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Prognostic value of coronary computed tomography angiographic derived fractional flow reserve: a systematic review and meta-analysis

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ABSTRACT

Objectives To obtain more powerful assessment of the prognostic value of fractional flow reserve_{CT} testing we performed a systematic literature review and collaborative meta-analysis of studies that assessed clinical outcomes of CT-derived calculation of FFR (FFR_{CT}) (HeartFlow) analysis in patients with stable coronary artery disease (CAD).

Methods We searched PubMed and Web of Science electronic databases for published studies that evaluated clinical outcomes following fractional flow reserve_{CT} testing between 1 January 2010 and 31 December 2020. The primary endpoint was defined as 'all-cause mortality (ACM) or myocardial infarction (MI)' at 12-month follow-up. Exploratory analyses were performed using major adverse cardiovascular events (MACEs, ACM+MI+unplanned revascularisation), ACM, MI, spontaneous MI or unplanned (>3 months) revascularisation as the endpoint.

Results Five studies were identified including a total of 5460 patients eligible for meta-analyses. The primary endpoint occurred in 60 (1.1%) patients, 0.6% (13/2126) with FFR_{CT}>0.80 and 1.4% (47/3334) with FFR_{CT}≤0.80 (relative risk (RR) 2.31 (95% CI 1.29 to 4.13), p=0.005). Likewise, MACE, MI, spontaneous MI or unplanned revascularisation occurred more frequently in patients with FFR_{CT}≤0.80 versus patients with FFR_{CT}>0.80. Each 0.10-unit FFR_{CT} reduction was associated with a greater risk of the primary endpoint (RR 1.67 (95% CI 1.47 to 1.87), p<0.001).

Conclusions The 12-month outcomes in patients with stable CAD show low rates of events in those with a negative FFR_{CT} result, and lower risk of an unfavourable outcome in patients with a negative test result compared with patients with a positive test result. Moreover, the FFR_{CT} numerical value was inversely associated with outcomes.

INTRODUCTION

The recent landmark PROspective Multicentre Study for Evaluation of Chest Pain (PROMISE) and SCOTish Tomography of Heart (SCOT-HEART) multicenter, randomised trials provide evidence for the initial use of coronary CT angiography (CTA) as an alternative to non-invasive functional testing with equivalent or more

favourable clinical outcomes when compared with usual practice, and no significant sacrifice on healthcare costs.¹⁻⁴ Accordingly, coronary CTA is now recommended by societal guidelines as a first-line test in patients with stable chest pain at low-intermediate pretest risk.^{5,6} Coronary CTA is the most accurate non-invasive test to exclude or detect coronary artery disease (CAD); however, in patients with moderate stenosis, it is often discordant with fractional flow reserve (FFR), which is the gold standard for detection of lesion-specific ischaemia and for decision-making in the catheterisation laboratory.⁷⁻⁹ Different techniques for non-invasive CT-derived calculation of FFR have been introduced,⁸⁻¹² with the majority of clinical experience and trial evidence based on the HeartFlow FFR_{CT} model.^{8,9,13-19} Recent real-world and prospective controlled studies indicate that FFR_{CT} may provide prognostic information.¹⁷⁻¹⁹ However, except for the ADVANCE (Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care) Registry,¹⁹ these studies were small and with low adverse event rates. Moreover, major determinants of prognosis such as the definition of outcomes and follow-up time periods varied substantially, making comparisons between studies difficult. To delineate further the prognostic value of FFR_{CT} in patients with stable CAD, we undertook a collaborative meta-analysis of studies that compared adverse clinical outcomes in patients with FFR_{CT}>0.80 versus ≤0.80.

METHODS

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).²⁰ PubMed and Web of Science electronic databases were searched for all published studies that evaluated clinical outcomes following FFR_{CT} testing in patients with stable CAD. The following keywords were used: computed tomography angiography, coronary and fractional flow reserve combined with prognosis, death and myocardial infarction. Studies using FFR_{CT} approved by the US Food and Drug Administration (FDA) were considered for



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inclusion. Eligible studies comparing $\text{FFR}_{\text{CT}} > 0.80$ vs ≤ 0.80 in non-emergent patients with stable chest pain including numbers of those with the following cardiovascular events were selected: all-cause mortality (ACM), non-fatal myocardial infarction (MI), spontaneous MI and any coronary revascularisation including percutaneous coronary intervention (PCI) and coronary artery by-pass grafting (CABG). All electronically published papers were screened by titles and/or abstracts and by reviewing full-text papers published in English language from 1 January 2010 until 31 December 2020. In addition, a manual screening of the cited references of all retrieved studies and key review papers was performed for eligible papers. The Newcastle-Ottawa Scale quality evaluation for observational studies²¹ was used for quality assessment of the included studies. No patient-level or other identifiable data were collected, and thus Independent Ethics Committee review was not required for this study.

