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CT angiography compared to invasive angiography for stable coronary disease as predictors of major adverse cardiovascular events- A systematic review and meta-analysis

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ABSTRACT

Background: Computational tomography coronary angiography (CTCA) is increasingly the diagnostic test of choice for investigating patients with stable anginal symptoms.
Objectives: We sought to conduct a systematic review and meta-analysis comparing CTCA with invasive coronary angiography (ICA) with regards to major adverse cardiovascular events (MACE), procedural complications and rates of revascularisation.
Methods: We conducted a systematic review and meta-analysis in line with the PRISMA statement. A literature search was conducted using PubMed, MEDLINE Ovid and Embase, with three studies included in meta-analysis. Statistical analysis was undertaken using Review Manager 5.3 for MacOS software and outcomes expressed as odds ratio, with 95% confidence intervals and sensitivity analysis was conducted.
Results: A total of 5662 patients were included in this study level meta-analysis. There was no difference in MACE between CT and angiography [2.97% v 3.45%, fixed-effect model, OR: 0.84 (0.62–1.14), $p = 0.26$, I^2 0%] and no difference found in rates of myocardial infarction, death or stroke. CTCA was associated with a reduced rate of revascularisation [12.6% v 18.3%, fixed-effects model, OR: 0.64 (0.55–0.75), $p<0.00001$, I^2 =0%]. However, CTCA was not associated with a significantly lower complication rate [0.5% v 1.72%, random effects model, OR: 0.52 (0.06–4.38), $p = 0.55$, I^2 52%].
Conclusion: CTCA is a safe strategy for investigating patients with stable angina with no associated increase in MACE but a reduction in revascularisation rates.

Introduction

The role of computational tomography coronary angiography (CTCA) as an initial diagnostic test for patients under investigation for suspected coronary disease or stable angina is increasingly taking favour in the rapid access chest pain clinic. This has been reflected in the guidelines for investigation for chronic coronary disease generally in patients with a low to intermediate probability of coronary disease, with the ESC guidelines recommending CTCA or functional ischaemic testing to be considered depending on patient characteristics and preference, availability and local experience.[1] The American Heart Association (AHA)/ American College of Cardiology (ACC) have recommended either CTCA or functional testing to investigate patients with stable chest pain and an intermediate-high risk of coronary disease.[2] The UK National Institute for Clinical Excellence (NICE) guidelines (updated 2016) have gone a step further and recommended CTCA as a first line diagnostic test for all patients with suspected angina without known underlying coronary disease.[3] Whilst CTCA is favoured in the guidelines, accessibility to service varies geographically throughout healthcare systems as even within European health care services, there is substantially less access to CTCA than is required to meet guideline recommendations.[4,5] As such even patients who would benefit from CTCA according to the guidelines still end up undergoing an invasive diagnostic angiogram as this is easier in the current infrastructure in many countries. Furthermore,

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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the Covid-19 pandemic has had significant impact on availability of CTCA which may have led to a reduction in its utilisation as a diagnostic test. Invasive angiography has remained a more accessible investigation in many centres. CTCA has been showed to be non-inferior to functional imaging in detecting coronary disease and in occurrence of major adverse cardiovascular events (MACE)[6] and the SCOT-HEART trial showed CTCA superior to standard care in reducing death and improving early symptomatic management.[7,8] Despite the paradigm shift to CTCA as a first line diagnostic test, the role of invasive coronary angiography remains recommended in cases of diagnostic uncertainty and in patients with intermediate-high probability of coronary disease. It is unclear whether invasive angiography as an early investigation strategy will lead to higher rates of revascularisation and if this would have any impact on MACE. With a recent study from the DISCHARGE trial group showing no difference in MACE in patients undergoing initial CTCA compared to ICA,[9] we sought to further quantify the impact of MACE when comparing a CTCA with an ICA.

