Bøttcher [a,b], on behalf of The Western Denmark Cardiac CT Study Group

[a] Department of Cardiology, Hospital Unit West, Herning, Denmark
[b] Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
[c] Department of Clinical Epidemiology, Aarhus University Hospital, Denmark
[d] Department of Nuclear Medicine, Aarhus University Hospital, Aarhus, Denmark
[e] Department of Cardiology, Lillebaelt Hospital-Vejle, Vejle, Denmark
[f] Department of Cardiology, Aarhus University Hospital, Denmark
[g] Department of Cardiology, Odense University Hospital, Odense, Denmark
[h] Department of Cardiology, Regional Hospital of Silkeborg, Silkeborg, Denmark
[i] Department of Cardiology, Odense University Hospital, Svendborg, Denmark
[j] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[k] Department of Cardiology, Regional Hospital of South Jutland, Aabenraa, Denmark
[l] Department of Cardiology, Regional Hospital of South West Denmark, Esbjerg, Denmark
[m] Department of Cardiology, Regional Hospital of Northern Jutland, Hjørring, Denmark

ARTICLE INFO

Keywords:
Coronary stenosis
Hybrid imaging
Single-photon emission computed tomography (SPECT)
Positron emission tomography (PET)
Cardiac magnetic resonance (CMR)

ABSTRACT

Purpose: Further diagnostic testing may be required after a coronary computed tomography angiography (CTA) showing suspected coronary stenosis. Whether myocardial perfusion imaging (MPI) provides further prognostic information post-CTA remains debated. We evaluated the prognosis for patients completing CTA stratified for post-CTA diagnostic work-up using real-world data.

Methods: We identified all patients in our uptake area with angina symptoms undergoing first-time CTA over a 10-year period. Follow-up time was a median of 3.7 years [1.9–5.8]. The primary endpoint was a composite of myocardial infarction or death. The secondary endpoint was late revascularization.

Results: During the study period 53,351 patients underwent CTA. Of these, 24% were referred for further downstream testing, 3,547 (7%) to MPI and 9,135 (17%) to invasive coronary angiography (ICA). The primary and secondary endpoints occurred in 2,026 (3.8%) and 954 (1.8%) patients. Patient-characteristic-adjusted hazard ratios for the primary and secondary endpoint using patients with a normal CTA as reference were 1.37 (1.21–1.55) and 2.50 (1.93–3.23) for patient treated medically, 1.68 (1.39–2.03) and 6.13 (4.58–8.21) for patients referred to MPI and 1.94 (1.69–2.23) and 9.18 (7.16–11.78) for patients referred for ICA, respectively. Adjusted analysis with stratification for disease severity at CTA showed similar hazard ratios for patients treated medically after CTA and patients referred for MPI and treated medically after the MPI.

Abbreviations: CABG, Coronary artery bypass graft; CAD, Coronary artery disease; CACS, Coronary Artery Calcium Score; CMR, Cardiac magnetic resonance; CTA, Computed tomography angiography; DNPR, Danish National Patient Register; ICA, Invasive coronary angiography; FFR, Fractional flow reserve; FFRct, Fractional flow reserve-computed tomography; MPI, Myocardial perfusion imaging; PCI, Percutaneous coronary intervention; PET, Positron emission tomography; SPECT, Single-photon emission computed tomography; WDHR, Western Denmark Heart Registry.

* Corresponding author. Department of Cardiology, Hospital Unit West, Gl. Landevej 61, DK-7400, Herning, Denmark.

E-mail addresses: sw@dadlnet.dk (S. Winther), ita@clin.au.dk (I.T. Andersen), lars.christian.gormsen@clin.au.dk (L.C. Gormsen), flemming.hald@rsyd.dk (F.H. Steffensen), lenehuche@gmail.com (L.H. Nielsen), erikgrov@rm.dk (E.L. Grove), axeldiederichsen@ouh.rsyd.dk (A.C.P. Diederichsen), Grazina.Urbonaviciene@viborg.rm.dk (G. Urbonaviciene), Jess.Lambrechtsen@rsyd.dk (J. Lambrechtsen), tz@rn.dk (T. Zaremba), frankpetere@googlemail.com (F.-P. Elpert), majed.h.husain@rsyd.dk (M. Husain), mwz@rn.dk (M.W. Zelechowski), heb@dadlnet.dk (H.E. Bøtker), morboett@rm.dk (M. Bøttcher).

https://doi.org/10.1016/j.jcct.2021.08.001
Received 31 May 2021; Received in revised form 27 July 2021; Accepted 16 August 2021
Available online 27 August 2021

Conclusion: In patients completing coronary CTA, second-line MPI testing seems to identify patients at low risk of future events. MPI seems to have the potential to act as gatekeeper for ICA after coronary CTA.

1. Introduction

Coronary computed tomography angiography (CTA) is an established test for ruling-out obstructive coronary artery disease (CAD) in patients with a low-to-intermediate pre-test CAD probability.[1] Prognostic studies have shown a trend towards improved prognosis when using coronary CTA compared with functional testing as first-line test in patients with symptoms suggestive of CAD.[2–4] However, due to only moderately positive predictive values of coronary CTA, downstream myocardial perfusion imaging (MPI) tests are recommended to avoid unnecessary elective invasive coronary angiographies (ICA). This approach is recommended to assess the hemodynamic importance of coronary stenoses identified by coronary CTA and to guide revascularization.[1,5]

Several MPI tests, including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and cardiac magnetic resonance (CMR), are used as second-line diagnostic tests after an abnormal coronary CTA. Diagnostic accuracy studies using invasive fractional flow reserve (FFR) as a reference have shown somewhat divergent results.[6,7] Two recent studies using ICA-FFR as reference tested the diagnostic accuracy of MPI as a selective imaging strategy.[8,9] Both these trials showed low concordance between myocardial perfusion defects and stenosis with FFR <0.80 but higher concordance between absence of myocardial perfusion defects and stenosis with FFR ≥0.80.