Data extraction and analysis

Authors of all the included studies provided the requested data for analyses. Available demographic data and available baseline characteristics were extracted as numbers or means \pm SD. Uniform outcome definitions across all studies were applied allowing for meaningful meta-analysis. Numbers of events for each endpoint in each comparison group were extracted. Overlapping patients between databases of the included studies were removed. The authors SG and JA experienced in systematic reviews and meta-analyses conducted the search and data management independently. Any disagreement was solved by consensus. First authors of all included studies assisted in providing data for the meta-analysis. HeartFlow employees assisted in capturing the data from the PLATFORM (Prospective Longitudinal Trial of FFR_{CT} : Outcome and Resource Impacts)¹⁸ and ADVANCE Registry study databases¹⁹ (CR, SM). Reasons for exclusion from the meta-analysis of patients from the original studies were registered. HeartFlow had no influence on planning the study or data analyses.

CT angiography derived fractional flow reserve

The scientific basis for FFR_{CT} has previously been described in detail.¹⁰ CTA images are transmitted to a central FFR_{CT} laboratory (HeartFlow, Redwood City, California, USA) for analysis by experienced personnel and dedicated computers.⁸ In general, a patient with all FFR_{CT} values > 0.80 (hereafter termed FFR_{CT} negative) is considered not to have haemodynamically significant CAD, while $\text{FFR}_{\text{CT}} \leq 0.80$ (FFR_{CT} positive) indicates the presence of haemodynamically significant coronary disease.^{8 9 13–17 19} Analyses were based on the lowest per-patient or lesion-specific FFR_{CT} value (table 1).

Definition of endpoints and follow-up

The primary composite endpoint was defined as a composite of ACM or any MI. Secondary endpoints were (1) major adverse cardiovascular events (MACEs) defined as a composite of ACM, any MI and unplanned revascularisation (PCI or CABG). Other secondary endpoints explored were (2) ACM, (3) any MI and (4) spontaneous MI. MI was defined according to the fourth universal definition of MI.²² Unplanned revascularisation was defined as a procedure performed > 3 months from the CTA investigation. Additionally, eligible studies were required to provide the composite of 'death and any MI' in different FFR_{CT} categories (< 0.61 , $0.61–0.70$, $0.71–0.80$, $0.81–0.90$ and > 0.90). Studies that did not meet these criteria or could not provide sufficient

data were excluded from this study. Follow-up was 12 months from the time of the CTA scan.

Statistics

Baseline variables from the included studies were pooled and analysed either as weighted means or absolute numbers. The weighted mean difference method was used for pooling of means and their SDs. The reported numbers of patients with 'ACM or MI', MACE, ACM, MI, unplanned revascularisation, PCI and CABG were pooled for the FFR_{CT} positive and negative groups in order to estimate the risk ratio (RR) with 95% CI. For the overall estimated RR, a p value ≤ 0.05 was considered statistically significant. The continuous relationship between the frequency of the primary endpoint and FFR_{CT} categorical values was assessed using weighted linear regression. Due to the relatively low event numbers and absence of significant heterogeneity between studies, we chose a fixed effects model (Mantel-Haenszel) in all analyses. Heterogeneity among studies was tested using Cochran's Q (p value < 0.05 was considered statistically significant). The I^2 ranging between 0% and 100% indicated the percentage of variation in the study results attributed to between-study heterogeneity and an I^2 value greater than 20% was considered statistically significant. Publication bias was assessed by the Egger's test. All analyses and plots were performed using the meta-analysis package of the statistic software program STATA V.15SE (STATA Corporation, Lakeway Drive, College Station, Texas, USA).

RESULTS

The search strategy and flow of the search process are shown in figure 1 and online supplemental table 1. Three multicentre prospective and two single-centre observational studies provided the required data and were included in the meta-analysis: PLATFORM trial,¹⁸ the Aarhus FFR_{CT} outcome study,¹⁷ NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) Trial,²³ the Vancouver FFR_{CT} outcome study²⁴ and the ADVANCE Registry.¹⁹

Study and patient characteristics

Characteristics of the five studies are summarised in table 1. Studies were published between 2016 and 2020. Sample size in the original studies varied between 177 and 4737. The total sample size in the original study cohorts was 6004, of whom 5460 (91%) patients were included in the meta-analysis. Reasons for patient exclusion were lack of 12-month follow-up data (n=502) or overlapping patients between databases (n=42) (table 1). Of the 5460 patients, 2126 were FFR_{CT} negative and 3334 FFR_{CT} positive. The proportion of patients with a least one diameter stenosis $\geq 50\%$ or $\text{FFR}_{\text{CT}} \leq 0.80$ varied between studies from 51% to 81% (average 72%) and from 32% to 67% (average 61%), respectively. When compared with FFR_{CT} negative patients, those with a positive test result were older, more often of male sex, more frequently smokers, diabetics and hypertensives, and more often had classical angina (table 2).