Methods

We performed a systematic review and meta-analysis of RCTs that compared a CTCA strategy with upfront invasive angiography strategy for the investigation of coronary disease, reporting MACE as outcomes. This was conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analyses statement[10] and has been prospectively registered with PROSPERO (CRD42022332518).

Search strategy

Literature search was undertaken using medical subject headings and keywords included 'CTCA', 'CT coronary', 'CT angiography', 'coronary angiography', 'invasive angiography', 'stable angina', 'atypical angina', 'chest pain'. The search was undertaken in MEDLINE (Ovid interface- 1948-week commencing 2nd May 2022), Embase (Ovid interface- 1980-week commencing 2nd May 2022) and PubMed Central (PMC). We also searched the reference lists of included papers to identify any further relevant studies. The references were imported to Covidence for the screening process. After removal of duplicates, 6251 abstracts were screened by two authors (NC, VT). If any uncertainty, a third author (VV) provided final adjudication. Full texts were screened for inclusion by two authors (NC, VT). This search strategy has been shown in Supp Fig. 1. Fig. 1 below outlines the literature search and screening strategy.

Inclusion criteria

In order for studies to be eligible for inclusion, they were required to be RCTs comparing CTCA with invasive coronary angiography and reporting MACE as outcomes.

Data extraction

Data extraction was undertaken by two independent authors (NC, VT) from downloaded PDFs using Covidence software. This included data on (1) publication details, (2) study design and methodology, (3) participants including baseline characteristics and sample size, (4) clinical outcomes.

Study endpoints

The primary outcome of the study is MACE. This has not been uniformly defined in the three included studies, and so individual outcomes of the composite MACE have also been reported (death, myocardial infarction and stroke).

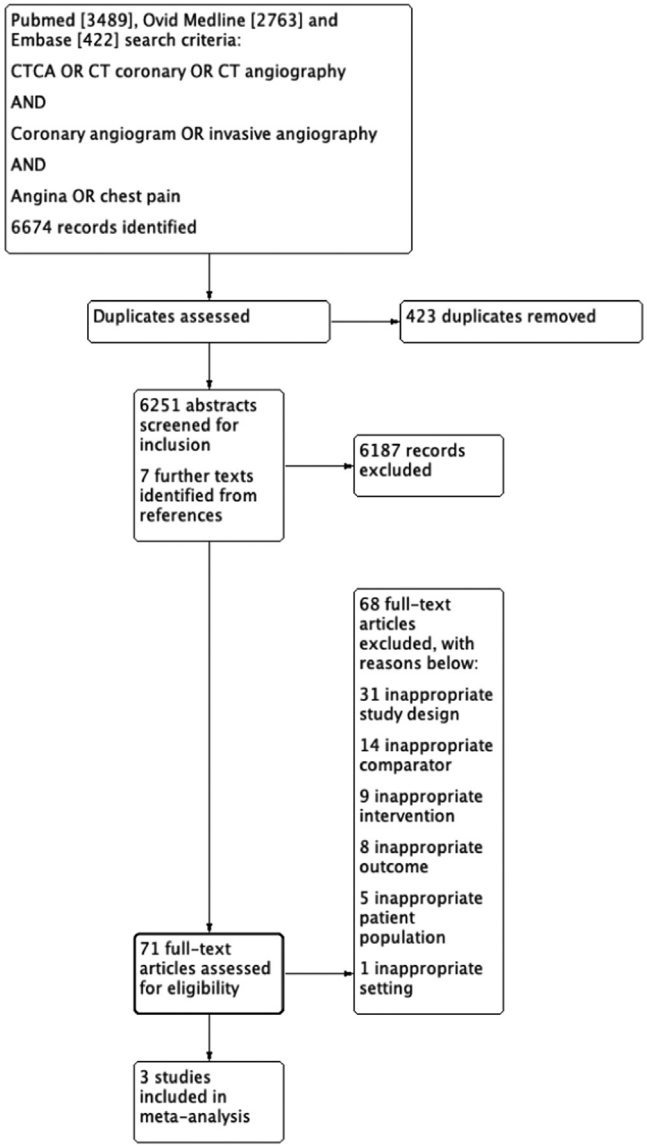

Fig. 1. Study flow diagram of literature search strategy and screening process.