Therefore, although a selective MPI strategy after coronary CTA appears to misclassify many patients with stenosis and FFR <0.80, the prognosis has previously been shown to be good in patients with symptoms suggestive of obstructive CAD managed with first-line MPI.[10] However, because of the low sensitivity found in patients after a primary CTA concerns have been raised regarding the use of MPI as a second-line diagnostic test.

The primary aim of this study was therefore to describe event-rates of mortality, myocardial infarction and late revascularization according to downstream testing in patients undergoing coronary CTA due to suspicion of chronic coronary syndrome.

2. Materials and methods

2.1. Study design

This cohort study was conducted using a regional Danish population-based clinical quality database, The Western Denmark Heart Registry (WDHR)[11] from which we identified all patients who underwent first-time coronary CTA from January 2008 to December 2017 at all hospitals (n = 13) in the Western part of Denmark (uptake area 3.3 million; 55% of the total Danish population). The cohort comprised all adult patients without previously documented CAD but with symptoms suggestive of stable obstructive CAD who completed a coronary CTA (Fig. 1). Patient characteristics were defined on the day of the coronary CTA. We categorized patients according to the downstream testing performed in a post-coronary CTA window of 120-days, and followed patients from day 120 to either death, migration or end of follow-up (June 30, 2018). This study was approved by the Danish Data Protection.

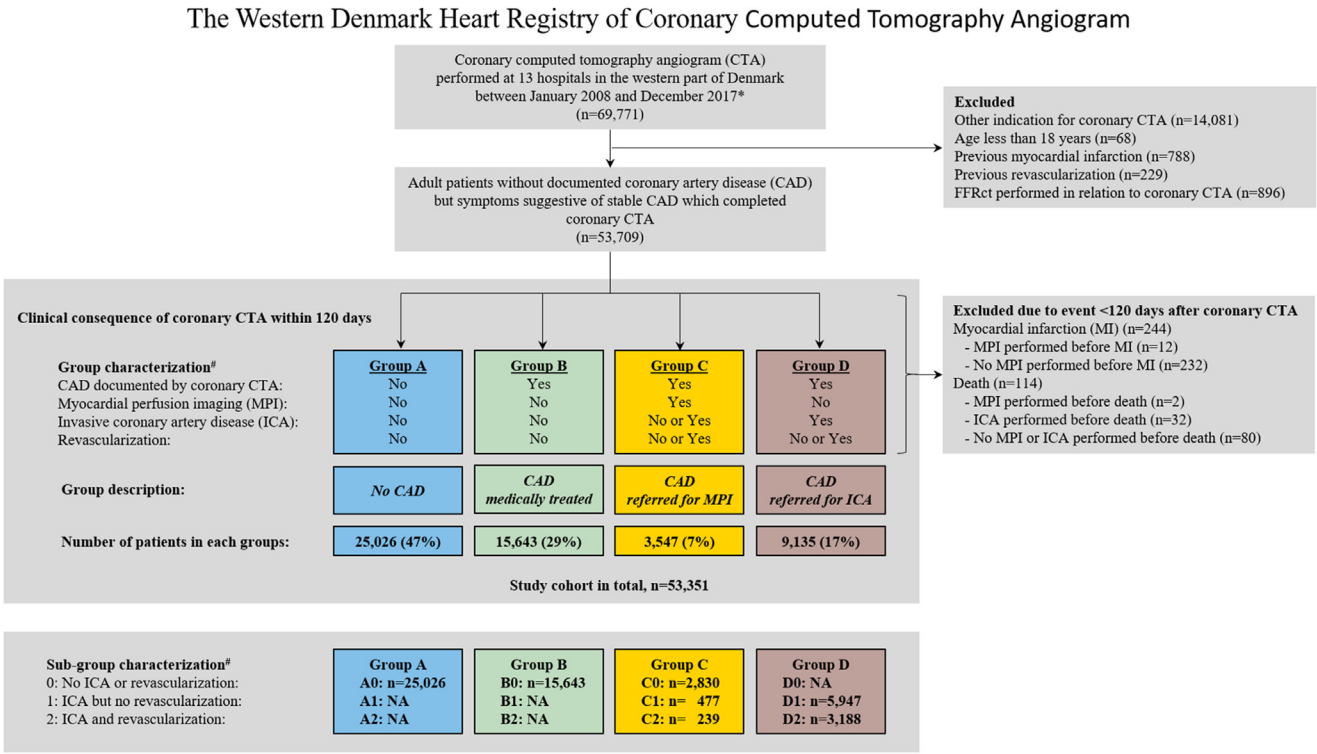

Fig. 1. Flow chart of study patients and of groups and subgroups defined by real-world clinical consequences of coronary CTA in the period within the first 120 days after coronary CTA.

* If a patient had more than one coronary CTA examination, only the first was included in the study.

