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


ABSTRACT

Objectives To obtain more powerful assessment of the prognostic value of fractional flow reserve (FFRct) testing we performed a systematic literature review and collaborative meta-analysis of studies that assessed clinical outcomes of CT-derived calculation of FFR (FFRct) (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 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 FFRct >0.80 and 1.4% (47/3334) with FFRct ≤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 FFRct ≤0.80 versus patients with FFRct >0.80. Each 0.10-unit FFRct 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 FFRct 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 FFRct 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 introduced9–12 with the majority of clinical experience and trial evidence based on the HeartFlow FFRct model.8,9,13–19 Recent real-world and prospective controlled studies indicate that FFRct may provide prognostic information.17–19 However, except for the ADVANCE (Assessing Diagnostic Value of Non-invasive FFRct 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 FFRct in patients with stable CAD, we undertook a collaborative meta-analysis of studies that compared adverse clinical outcomes in patients with FFRct >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 FFRct 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 FFRct approved by the US Food and Drug Administration (FDA) were considered for...
Review

Inclusion. Eligible studies comparing FFR<sub>CT</sub> > 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 studies 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±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<sub>CT</sub> Outcome and Resource Impacts) and ADVANCE Registry study databases (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<sub>CT</sub> has previously been described in detail. CTA images are transmitted to a central FFR<sub>CT</sub> laboratory (HeartFlow, Redwood City, California, USA) for analysis by experienced personnel and dedicated computers. In general, a patient with all FFR<sub>CT</sub> values >0.80 (hereafter termed FFR<sub>CT</sub> negative) is considered not to have haemodynamically significant CAD, while FFR<sub>CT</sub> ≤0.80 (FFR<sub>CT</sub> positive) indicates the presence of haemodynamically significant coronary disease. Analyses were based on the lowest per-patient or lesion-specific FFR<sub>CT</sub> 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. 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<sub>CT</sub> 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<sub>CT</sub> 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<sub>CT</sub> 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 Cochranes Q (p value <0.05 was considered statistically significant). The I² ranging between 0% and 100% indicated the percentage of variation in the study results attributed to between-study heterogeneity and an I² 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.11SE (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, the Aarhus FFR<sub>CT</sub> outcome study, NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) Trial, the Vancouver FFR<sub>CT</sub> outcome study and the ADVANCE Registry.

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<sub>CT</sub> negative and 3334 FFR<sub>CT</sub> positive. The proportion of patients with a least one diameter stenosis ≥50% or FFR<sub>CT</sub> ≤0.80 varied between studies from 51% to 81% (average 72%) and from 32% to 67% (average 61%), respectively. When compared with FFR<sub>CT</sub> 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<sub>CT</sub> result versus 1.5%–73.4% in those with a positive test result. The meta-analysis primary endpoint occurred more frequently in FFR<sub>CT</sub> positive versus FFR<sub>CT</sub> negative patients, 1.4% (47/3334)
ings were consistent even after exclusion of the ADVANCE registry

FFRCT positive than in test negative patients (figure 1.3%; RR 3.20 (2.13 to 4.80); p<0.001) were more frequent in

1.9% 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 FFRCT 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 I²=0 for heterogeneity and insignificant p values >0.4.

Primary endpoint in reduced FFRCT categorical values

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

<table>
<thead>
<tr>
<th>Study design</th>
<th>Funding</th>
<th>Location/number of sites</th>
<th>Patients</th>
<th>Type of scanner/ acquisition mode*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATFORM, Douglas et al 2016, n=177118</td>
<td>Multicentre prospective cohort study, CTA and FFRCT local site read</td>
<td>HeartFlow</td>
<td>Europe/11</td>
<td>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</td>
</tr>
<tr>
<td>Aarhus study, Nørgaard et al 2018, n=4737</td>
<td>Single-centre observational registry, CTA and FFRCT local site read</td>
<td>Investigator-initiated</td>
<td>Denmark/1</td>
<td>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</td>
</tr>
<tr>
<td>ADVANCE Registry, Patel et al 2020, n=4737</td>
<td>Multicentre prospective registry, CTA and FFRCT local site read</td>
<td>HeartFlow</td>
<td>Europe, Japan, North America/38</td>
<td>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</td>
</tr>
<tr>
<td>NXT, Ihidayhid et al 2019, n=20623</td>
<td>Subanalysis of prospective multicentre study, CTA and FFRCT core-lab analysis</td>
<td>Investigator-initiated</td>
<td>Europe, Japan, Australia, South Korea/9</td>
<td>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</td>
</tr>
<tr>
<td>Vancouver study, McNabney et al 2019, n=20623</td>
<td>Single-centre observational registry, CTA local site read</td>
<td>Investigator-initiated</td>
<td>Canada/1</td>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (ref), publication year, N</th>
<th>FFCT reading point</th>
<th>Proportion of patients with CTA stenosis ≥50%/ FFRCT ≤0.80</th>
<th>Number of patients included in meta-analysis/% relative to the total number of patients in the mother study (reason for exclusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATFORM, Douglas et al 2016, n=177118</td>
<td>The lowest per-patient value</td>
<td>51%/39%</td>
<td>1771/100%</td>
</tr>
<tr>
<td>Aarhus study, Nørgaard et al 2018, n=177</td>
<td>Two centimetres distal to stenosis in the event of lesion-specific ischaemia, otherwise the lowest per-patient value+</td>
<td>75%/36%</td>
<td>584/86% (1-year follow-up data were not available in 93 patients)</td>
</tr>
<tr>
<td>ADVANCE Registry, Patel et al 2020, n=4737</td>
<td>The lowest per-patient value</td>
<td>72%/66%</td>
<td>432/91% (1-year follow-up data were not available in 409 patients)</td>
</tr>
<tr>
<td>NXT, Ihidayhid et al 2019, n=20623</td>
<td>In a blinded fashion corresponding to the location of the pressure wire (lesion-specific ischaemia)</td>
<td>81%/53%</td>
<td>206/100%</td>
</tr>
<tr>
<td>Vancouver study, McNabney et al 2019, n=20623</td>
<td>Two centimetres distal to stenosis (lesion-specific ischaemia)</td>
<td>65%/32%</td>
<td>165/80% (42 patients were included in the ADVANCE Registry)</td>
</tr>
</tbody>
</table>