Clinical outcomes

Definition of the primary endpoint and length of follow-up varied between studies (table 3). Accordingly, frequency of the primary endpoint varied substantially, 0.8%–13.4% in patients with a negative FFR_{CT} result versus 1.5%–73.4% in those with a positive test result. The meta-analysis primary endpoint occurred more frequently in FFR_{CT} positive versus FFR_{CT} negative patients, 1.4% (47/3334)

Table 1 Studies included in the meta-analysis: design, patient, CT acquisition and selection characteristics

Study (ref), publication year, N	Study design	Funding	Location/number of sites	Patients	Type of scanner/ acquisition mode*
PLATFORM, Douglas <i>et al</i> 2016, n=1771 ¹⁸	Multicentre prospective cohort study, CTA and FFR _{CT} local site read	HeartFlow	Europe/11	<ul style="list-style-type: none"> ▶ Clinically suspected CAD ▶ Mean age, 61 years ▶ Male gender, 60% ▶ Mean pretest likelihood of obstructive CAD, 49% ▶ Minimum CTA diameter stenosis ≥30% 	Single-source or dual-source CT scanners with a minimum of 64 detector rows/ Prospective ECG triggering or retrospective gating
Aarhus study, Nørgaard <i>et al</i> 2018, n=677 ¹⁷	Single-centre observational registry, CTA and FFR _{CT} local site read	Investigator-initiated	Denmark/1	<ul style="list-style-type: none"> ▶ Clinically suspected CAD ▶ Mean age, 61 years ▶ Male gender, 66% ▶ Mean pretest likelihood of obstructive CAD, 45% ▶ Minimum CTA diameter stenosis ≥30% 	Somatom Definition Flash or Force, Siemens/ Prospective ECG triggering
ADVANCE Registry, Patel <i>et al</i> 2020, n=4737 ¹⁹	Multicentre prospective registry, CTA and FFR _{CT} local site read	HeartFlow	Europe, Japan, North America/38	<ul style="list-style-type: none"> ▶ Clinically suspected CAD ▶ Mean age, 66 years ▶ Male gender, 66% ▶ Mean pretest likelihood of obstructive CAD, 62% ▶ Minimum CTA diameter stenosis ≥30% 	Single-source or dual-source CT scanners with a minimum of 64 detector rows/ Prospective ECG triggering or retrospective gating
NXT, Ihsdayhid <i>et al</i> 2019, n=206 ²³	Subanalysis of prospective multicentre study, CTA and FFR _{CT} core-lab analysis	Investigator-initiated (the original NXT study was funded by HeartFlow, but the follow-up study was performed by investigators independently of HeartFlow).	Europe, Japan, Australia, South Korea/9	<ul style="list-style-type: none"> ▶ Clinically suspected CAD ▶ Mean age, 64 years ▶ Male gender, 68% ▶ Mean pretest likelihood of obstructive CAD, 54% ▶ Min CTA diameter stenosis ≥30% 	Single-source or dual-source CT scanners with a minimum of 64 detector rows/ Prospective ECG triggering or retrospective gating
Vancouver study, McNabney <i>et al</i> 2019, n=207 ²⁴	Single-centre observational registry, CTA local site read	Investigator-initiated	Canada/1	<ul style="list-style-type: none"> ▶ Suspected stable CAD ▶ Mean age, 62 years ▶ Male gender, 76% ▶ Mean pretest likelihood of obstructive CAD, information not available ▶ Minimum CTA diameter stenosis ≥30% 	Either 64-row (Discovery 750HD, GE) or 256-row (Revolution, GE) scanners/ Prospective ECG triggering or retrospective gating
Study (ref), publication year, N	FFR _{CT} reading point	Proportion of patients with CTA stenosis ≥50%/ FFR _{CT} ≤0.80	Number of patients included in meta-analysis/% relative to the total number of patients in the mother study (reason for exclusion)		
PLATFORM, Douglas <i>et al</i> 2016, n=1771 ¹⁸	The lowest per-patient value	51%/39%	177/100%		
Aarhus study, Nørgaard <i>et al</i> 2018, n=677 ¹⁷	Two centimetres distal to stenosis in the event of lesion-specific ischaemia, otherwise the lowest per-patient value†	75%/36%	584/86% (1-year follow-up data were not available in 93 patients)		
ADVANCE Registry, Patel <i>et al</i> 2020, n=4737 ¹⁹	The lowest per-patient value	72%/66%	4328/91% (1-year follow-up data were not available in 409 patients)		
NXT, Ihsdayhid <i>et al</i> 2019, n=206 ²³	In a blinded fashion corresponding to the location of the pressure wire (lesion-specific ischaemia)	81%/53%	206/100%		
Vancouver study, McNabney <i>et al</i> 2019, n=207 ²⁴	Two centimetres distal to stenosis (lesion-specific ischaemia)	65%/32%	165/80% (42 patients were included in the ADVANCE Registry)		

*Scan acquisition was performed in accordance with the Society of Cardiovascular Computed Tomography (SCCT) best practice guidelines in all studies.

†Only 201 out of the 584 patients included in the study had FFR_{CT} prescribed, of whom FFR_{CT} was analysable in 177.

‡For this meta-analysis, the lowest per-patient FFR_{CT} value was used.