Based on information from the first 4 months after CTA.

Abbreviations: CTA: computed tomography angiography; CAD: coronary artery disease; MPI: myocardial perfusion imaging; ICA: invasive coronary angiography; FFRct: fractional flow reserve calculated from CTA images.

2.2. Data sources

In Denmark, all registered residents are automatically entitled to publicly financed healthcare. In the Western part of Denmark, all cardiac centers are required to enter all coronary CTA, ICA and revascularizations with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) procedures into the WDHR. Patient baseline characteristics, including cardiac risk factors and symptoms as well as indications and findings at coronary CTA and ICA, are also registered in the WDHR.

We used the National Patient Registry (DNPR), which contains information on all hospital/outpatient diagnosis, tests, and procedures performed in Denmark. Since 1994, the diagnosis codes have followed the International Classification of Diseases, 10th Revision (ICD-10). Myocardial perfusion imaging was identified by procedural codes. SPECT and PET tracers used for the MPIs were sestamibi (^{99m}Tc) and rubidium (^{82}Rb) and only NaI(Tl)- based detector were used for SPECT in the region. ICA, PCI and CABG were identified from the WDHR and/or the DNPR. Information on mortality was obtained in the Danish Civil Personal Register; and myocardial infarction and comorbidity from the DNPR. ICD-10, procedural and anatomical therapeutic classification codes used in this study are presented in eTable 1.

2.3. Clinical consequence of procedures

We used a post-coronary CTA 120-day window to categorize patients into groups and subgroups according to the coronary CTA results and the post-CTA clinical consequence of a) either testing with MPI or ICA and b) either no early revascularization or early revascularization (Fig. 1).

Patients were divided into four groups: Group A (*No CAD*); absence of any coronary calcium or plaque at the initial coronary CTA and no MPI or ICA performed in the 120-day post-coronary CTA window. Group B (*CAD treated medically*); presence of coronary calcium or plaque at the initial coronary CTA but no MPI or ICA performed in the 120-day post-coronary CTA window. Group C (*referred for MPI*); MPI performed in the 120-day post-coronary CTA window. Group D (*referred for ICA*); ICA performed in the 120-day post-coronary CTA window without MPI being performed between the coronary CTA and ICA. Obstructive disease at coronary CTA were defined as a >50% diameter stenosis and at ICA defined as a >50% diameter stenosis and fractional flow reserve <0.80 if measured.

Subgroups of group C and D (*referred for MPI and ICA*) were defined according to whether ICA or revascularization were performed as outlined in Fig. 1. Patients in group A and B, as well as subgroup C0, were all managed non-invasively; these patients had no CAD, CAD treated medically after coronary CTA or treated medically after MPI. Patients in subgroups C1 and D1 underwent ICA and were treated medically with or without prior MPI. Patients in subgroups C2 and D2 were revascularized in the 120-day post-coronary CTA window, with or without MPI being performed between the coronary CTA and the ICA. Late revascularization was defined as PCI or CABG performed >120-day post-coronary CTA. The 120 day window was chosen to avoid including revascularizations related to the initial CTA investigation in the end-point.

2.4. Statistical analysis

The primary endpoint was defined as a composite of all-cause mortality and myocardial infarction. A secondary endpoint was late revascularization. Follow-up regarding both endpoints started 120 days after coronary CTA. Patients who died or had a myocardial infarction within 120 days after coronary CTA were excluded from the follow-up analysis (Fig. 1).

Time-to-event analysis was performed using univariate and multivariate Cox regression of the cause-specific hazard ratios (HR). Cumulative incidence functions for each endpoint were generated to illustrate the risk over time. For the Cox multiple regression analysis, we included age, gender, smoking status and Charlson comorbidity index at baseline together with post-test use of antihypertensive and lipid-lowering therapy. All incomplete smoking data (8%) were created by multiple imputation for the adjusted analysis. Stratified analysis was performed for the primary endpoint according to groups medically treated after coronary CTA, and for patients who were referred to MPI or ICA. We stratified based on CACS with a cut-off of 400 and according to the number of major coronary vessels with suspected obstructive disease. For the stratified analysis, missing data regarding coronary stenosis at coronary CTA were imputed from ICA, if performed. However, 1,088 (2%) patients had missing data despite this imputation.

Table 1
Baseline characteristics of included patients.

Table 1. Patient demographics

Groups	Total
	All patients
Number of patients	53,351 (100%)
Characteristics	
Sex, male	24,402 (45.7%)
Age (years)	57.4 ± 11.3
- <50	13,775 (25.8%)
- 50- <60	16,565 (31.1%)
- 60 - <70	15,851 (29.7%)
- ≥70	7,160 (13.4%)
Body Mass Index (kg/m^2)[a]	26.7 ± 4.4
Smoking	
- Never	20,573 (38.6%)
- Former	17,338 (32.5%)
- Active	11,160 (20.9%)
- Missing	4,280 (8.0%)
Symptoms	
- Typical chest pain	5,105 (9.6%)
- Atypical chest pain	20,702 (38.8%)
- Non-specific chest pain	13,816 (25.9%)
- Dyspnea	3,181 (6.0%)
- Missing[b]	10,547 (19.8%)
Pre-test probability risk score[c]	9% [5–18]
Comorbidity	
Hypercholesterolemia	18,866 (35.4%)
Hypertension	25,270 (47.4%)
Diabetes	4,594 (8.6%)
Charlson comorbidity	
- No comorbidity (0 points)	35,303 (66.2%)
- Moderate comorbidity (1 points)	9,925 (18.6%)
- Severe comorbidity (≥2 points)	8,123 (15.2%)
Coronary artery calcium score and computed tomography angiography	
CACS	0 [0–83]
- 0	23,350 (43.8%)
- 1-99	12,299 (23.1%)
- 100-399	6,013 (11.3%)
- ≥400	4,797 (9.0%)
- Missing	6,892 (12.9%)
Disease severity by CTA:	
- No CAD	26,001 (48.9%)
- Non-obstructive CAD	15,789 (29.7%)
- 1-vessel obstructive disease	5,658 (10.6%)
- 2-vessel obstructive disease	1,746 (3.3%)
- 3-vessel obstructive disease	675 (1.3%)