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

1Only 201 out of the 584 patients included in the study had FFRCT, prescribed, of whom FFRCT was analysable in 177.

If this meta-analysis, the lowest per-patient FFRCT, value was used. ADVANCE, Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care registry; CAD, coronary artery disease; CTA, CT angiography; FFRCT, 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 FFRCT positive than in test negative patients (figure 2). These findings were consistent even after exclusion of the ADVANCE registry

FFRCT 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 I²=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<sub>CT</sub> result (>0.80) in patients with stable CAD was associated with a low incidence

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline characteristics of patients with FFR&lt;sub&gt;CT&lt;/sub&gt;&gt;0.80 compared with those with FFR&lt;sub&gt;CT&lt;/sub&gt;≤0.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies providing data</td>
<td>FFR&lt;sub&gt;CT&lt;/sub&gt;&gt;0.80 (n=2126)</td>
</tr>
<tr>
<td>Age (years, SD)</td>
<td>5</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>5</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>3</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>Typical angina</td>
<td>5</td>
</tr>
<tr>
<td>Atypical angina</td>
<td>5</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study (ref), publication year, N</th>
<th>Primary outcome endpoint</th>
<th>Endpoint source</th>
<th>Endpoint adjudication</th>
<th>Follow-up</th>
<th>Primary endpoint frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATFORM, Douglas et al 2016, n=177*</td>
<td>Composite of ACM, non-fatal MI or unplanned revascularisation for chest pain leading to urgent revascularisation</td>
<td>Clinical visits (97.4%), chart review (2.6%)</td>
<td>Independent clinical events committee whose members were blinded to clinical and coronary CTA/FFRCT data using standard prospectively determined definitions</td>
<td>1 year</td>
<td>The endpoint was reported according to the patient management strategy and not the FFR result. (Overall, the endpoint occurred in two patients, 1.1%)</td>
</tr>
<tr>
<td>Aarhus study, Nørgaard et al 2018, n=677</td>
<td>Composite of ACM, non-fatal MI, hospitalisation for unstable angina or unplanned revascularisation</td>
<td>Data were retrieved from Danish National registries*</td>
<td>Endpoint data were retrieved from national complete registries*†</td>
<td>Median (range) 0.7–3.4 years</td>
<td>3.9% (n=22)/9.4% (n=66) in the medical treatment only group and 6.6% (n=7) in those having ICA performed (no statistical testing)</td>
</tr>
<tr>
<td>ADVANCE Registry, Patel et al 2020, n=47379</td>
<td>Composite of ACM, non-fatal MI or unplanned hospitalisation for ACS leading to revascularisation</td>
<td>Reported from each site to an electronically case record form</td>
<td>Independent clinical events committee whose members were blinded to clinical and coronary CTA/FFRCT data using standard prospectively determined definitions</td>
<td>1 year</td>
<td>0.7% (n=12)/1.4% (n=43) (RR 1.81, 95% CI 0.96 to 3.43; p=0.06)</td>
</tr>
<tr>
<td>NXT, Ihdayhid et al 2019, n=207</td>
<td>Composite of ACM, non-fatal MI or any revascularisation</td>
<td>Medical records or telephone interview</td>
<td>Clinical events were adjudicated by physicians who were blinded to clinical and coronary CTA/FFRCT data using standard determined definitions</td>
<td>Median (range) 4.7 (4.4–5.3) years</td>
<td>13.4% (n=13)/73.4% (n=80) (HR 9.2, 95% CI 5.1 to 17; p&lt;0.01)</td>
</tr>
<tr>
<td>Vancouver study, McNabney et al 2019, n=207</td>
<td>ACM, non-fatal MI, late revascularisation (&gt;90 days)</td>
<td>Medical records and self-reported questionnaires</td>
<td>Clinical events were adjudicated by physicians who were blinded to clinical and coronary CTA/FFRCT data using standard determined definitions</td>
<td>Median (IQR) 1.3 (0.7–2.4) years</td>
<td>5.8% (n=8)/28.6% (n=18) (no statistical testing)</td>
</tr>
</tbody>
</table>