ADVANCE, Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care registry; CAD, coronary artery disease; CTA, CT angiography; FFR_{CT}, CTA-derived fractional flow reserve; NXT, Analysis of Coronary Blood Flow Using CT Angiography, Next Steps trial; PLATFORM, Prospective Longitudinal Trial of FFRCT: Outcome and Resource impacts trial.

vs 0.6% (13/2126), RR 2.31 (95% CI 1.29 to 4.13), $p=0.005$ (figure 2). Likewise, MACE (5.2% vs 1.9%; RR, 2.69 (95% CI 1.91 to 3.78); $p<0.001$), 'any MI' (0.5% vs 0.2%; RR, 3.28 (1.33 to 8.06); $p=0.010$), 'spontaneous MI' (0.4% vs 0.2%; RR, 2.63 (1.05 to 6.68); $p=0.038$) or 'unplanned revascularisation' (4.1% vs 1.3%; RR 3.20 (2.13 to 4.80); $p<0.001$) were more frequent in FFR_{CT} positive than in test negative patients (figure 2). These findings were consistent even after exclusion of the ADVANCE registry

data (online supplemental figure 1). Meta-analysis of revascularisation data is shown in online supplemental figure 2. All analyses were fairly homogeneous with $I^2=0$ for heterogeneity and insignificant p values >0.4 .

Primary endpoint in reduced FFR_{CT} categorical values

The relationship between the risk of the primary endpoint and the numerical FFR_{CT} value is shown in figure 3. Each 0.10-unit

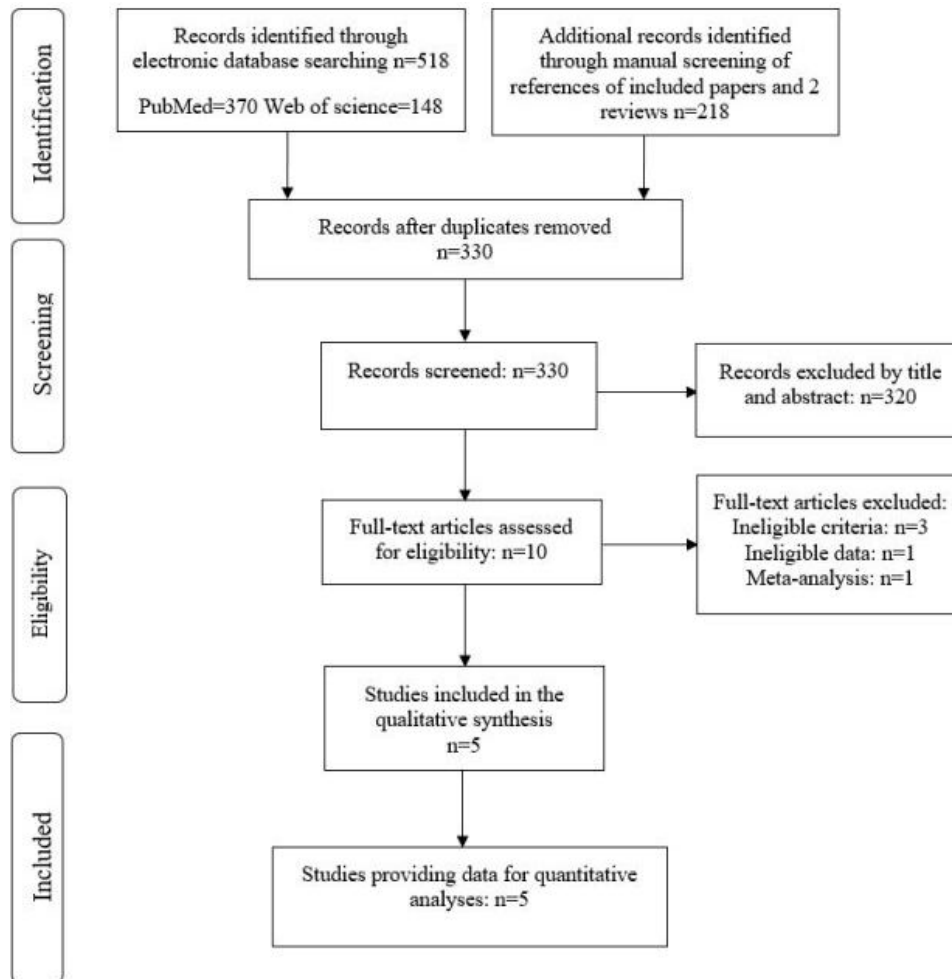


Figure 1 Flowchart of search and selection of eligible studies.

FFR_{CT} reduction was associated with a greater risk of the primary endpoint, RR 1.67 (95% CI 1.47 to 1.87), $p < 0.001$, with $I^2 = 0.0\%$ and p value = 0.72.

Quality assessment of included studies

Study quality assessed by the Newcastle-Ottawa scale showed high quality of the included studies (online supplemental

table 2). Egger's test for publication bias was not significant, $p = 0.59$.