Values are n (%) or mean ± SD or median [IQR].
[a] BMI data are missing in 14% of patients.
[b] In the early inclusion period symptoms was not a mandatory field in the WDHR.
[c] The CAD consortium basic pre-test probability risk model was used.

3. Results

A total of 67,771 first-time coronary CTAs were performed in the Western part of Denmark between 2008 and end of 2017 (Fig. 1 and eFig. 1). The study cohort was restricted to 53,709 (79%) adult patients

Table 2
Medical treatment, use of diagnostic test, and revascularization within 120 days after coronary CTA. Definitions of the groups are described in Figs. 1 and 2.

Table 2. Diagnostic test and revascularization within 120 days after coronary CTA

Groups	Total	A	B	C	D
	All patients	No CAD	CAD medically treated	Referred for MPI	Referred for ICA
Number of patients	53,351 (100%)	25,026 (46.9%)	15,643 (29.3%)	3,547 (6.7%)	9,135 (17.1%)
Myocardial perfusion imaging					
MPI	3,547 (6.7%)	Non	Non	3,547 (6.7%)	Non
Type of MPI					
- SPECT	2,153 (60.7%)	Non	Non	2,153 (60.7%)	Non
- PET	760 (21.4%)	Non	Non	760 21.4%)	Non
- CMR	634 (17.9%)	Non	Non	634 (17.9%)	Non
Time, coronary CTA to MPI	28 [14–49]	Non	Non	28 [14–49]	Non
Time, MPI to ICA	23 [12–38]	Non	Non	23 [12–38]	Non
Invasive coronary angiography					
ICA	9,851 (18.5%)	Non	Non	716 (20.2%)	9,135 (100%)
Indication for ICA					
- Stable angina pectoris	8,637 (90.1%)	Non	Non	648 (90.1%[a])	7,989 (90.0%)
- Unstable angina pectoris	257 (2.7%)	Non	Non	12 (1.7%[a])	245 (2.8%)
- Other	692 (7.2%)	Non	Non	45 (6.4%[a])	647 (7.3%)
Disease severity at ICA:					
- Non-obstructive disease	5,282 (54.0%)	Non	Non	408 (57.1%)	4,874 (53.8%)
- 1-vessel obstructive disease	2,677 (27.4%)	Non	Non	190 (26.6%)	2,487 (27.5%)
- 2-vessel obstructive disease	1,149 (11.8%)	Non	Non	88 (12.3%)	1,061 (11.7%)
- 3-vessel obstructive disease	667 (6.8%)	Non	Non	28 (3.9%)	639 (7.1%)
Time, coronary CTA to ICA	21 [11–34]	Non	Non	39 [27–63]	20 [11–31]
Revascularization - Early					
Revascularization	3,428 (6.4%)	Non	Non	240 (33.5%[a])	3,188 (34.9%)
- Percutaneous coronary intervention	2,660 (5.0%)	Non	Non	175 (25.0%[a])	2,485 (27.2%)
- Coronary artery bypass grafting	821 (1.5%)	Non	Non	65 (6.8%[a])	756 (8.3%)
Time, coronary CTA to revascularization	30 [19–48]	Non	Non	47 [27–73]	30 [19–46]

Values are n (%) or median [IQR]. Times are given in days.
[a] Percentage of the patients referred for ICA, (n = 716).

without previously documented CAD, but with symptoms suggestive of obstructive CAD and no FFRct performed in relation to the coronary CTA. Of these patients, 40,669 (76%) did not undergo further coronary investigation – 25,026 (47%) due to no CAD (Group A) and 15,643 (29%) due to CAD which were treated medically (Group B). In a 120-day time-window from the coronary CTA, 3,547 (7%) patients completed a MPI diagnostic test (Group C) and 9,135 (17%) were referred to and completed an ICA (Group D). Finally, 358 (0.7%) patients were not categorized and were excluded due to myocardial infarction (n = 244) or death (114) in the 120-day time-window from the coronary CTA (Fig. 1).

Baseline characteristics, symptoms, pre-test probability of CAD, co-morbidity and coronary CTA findings are presented in Table 1 and for each of the four groups in eTable 2. Patients referred to further diagnostic testing, especially ICA, were more frequently, males, were older and had typical symptoms. Furthermore, CACS was higher and multi-vessel disease was more frequently present.