*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	extsubscript{CT} result had more subsequent clinical adverse events compared with those with a negative test result. (3) Each FFR	extsubscript{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	extsubscript{CT} against measured FFR is high and superior to coronary CTA and conventional non-invasive ischaemia testing. Moreover, FFR	extsubscript{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). and emerging data indicate that the FFR	extsubscript{CT} result may predict clinical outcomes. Because FFR	extsubscript{CT} requires off-site analysis, there is much interest in past generations of reduced order computational fluid dynamics or newer principles requiring less comprehensive anatomical modelling and computational activity thus enabling workstation based on-site analysis. 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	extsubscript{CT}. Therefore, the present review and meta-analysis included only studies reporting clinical outcomes after FFR	extsubscript{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	extsubscript{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’.

The present meta-analysis adds to the literature by demonstrating that FFR	extsubscript{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	extsubscript{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	extsubscript{CT} was predictive of ‘ACM or any MI’ in the meta-analysis even though death or MI occurred in only 2.6% of patients.
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<sub>CT</sub> 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<sub>CT</sub> risk continuum, with lower values being associated with higher risk.17 19 23 The integration of an FFR<sub>CT</sub> 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<sub>CT</sub> 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<sub>CT</sub> testing to inform clinical outcomes in patients with stable CAD. Importantly, a normal FFR<sub>CT</sub> 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<sub>CT</sub> for prediction of ischaemia support integration of FFR<sub>CT</sub> 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<sub>CT</sub> 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
of the studies, individual CT operators may have integrated different ‘thresholds’ for prescribing FFRCT testing potentially affecting the ratio between negative and positive FFRCT results and patient risk. Moreover, post-CTA-FFRCT patient and clinician decisions on downstream medical therapy, referral to ICA or revascularisation may have been influenced by the FFRCT 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, FFRCT analysis cannot be performed in all patients. In selected real-world data, CT image quality was inadequate for FFRCT computation in up to 5% of the cases. 19 24 Preliminary data indicate that patients in whom CTA or FFRCT 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 FFRCT values. 33 More studies are needed to assess the clinical implications of lesion-specific versus distal segment only FFRCT positivity. The added prognostic information of FFRCT 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 FFRCT result was low (1.3%) at 1 year. As specific causes

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>T</th>
<th>t</th>
<th>RR 0.90 vs 0.81</th>
<th>RR 0.81 vs 0.71</th>
<th>RR 0.71 vs 0.61</th>
<th>RR 0.61 vs 0.50</th>
<th>RR 0.50 vs 0.40</th>
<th>RR 0.40 vs 0.31</th>
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<td>3</td>
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<td>1.99 (0.97, 4.1)</td>
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<td>1.89 (0.11, 3.1)</td>
<td>1.89 (0.11, 3.1)</td>
</tr>
</tbody>
</table>

Figure 3 Relationship between the primary endpoint (death or MI) and the pooled numerical FFRCT value. FFRCT >0.90: N=number of patients with adverse events; T=total number of patients. FFRCT 0.10-unit reduction strata: n=number of patients with adverse events and t=number of patients. Strata with zero events were not included in the analysis. Each 0.10-unit FFRCT 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.

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, FFRCT correlate to measured fractional flow reserve (FFR), and FFRCT 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 FFRCT 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 FFRCT testing in clinical practice.

How might this impact on clinical practice?
- The findings in this study, together with the high negative predictive value of FFRCT, are important for the diagnostic workup of patients with CAD. FFRCT, fractional flow reserve; MI, myocardial infarction; RR, relative risk.
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<sub>CT</sub> 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<sub>CT</sub> result. The FFR<sub>CT</sub> 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<sub>CT</sub> result. Large-scale studies assessing the safety of FFR<sub>CT</sub> testing in patients with higher risk CAD anatomy and with long-term follow-up are warranted.

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Funding This work was supported by the Department of Cardiology, Aarhus University Hospital, and Faculty of Health Sciences, Aarhus University, Aarhus, Denmark.

Competing interests BLN has received unrestricted institutional research grants from Siemens and HeartFlow. TF has served on the Speakers Bureau for HeartFlow. PD has received research grants from HeartFlow. MRP has received research grants from HeartFlow, Bayer, Janssen, and the National Heart, Lung, and Blood Institute, and has served on the advisory board for HeartFlow, Bayer and Janssen. C.R is employee of and owns equity in HeartFlow. SM is an employee of and owns equity in HeartFlow. KN has received institutional research support from Siemens Healthcare. HeartFlow, GE Healthcare and Bayer Healthcare. JL has served as a consultant for and owns stock options in Circle CVI and HeartFlow.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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