DISCUSSION

Major findings in this systematic review and meta-analysis can be summarised as follows: (1) A negative FFR_{CT} result (> 0.80) in patients with stable CAD was associated with a low incidence

Table 2 Baseline characteristics of patients with FFR_{CT} > 0.80 compared with those with FFR_{CT} ≤ 0.80

	Number of studies providing data	FFR _{CT} > 0.80 (n=2126)	FFR _{CT} ≤ 0.80 (n=3334)	P values
Age (years, SD)	5	64.0 \pm 10.1	65.6 \pm 9.7	<0.001
Sex (male)	5	1243/2126 (58.5%)	2342/3334 (70.2%)	<0.001
Body mass index (SD)	5	26.4 \pm 4.6	26.3 \pm 4.3	0.067
Diabetes mellitus	5	331/2118 (15.6%)	784/3334 (23.5%)	<0.001
Hypertension	5	1112/2118 (52.5%)	2060/3333 (61.8%)	<0.001
Current smoker	3	349/2106 (16.6%)	610/3322 (18.4%)	0.005
Family history of CAD	3	251/566 (44.3%)	157/359 (43.7%)	0.68
Angina				
Typical angina	5	374/2106 (17.8%)	848/3315 (25.6%)	<0.001
Atypical angina	5	1004/2106 (47.7%)	1169/3315 (35.3%)	<0.001
Non-cardiac chest pain	5	168/2106 (8.0%)	190/3315 (5.7%)	0.002
Dyspnoea	5	196/2116 (9.3%)	330/3315 (10.0%)	0.61

Values presented are means or numbers (percentages) if not stated otherwise, with p values for the differences between the two groups. CAD, coronary artery disease; FFR, fractional flow reserve.

Table 3 Studies included in the meta-analysis: primary outcome analysis

Study (ref), publication year, N	Primary outcome endpoint	Endpoint source	Endpoint adjudication	Follow-up	Primary endpoint frequency FFR _{CT} >0.80 (no of patients with an event)/FFR _{CT} ≤0.80 (no of patients with an event) (statistical significance)
PLATFORM, Douglas <i>et al</i> 2016, n=177* ¹⁸	Composite of ACM, non-fatal MI or unplanned revascularisation for chest pain leading to urgent revascularisation	Clinical visits (97.4%), chart review (2.6%)	Independent clinical events committee whose members were blinded to clinical and coronary CTA/FFR _{CT} data using standard prospectively determined definitions	1 year	The endpoint was reported according to the patient management strategy and not the FFR _{CT} result. (Overall, the endpoint occurred in two patients, 1.1%.)
Aarhus study, Nørgaard <i>et al</i> 2018, n=677 ¹⁷	Composite of ACM, non-fatal MI, hospitalisation for unstable angina or unplanned revascularisation	Data were retrieved from Danish National registries*	Endpoint data were retrieved from national complete registries* r	Median (range) 2 (0.7–3.4) years	†3.9% (n=11)/9.4% (n=6) in the medical treatment only group and 6.6% (n=7) in those having ICA performed (no statistical testing)
ADVANCE Registry, Patel <i>et al</i> 2020, n=4737 ¹⁹	Composite of ACM, non-fatal MI or unplanned hospitalisation for ACS leading to revascularisation	Reported from each site to an electronically case record form	Independent clinical events committee whose members were blinded to clinical and coronary CTA/FFR _{CT} data using standard prospectively determined definitions	1 year	0.7% (n=12)/1.4% (n=43) (RR 1.81, 95% CI 0.96 to 3.43; p=0.06)
NXT, Ihdajhid <i>et al</i> 2019, n=206 ²³	Composite of ACM, non-fatal MI or any revascularisation	Medical records or telephone interview	Clinical events were adjudicated by physicians at each site who were blinded to CTA and FFR _{CT} data using standard determined definitions	Median (range) 4.7 (4.4–5.3) years	13.4% (n=13)/73.4% (n=80) (HR 9.2, 95% CI 5.1 to 17; p<0.01)
Vancouver study, McNabney <i>et al</i> 2019, n=207 ²⁴	ACM, non-fatal MI, late revascularisation (>90 days)	Medical records and self-reported questionnaires	Clinical events were adjudicated by physicians who were blinded to CTA and FFR _{CT} data using standard determined definitions	Median (IQR) 1.3 (0.7–2.4) years	5.8% (n=8)/28.6% (n=18) (no statistical testing)

*The Danish National Patient Registry records discharge diagnosis in accordance with the International Classification of Diseases classification system from all hospitalisations and outpatient clinic visits in Denmark. The Civil Registration Registry contains complete data on mortality.

†Cumulative incidence proportions.

ACM, all-cause mortality; CTA, CT angiography; ICA, invasive coronary angiography; MI, myocardial infarction; RR, relative risk.

of death or MI at 12 months. (2) Patients with a positive FFR_{CT} result had more subsequent clinical adverse events compared with those with a negative test result. (3) Each FFR_{CT} unit reduction was associated with an increased risk of ‘death or any MI’. Notably, this meta-analysis provides consistency across fairly homogeneous study designs, and by applying a uniform outcome measure in all studies included in the analysis.