Information regarding post-coronary CTA, MPI, ICA and re-vascularizations performed within the 120-day time-window from the coronary CTA are presented in Table 2. The fraction of patients redeeming prescriptions for lipid-lowering therapy after coronary CTA were 17.7% for group A (*no CAD*), 47.3% for group B (*CAD medically treated*), 58.0% for group C (*referred for MPI*) and 84.5% for group D (*referred for ICA*). Changes in medical therapy after the primary coronary CTA according to groups are listed in eTable 3.

Follow-up time was up to 10.1 years, median 3.7 years [1.9–5.8], and a total of 210,178 patient years were at risk.

3.1. Mortality and myocardial infarction

During follow-up, the primary endpoint occurred in 2,026 (3.8%) patients later than 120 days after coronary CTA. In total, 1,516 (2.8%) patients died and 573 (1.1%) had a myocardial infarction. Event rates at 1 and 5 years, unadjusted and adjusted HR, and the cumulative incidence for each of the four groups are presented in Fig. 2 and eTable 4. The unadjusted HR of the primary endpoint with group A (*no CAD*) as reference increased between groups, so that the HRs were 2.39 (2.13–2.68) for group B (*CAD medically treated*), 2.83 (2.37–3.39) for group C (*referred for MPI*) and 3.87 (3.45–4.34) for group D (*referred for ICA*). Patient characteristics-adjusted HRs ratios for the primary endpoint with group A (*No CAD*) as a reference were 1.37 (1.21–1.55) for group B (*CAD medically treated*), 1.68 (1.39–2.03) for group C (*referred for MPI*) and 1.94 (1.69–2.23) for group D (*referred for ICA*).

3.2. Stratified analysis of subgroup

Group C (*referred for MPI*) was divided into subgroups C0, C1 and C2, according to whether the patients underwent no further testing after MPI, further downstream testing with ICA or ICA with early revascularization, respectively (Fig. 1). Group D (*referred for ICA*) was divided into subgroups D1 and D2, according to whether early revascularization was deferred or performed.

Within 120 days from the coronary CTA, ICA was performed after MPI in 716 (20.2%) patients. The early revascularization rate was 33.5% in patients completing both MPI and ICA and 34.9% in patients referred directly to ICA after coronary CTA (Table 2).

For the primary endpoint, the cumulative incidence of the subgroups (A0, B0, C0, C1, C2, D1 and D2) are illustrated in Fig. 2 and the unadjusted HRs are presented in eTable 5.

When comparing the subgroups; medically treated after coronary CTA (B), undergoing MPI (C0) and undergoing ICA (D1) (Fig. 1), the subgroups B and D1 had an unadjusted HR of 0.87 (0.72–1.05) and 1.30 (1.07–1.59) and an adjusted HR of 0.81 (0.67–0.98) and 1.08 (0.89–1.33) with subgroup C0 (n = 2,830) as a reference (Table 3).

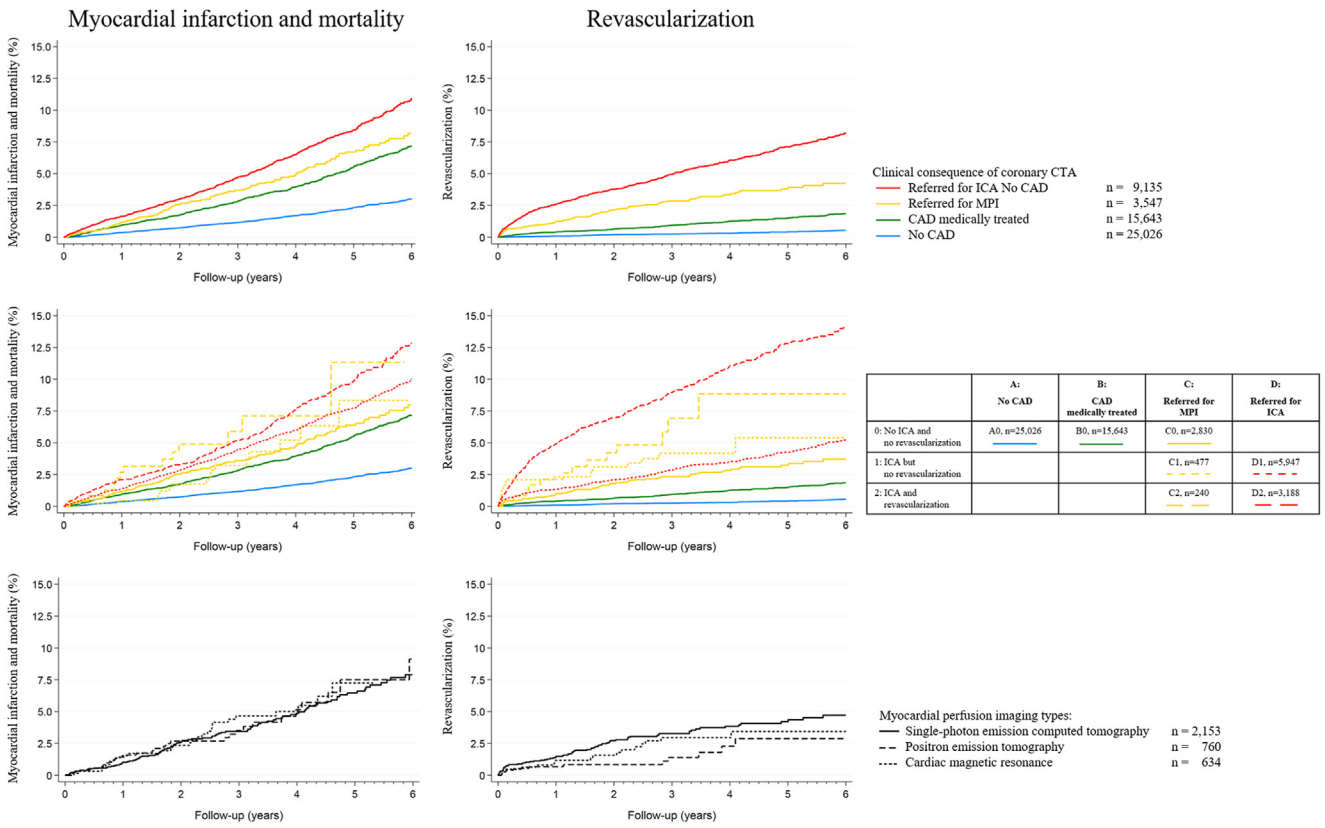

Fig. 2. Cumulative incidence of the combined primary endpoint all-cause mortality and myocardial infarction occurring more than 120 days after coronary CTA and the secondary endpoint late revascularization.
Groups (A and B) and subgroups (C and D) are defined within 120 days after coronary CTA according to the results of coronary CTA, the real-world diagnostic work-up and early revascularization procedures after coronary CTA. Finally, cumulative incidence is illustrated according to the type of MPI used in diagnostic work-up within 120 days after coronary CTA (E and F).
Abbreviations: Similar abbreviations as Fig. 1.

3.3. Stratified analysis according to disease-severity

Stratified analysis based on disease severity at coronary CTA in the subgroups medical treated after coronary CTA (B), MPI (C0) and ICA (D1), showed similarly adjusted HRs for the subgroups for strata with low CACS, no/non-obstructive disease and multi-vessel disease, respectively. Patients with single-vessel obstructive disease at coronary CTA had a better prognosis in subgroup C0 than in group B and a similar prognosis to subgroup D1. Finally, patients with CACS ≥400 at coronary CTA had a similar prognosis in subgroup C0 as group B but the prognosis was poorer compared to subgroup D1 as showed in Table 3, eFigs. 2 and 3.

3.4. Type of myocardial perfusion imaging

In total, 3,547 (6.7%) were referred to MPI after coronary CTA; 2,153 (60.7%) SPECT, 760 (21.4%) PET and 634 (17.9%) CMR (Table 2). No difference in cumulative incidence of the primary endpoint was observed according to type of MPI used (SPECT, PET or CMR) (Fig. 2).

3.5. Secondary endpoint of late revascularization

Revascularization more than 120 days after the coronary CTA occurred in 954 (1.8%) patients in the follow-up period. For revascularization and with group A (*No CAD*) as a reference, the unadjusted HR increased between groups, so that the HR was 3.45 (2.70–4.43) in group B (*CAD medically treated*), 8.90 (6.73–11.77) for group C (*referred for MPI*) and 16.63 (13.39–20.65) group D (*referred for ICA*) (Fig. 2 and eTable 4). The cumulative incidences in the subgroups and HRs are presented in Fig. 2 and eTable 5. In subgroup C1 (*referred for MPI and finally ICA, but no early revascularization*), there was an increased revascularization rate (n = 10) between 120 and 180 days after coronary CTA. However, 7 (70%) of these revascularizations were delayed CABGs. No difference in cumulative incidence of late revascularization was observed according to type of MPI as illustrated in Fig. 2.

4. Discussion

In this large cohort of patients referred to coronary CTA suspected of chronic coronary syndrome over the last 10 years, we investigated the prognosis of patients based on the post coronary CTA diagnostic work-up. Our data indicate that the current strategy of MPI as second-line test in selected patients appears effective as it defers more that 80% of patients from ICA and is associated with low event-rates of myocardial infarction and all-cause mortality comparable to those observed in patients receiving only medical treatment for their CAD after coronary CTA. After adjusting for patient baseline characteristics and medical treatment, patients referred for MPI and ICA had similar event-rates. Furthermore, patients managed non-invasively with MPI had a low long-term revascularization rate of <1% per year, indicating good medical symptom management. However, our study also demonstrated a lower number of redeemed prescriptions on lipid-lowering therapy after MPI compared with ICA. Interestingly, stratified analysis identified a subgroup of patients with CACS ≥400 who seemed to have a better prognosis if investigated by ICA than by MPI.

Coronary CTA is recommended as first-line diagnostic test in patients with a low-to-intermediate pre-test probability of CAD.[1] Coronary CTA has a high negative predictive value for obstructive CAD and allows for accurate visualization and quantification of atherosclerotic disease and

Table 3
Prognosis regarding the primary endpoint, mortality and myocardial infarction, in subgroups of patient which were medically treated after coronary CTA, MPI and ICA, respectively. Further stratified analysis based on coronary calcium severity and obstructive disease severity at the baseline coronary CTA. Values are numbers and hazard ratios (CI 95%).