In patients with stable chest pain and stenosis of uncertain functional significance, the diagnostic performance and correlation of FFR_{CT} against measured FFR is high and superior to coronary CTA and conventional non-invasive ischaemia testing.^{8,9} Moreover, FFR_{CT} shows promise to guide clinical decision-making in patients with CAD (eg, by reducing the number of referrals to invasive coronary angiography (ICA) after CTA, and by identification of patients most likely to require revascularisation),^{13–18} and emerging data indicate that the FFR_{CT} result may predict clinical outcomes.^{17–19,23,24} Because FFR_{CT} requires off-site analysis, there is much interest in past generations of reduced order computational fluid dynamics or newer principles requiring less comprehensive anatomic modelling and computational activity thus enabling workstation based on-site analysis.^{11,12} Although diagnostically of incremental value to CTA, these on-site functional applications are not used in clinical practice hence knowledge regarding their ability to inform clinical outcomes is limited. Inclusion of studies that used early on-site CT-derived FFR prototypes in this meta-analysis would not be meaningful since these tools have not yet reached clinical-use standards and because they apply fundamentally different technologies than FFR_{CT}.²⁵ Therefore, the present review and meta-analysis

included only studies reporting clinical outcomes after FFR_{CT} testing.

The five studies included in the present meta-analysis applied different definitions of clinical outcomes and varying follow-up periods hence substantial differences in the frequency of outcomes were demonstrated. However, in the present collaboration, similar outcome measures were captured from each study to enable meaningful outcome meta-analysis. Importantly, all previous studies reporting clinical outcomes in relation to the FFR_{CT} result included in addition to ‘death and MI’ also ‘revascularisation’ as a component in the primary composite endpoint. This strategy increases the incidence rate of the composite endpoint, the statistical power and the ability to detect statistical differences between groups. However, this strategy is problematic since ‘revascularisation’ is under influence of perceptions from both the patient and the healthcare provider, and thus is less bias-resistant than death or MI. Moreover, death or MI typically occurs with marked less frequency than ‘revascularisation’; for example, in the ADVANCE registry, almost three out of four adverse events during follow-up were ‘late revascularisation’.¹⁹ The present meta-analysis adds to the literature by demonstrating that FFR_{CT} analysis in stable CAD is predictive of a hard endpoint comprising ‘ACM or any MI’. Moreover, exploratory analyses demonstrated a potential role of FFR_{CT} testing in predicting MI alone. When interpreting these findings, it should be acknowledged that overall event rates were low, and that the ADVANCE registry accounted for approximately 80% of the total number of patients and adverse events in this study. However, FFR_{CT} was predictive of ‘ACM or any MI’ in the meta-analysis even