Table 3. Subgroup and stratified analysis of primary endpoint

Sub-group	B	C0	D1
	Medically treated after coronary CTA	Medically treated after MPI	Medically treated after ICA
Number of patients	15,643	2,830	5,947
Follow-up time, years[a]	3.4 [1.7–5.6]	3.2 [1.8–4.7]	4.1 [1.8–6.1]
Primary endpoint: Mortality and myocardial infarction			
Number of patients	15,643	2,830	5,947
Number of events	672 (4.3%)	127 (4.5%)	437(7.4%)
- Death/MI	512 (3.3%)/160 (1.0%)	90 (3.2%)/37 (1.3%)	315 (5.3%)/122 (2.1%)
Hazard ratios, unadjusted	0.87 (0.72–1.05)	Ref	1.30 (1.07–1.59)
Hazard ratios, adjusted[a]	0.81 (0.67–0.98)	Ref	1.08 (0.89–1.33)
Stratified analysis: Mortality and myocardial infarction			
Stratum: Coronary artery calcium score <400			
Number of patients	14,051	2,202	3,403
Number of events	529 (3.8%)	70 (3.2%)	166 (4.9%)
- Death/MI	401 (2.9%)/128 (0.9%)	53 (2.4%)/17 (0.8%)	114 (3.4%)/52 (1.5%)
Hazard ratios, unadjusted	1.12 (0.87–1.43)	Ref	1.21 (0.91–1.60)
Hazard ratios, adjusted[a]	0.97 (0.76–1.25)	Ref	1.13 (0.85–1.50)
Stratum: Coronary artery calcium score ≥400			
Number of patients	806	384	1,934
Number of events	110 (13.7%)	45 (11.7%)	213 (11.0%)
- Death/MI	90 (11.2%)/20 (2.5%)	28 (7.3%)/17 (4.4%)	159 (8.2%)/54 (2.8%)
Hazard ratios, unadjusted	0.89 (0.63–1.26)	Ref	0.67 (0.48–0.92)
Hazard ratios, adjusted[a]	0.83 (0.59–1.18)	Ref	0.68 (0.49–0.94)
Stratum: No or non-obstructive CAD at coronary CTA			
Number of patients	13,883	1,319	2,174
Number of events	512 (3.7%)	51 (3.9%)	191 (8.8%)
- Death/MI	396 (2.9%)/116 (0.8%)	34 (2.6%)/17 (1.3%)	150 (6.9%)/41 (1.9%)
Hazard ratios, unadjusted	0.95 (0.71–1.27)	Ref	1.86 (1.37–2.54)
Hazard ratios, adjusted[a]	0.80 (0.60–1.06)	Ref	1.25 (0.91–1.71)
Stratum: 1-vessel disease at coronary CTA			
Number of patients	925	953	2,668
Number of events	69 (7.5%)	29 (3.0%)	141 (5.3%)
- Death/MI	47 (5.1%)/22 (2.4%)	24 (2.5%)/5 (0.5%)	94 (3.5%)/47 (1.8%)
Hazard ratios, unadjusted	1.92 (1.24–2.97)	Ref	1.45 (0.97–2.16)
Hazard ratios, adjusted[a]	1.62 (1.04–2.51)	Ref	1.39 (0.92–2.08)
Stratum: 2-or 3-vessel disease at coronary CTA			
Number of patients	215	156	1,063
Number of events	35 (16.3%)	13 (8.3%)	104 (9.8%)
- Death/MI	25 (11.6%)/10 (4.7%)	10 (6.4%)/3 (1.9%)	71 (6.7%)/33 (3.1%)
Hazard ratios, unadjusted	1.53 (0.81–2.91)	Ref	0.94 (0.53–1.68)
Hazard ratios, adjusted[a]	1.08 (0.56–2.07)	Ref	0.79 (0.44–1.44)

[a] Hazard ratios are adjusted for age, gender, smoking status and comorbidity at baseline together with post-test use of antihypertensive and lipid-lowering therapy.

therefore enable risk factor management.[3] However, once possible obstructive CAD is diagnosed with coronary CTA, selective non-invasive imaging is recommended to avoid unnecessary ICAs due to the low positive predictive value of coronary CTA and the lack of evidence of a survival benefit of revascularization over medical treatment in patients with chronic coronary syndrome.[12–14] Consequently, personalized diagnostic strategies are warranted after coronary CTA-proven disease has been established.

Two studies have demonstrated that intermediate-to-high-risk patients with symptoms suggestive of CAD have similar 1-year clinical outcomes when randomized to investigative strategies with management decisions guided either by CMR or ICA-FFR.[10,15] Hence, imaging with selective functional testing in patients without high-risk coronary plaque features seems attractive as a gatekeeper strategy for ICA. In the present study, only 20% of patients investigated with MPI after coronary CTA were referred for ICA, illustrating the impact of MPI as a gatekeeper for ICA. However, a second non-invasive test introduces further delay of potential revascularization and the revascularization rate after a hybrid imaging strategy remained low (34%) in our study compared with that reported in other studies.[4,16]

Several studies have demonstrated that conclusions about the hemodynamic effect of coronary stenosis based on MPI and ICA-FFR are discordant in many patients.[8,9,17] These discordances are also present in up to 30–40% of patients when coronary stenosis is are evaluated based on FFR and invasively measured coronary flow reserve.[18] No studies have assessed the value of revascularization based on an abnormal FFR in patients with no myocardial ischemia demonstrated at MPI.

The recently published ISCHEMIA trial assigned patients with moderate or severe ischemia to an initial invasive strategy or to a conservative strategy with angiography only if medical therapy failed.[14] This study did not find evidence that an initial invasive strategy reduced the risk of myocardial infraction or death. In contrast, we studied patients investigated with an initial strategy of coronary CTA and selective MPI and demonstrated that patients terminated after MPI had a good prognosis

and a low long-term revascularization rate indicating good medical symptom management.

Our stratified analysis showed a tendency towards that patients with less advanced disease severity had a more favourable outcome when evaluated with MPI compared to ICA and that patients with advanced disease had a more favourable outcome when evaluated with ICA. However, these sub-analyses were based on a relatively low number of events and showed only differences in patients with quite severe calcification in whom an invasive strategy reduced the primary endpoint compared with a non-invasive strategy with selective MPI. These findings might be explained by balanced vessel disease, which may not be diagnosed without myocardial blood flow quantification or other factors related to referral bias. Our study was not sufficiently powered to perform further detailed sub-analyses comparing SPECT with PET and CMR. Additionally, the reduced number of redeemed prescriptions on lipid-lowering therapy after MPI might have impacted the results.

5. Limitations

Our study included a large real-world cohort of symptomatic patients from all hospitals in Western Denmark. Inter-observer and inter-site variability of post-coronary CTA management entails heterogeneity in the choice of treatment and diagnostic strategy.

No data regarding the extent of perfusion defects on the MPIs were available. Nonetheless, all center performing MPI operate according to national guidelines recommending in general that patients with more than 10% reversible ischemia are referred to ICA. However, this preclude us from identifying patients with minor perfusion defects routinely terminated without ICA.

Due to statistically considerations, our follow-up started 120 days after coronary CTA to enable classification of patients into subgroups according to MPI, ICA and revascularization procedures performed in relation to coronary CTA. Hence, we excluded 244 patients with myocardial infarction and 114 patients dying within the first 120 days after coronary CTA. Among these, only 12 (4.9%) patients with myocardial infarctions and 2 (1.8%) who died had this early event after completing the MPI test (Fig. 1). Therefore, it is reasonable to believe that the prognosis in the early period after coronary CTA was good in the MPI subgroup and that it is unlikely that exclusion of these patients impacted the results substantially.

Finally, inherent to the real-world observational design is the risk of residual confounding between groups. Although we used statistical methods to adjust for baseline characteristics, CAD severity and post-coronary CTA medical treatment, selection/referral bias might have impacted the results. Hence, some centers might have used MPI in patients with less pronounced disease. Others in highly selective patients, who were unsuitable for ICA with revascularization and antiplatelet therapy.

6. Conclusion

Using real-world data, this study confirms that clinicians seem to be able to selected patients for medical treatment or second-line testing with MPI or ICA accordingly to the patients future risk of death or myocardial infarction and late revascularization after coronary CTA. In addition, in patients with an initial coronary CTA and need for further selective diagnostic testing, patients referred for MPI had a low long-term cardiac event rates. These results indicate that MPI can be used to safely defer patient from ICA after a coronary CTA but validation in prospective trials are needed.

ClinicalTrials.gov identifier

None.

Funding

Health Research Fund of the Central Denmark Region.

Declaration of competing interest

The authors have no disclosures related to this project, but report the following general disclosures: S. Winther and M Bøttcher acknowledges support from Acarix in the form of an institutional research grant. M Bøttcher discloses advisory board participation for NOVO Nordisk, AstraZeneca, Bayer, Sanofi and Acarix. ELG has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD, Portola Pharmaceuticals and Roche and research grants from Boehringer Ingelheim. The remaining authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2021.08.001.

References

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.
2. Investigators S-H, Newby DE, Adamson PD, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379:924–933.
3. investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385:2383–2391.
4. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165.
6. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–1107.
7. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging*. 2015:8.
8. Nissen L, Winther S, Westra J, et al. Diagnosing coronary artery disease after a positive coronary computed tomography angiography: the Dan-NICAD open label, parallel, head to head, randomized controlled diagnostic accuracy trial of cardiovascular magnetic resonance and myocardial perfusion scintigraphy. *Eur Heart J Cardiovasc Imaging*. 2018;19:369–377.
9. Sand NPR, Veien KT, Nielsen SS, et al. Prospective comparison of FFR derived from coronary CT angiography with SPECT perfusion imaging in stable coronary artery disease: the ReASSESS study. *JACC Cardiovasc Imaging*. 2018;11:1640–1650.
10. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med*. 2019;380:2418–2428.
11. Schmidt M, Maeng M, Madsen M, Sorensen HT, Jensen LO, Jakobsen CJ. The western Denmark heart registry: its influence on cardiovascular patient care. *J Am Coll Cardiol*. 2018;71:1259–1272.
12. Sedlis SP, Hartigan PM, Teo KK, et al. Effect of PCI on long-term survival in patients with stable ischemic heart disease. *N Engl J Med*. 2015;373:1937–1946.
13. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med*. 2018;379:250–259.
14. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.
15. Buckert D, Witzel S, Steinacker JM, Rottbauer W, Bernhardt P. Comparing cardiac magnetic resonance-guided versus angiography-guided treatment of patients with stable coronary artery disease: results from a prospective randomized controlled trial. *JACC Cardiovasc Imaging*. 2018;11:987–996.
16. Nissen L, Winther S, Westra J, et al. Influence of Cardiac CT based disease severity and clinical symptoms on the diagnostic performance of myocardial perfusion. *Int J Cardiovasc Imag*. 2019;35:1709–1720.
17. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73:161–173.
18. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. *J Am Coll Cardiol*. 2016;67:1158–1169.