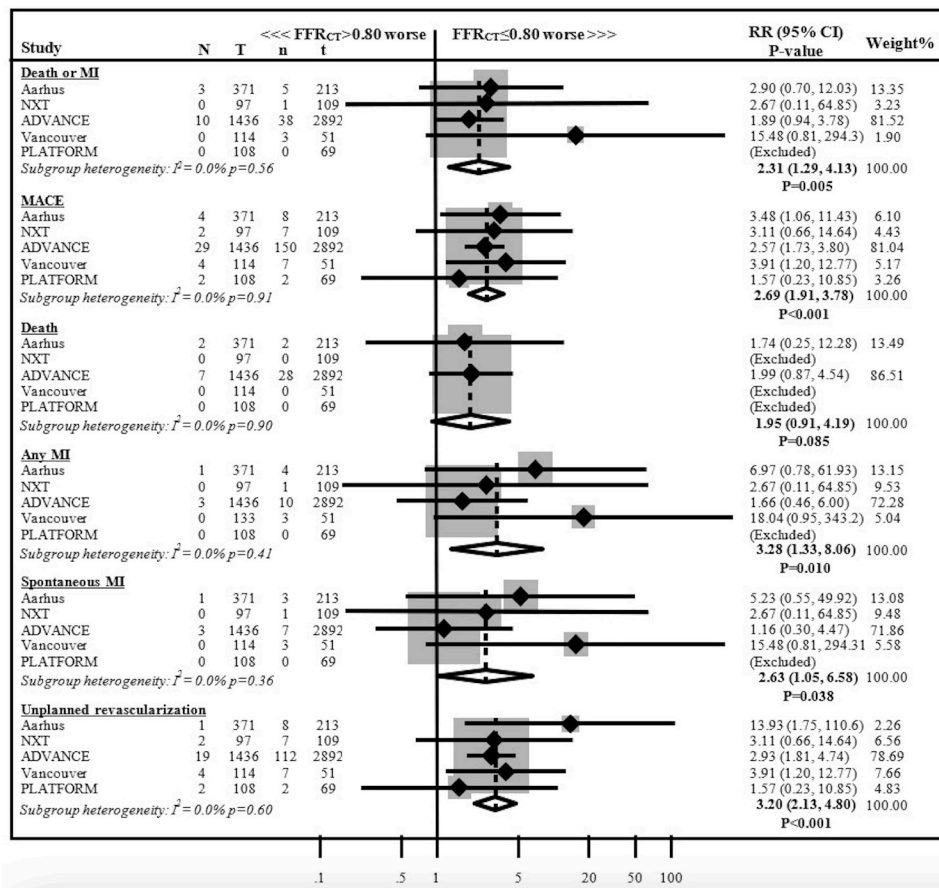


Figure 2 Meta-analysis of the primary composite endpoint (death or any MI) and secondary endpoints at 12-month follow-up. FFR_{CT}>0.80: N=number of patients with adverse events; T=total number of patients. FFR_{CT}≤0.80: n and t=number of patients with adverse events and total number of patients. Strata with zero events were not included in the analysis. MACE (major adverse cardiac event) was defined as a composite of death, any MI or unplanned revascularisation. Unplanned revascularisation was defined as any revascularisation (percutaneous coronary intervention and/or coronary artery bypass grafting) occurring between 3-month and 12-month follow-up. ADVANCE, Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care' study¹⁹; FFR_{CT}, CTA-derived fractional flow reserve; MI, myocardial infarction; NXT, Analysis of Coronary Blood Flow Using CT Angiography: Next Steps trial²³; PLATFORM, Prospective Longitudinal Trial of FFRCT: Outcome and Resource impacts trial¹⁸; RR, risk ratio.

after exclusion of the ADVANCE registry data. Moreover, when comparing the frequency of the primary endpoint of 'ACM or any MI' in the ADVANCE registry versus the pooled data in this meta-analysis, the statistical power increased from 0.60 to 0.75 which is above the average observed in meta-analyses of cardiovascular trials.²⁶ On the other hand, for the prediction of 'spontaneous MI' the statistical power increased from 0.20 in the ADVANCE registry to 0.28 in the pooled analysis which is still well below the optimum of 0.80–0.90.

The use of a dichotomous FFR_{CT} threshold to guide patient management decisions, namely, to avoid further downstream testing and revascularisation, remains controversial because of difficulty in confidence for any binary interpretation of values close to the threshold and since it is well known from the invasive literature that the highest risk of an unfavourable clinical outcome and the greatest benefit of revascularisation is obtained in patients with the lowest FFR value.^{27–28} The present study confirms in a large dataset previous findings demonstrating an FFR_{CT} risk continuum, with lower values being associated with higher risk.^{17–19,23} The integration of an FFR_{CT} continuous interpretation strategy with emerging CTA-derived metrics such as quantification of high-risk plaques,²⁹ haemodynamic plaque forces³⁰ and the ischaemic myocardium³¹ may potentially allow for a more individualised CTA 'one-stop-shop' platform for

guiding therapeutic decision-making and for predicting clinical outcomes.²⁷ More studies are needed to elucidate the risk/benefit trade-offs of a continuous versus a dichotomous FFR_{CT} interpretation strategy in clinical practice.

This meta-analysis confirms the findings in previously published single-centre and multicentre studies, as well as the invasive physiology literature, the value of FFR_{CT} testing to inform clinical outcomes in patients with stable CAD. Importantly, a normal FFR_{CT} result in this large cohort of symptomatic patients, where almost three out of four had at least one coronary diameter stenosis ≥50%, was associated with a very low risk of 12-month death or MI (~0.6%). These findings together with the high negative predictive value of FFR_{CT} for prediction of ischaemia support integration of FFR_{CT} in the diagnostic workup of patients with CAD to safely mitigate the use of additional downstream testing after CTA.

Limitations

Although this meta-analysis comprised a large and representative number of patients undergoing CTA-FFR_{CT} testing in clinical practice, data are based on observational and registry studies, and as such, may be subject to referral bias. Because downstream patient management was not mandated or randomised in any

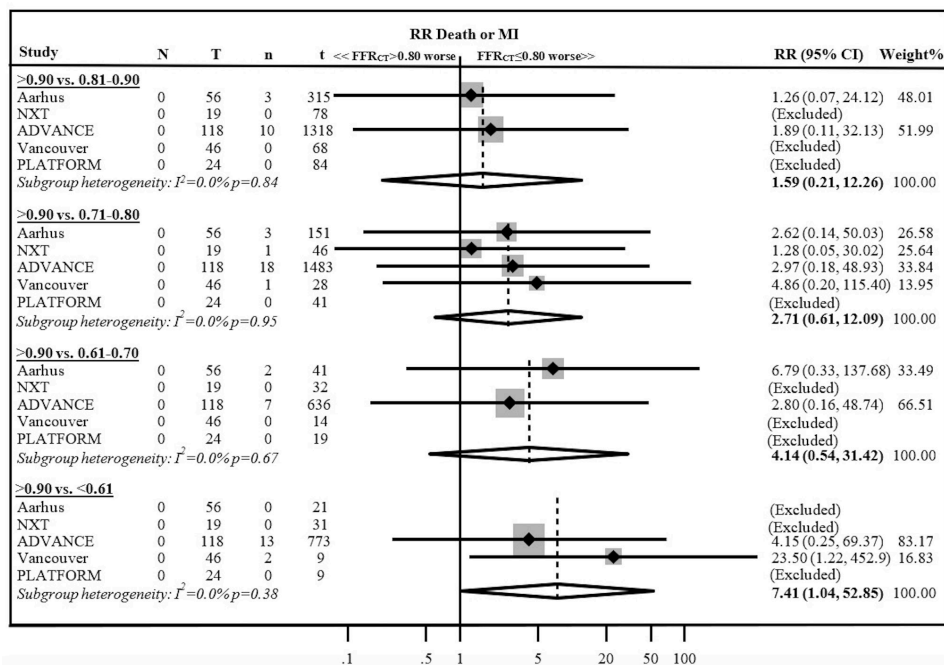


Figure 3 Relationship between the primary endpoint (death or MI) and the pooled numerical FFR_{CT} value. FFR_{CT} >0.90: N=number of patients with adverse events; T=total number of patients. FFR_{CT} 0.10-unit reduction strata: n and t=number of patients with adverse events and total number patients. Strata with zero events were not included in the analysis. Each 0.10-unit FFR_{CT} reduction was associated with a higher frequency of the primary endpoint, RR 1.67 (95% CI 1.47 to 1.87), $p<0.001$. FFR, fractional flow reserve; MI, myocardial infarction; RR, relative risk.

of the studies, individual CT operators may have integrated different ‘thresholds’ for prescribing FFR_{CT} testing potentially affecting the ratio between negative and positive FFR_{CT} results and patient risk. Moreover, post-CTA-FFR_{CT} patient and clinician decisions on downstream medical therapy, referral to ICA or revascularisation may have been influenced by the FFR_{CT} result, and thus to a varying degree affected the estimated risk estimate (‘confounding by indication’). Accordingly, the present data do not inform any treatment guidance. Another potential source of bias was the fact that not all patients from the original studies were included in the meta-analysis and that the number of adverse events were relatively low. Similar to CTA testing, FFR_{CT} analysis cannot be performed in all patients. In selected real-world data, CT image quality was inadequate for FFR_{CT} computation in up to 5% of the cases.^{19,24} Preliminary data indicate that patients in whom CTA or FFR_{CT} cannot be performed may represent a high-risk group requiring special management attention.³² Outcome data in this patient category were not available for meta-analysis. We were not able, from the present dataset, to perform individual or adjusted data analysis. Patients in this meta-analysis were at relatively low risk of an unfavourable clinical outcome, thus the present findings may not be generalisable to higher risk cohorts. Information on the temporal distribution of adverse events was not available. Information on post-test medication was not available for this analysis. Although the lowest per-patient value was registered in the vast majority of patients (~94% of the total cohort), it cannot be excluded that a similar interpretation strategy in those patients where a lesion-specific reading strategy was applied would have reclassified some to lower FFR_{CT} values.³³ More studies are needed to assess the clinical implications of lesion-specific versus distal segment only FFR_{CT} positivity. The added prognostic information of FFR_{CT} relative to CTA determined stenosis severity or coronary plaque burden cannot be assessed from the present dataset. An important limitation is the lack of

information related to post-test angina. However, the overall rate of unplanned revascularisation among patients with a normal FFR_{CT} result was low (1.3% at 1 year). As specific causes

Key messages

What is already known about the subject?

- ▶ CT angiography (CTA) has emerged as a guideline-directed first-line test in patients with suspected stable coronary artery disease (CAD).
- ▶ In coronary stenosis of uncertain functional significance, FFR_{CT} correlate to measured fractional flow reserve (FFR), and FFR_{CT} is of value to guide clinical decision-making in patients with stable CAD, for example, by reducing the number of referrals to ICA after CTA, and by identification of patients most likely to require revascularisation.
- ▶ Existing knowledge on the prognostic value of FFR_{CT} is based on studies with different definitions of adverse events, different length of follow-up periods and overall low adverse event rates.

What might this study add?

- ▶ By applying a uniform outcome measure across studies, this meta-analysis may provide more powerful and reliable assessment of the prognostic value of FFR_{CT} testing in clinical practice.

How might this impact on clinical practice?

- ▶ The findings in this study, together with the high negative predictive value of FFR_{CT} for prediction of ischaemia, may support integration of FFR_{CT} in the diagnostic workup of patients with CAD to safely mitigate the use of additional downstream testing after CTA.

of mortality were not available in all studies, the overall rate of mortality being attributable to cardiovascular events is not known. However, ACM is of unparalleled relevance and is the most unbiased method to report death.³⁴ Importantly, participating authors of the included studies collaborated on data extraction, which resulted in homogenised datasets minimising biases that otherwise can significantly influence data combination. The comprehensive systematic literature review, as well as the awareness of the participating expert authors of ongoing studies and published literature in this field, has substantially reduced risk of publication bias. Studies with longer follow-up are needed to confirm the present findings.

Conclusions

In patients with stable CAD, this meta-analysis demonstrates that a negative FFR_{CT} result is associated with a low incidence of adverse events at 12 months, with significantly lower risk of death or MI compared with those with a positive FFR_{CT} result. The FFR_{CT} numerical value was inversely related to clinical outcomes. The present study confirms the intermediate-term safety of deferring additional downstream testing in patients with a negative FFR_{CT} result. Large-scale studies assessing the safety of FFR_{CT} testing in patients with higher risk CAD anatomy and with long-term follow-up are warranted.

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