Statistical analysis

Statistical analysis was conducted using Review Manager 5.3 for MacOS software. The Cochrane Risk of Bias Assessment tool (RoB 2) was used to identify quality of RCTs included in the analysis. Odds ratios (OR) with 95% confidence intervals (CI) were used as summary estimates. Heterogeneity amongst trials was quantified using I^2 statistics with I^2 of 0–25% considered low, 25–50% moderate and >50% high heterogeneity. Fixed effects models using Inverse Variables method was used, with random effects models used in the presence of high heterogeneity. All p vales are two sided with significance set at $P<0.05$. Publication bias was not assessed as this meta-analysis included only three studies. To assess stability of results, sensitivity analysis was conducted by removing one study at a time.

Results

Of an initial search strategy of 6674 references, 423 duplicates were removed, 6251 abstracts were screened, with a further seven studies identified through screening references, and 68 full text studies were screened for inclusion. In total, three papers were included

Table 1
Baseline characteristics of included studies.

Study/ author	Year	Patients, n CT	ICA	Inclusion criteria	Age	Female sex (%)	Hypertension	Dyslipidaemia	Diabetes
Dewey et al.[9]	2016	167	162	Atypical CP with 2/3 from: retrosternal pain, precipitate by exertion, relieved by rest or GTN,	60.4 (11.3)	48.9	223 (67.8)	176 (53.5)	45 (13.7)
Chang et al[10]	2019	784	719	Referral for ICA based on ACC/AHA guidelines Positive stress test or symptoms of CAD	60.8 (11.5)	43.1	870 (54)	508 (31.5)	415 (27.6)
Maurovich-Horvat et al.[7]	2022	1808	1753	Aged 30 or over Stable angina Referred with intermediate (10–60%) pre-test probability of CAD	60.9 (11.9)	56.2	2122 (59.6)	1706 (47.9)	557 (15.6)

for meta-analysis, which is a total of 5662 patients included in the analysis.

Baseline characteristics

As shown in Table 1, 2864 (50.5%) were female. The median age was 60 in the three studies and the occurrence of hypertension was the most common risk factor (56.8%). The presence of known coronary artery disease was an exclusion criteria in all three studies, as was the presence of haemodialysis or previous haemodialysis.

Table 2 highlights the classification of the angina based on history taking, examination and electrocardiography interpretation in the initial clinical assessment of patients. Dewey et al. excluded patients with typical angina. Of the included patients, 17% had typical angina, 42.1% had atypical angina, 26.8% were felt to have non-cardiac chest pain and a remaining 4.8% were either asymptomatic or "other".

Of the patients in the CTCA arm, 603/2757 (21.8%) subsequently underwent invasive angiography. The findings of coronary disease was present in 29% of the invasive angiography arm compared with 26.94% in the CTCA arm. Only one study reported the number of non-diagnostic studies, which was 5.7% in the CTCA arm compared with 0.3%.

Risk of bias assessment is included in the supplementary material (Supp figure 2) and overall studies scored at low risk of bias with the exception of the lack of blinding across all three studies, where performance bias was considered to be high risk.

Outcomes

The median follow-up period in days was 1204.5 days. The definitions of MACE in Dewey et al. was myocardial infarction (MI), cardiac death or stroke.[11] Chang et al. defined MACE as any death, acute MI, stroke, cardiac hospitalisation or unstable angina.[12] Maurovich-Horvat et al. defined MACE as cardiac death, non-fatal MI and stroke.[9] There was no statistically significant difference in MACE [2.97% v 3.45%, fixed-effect model, OR: 0.84 (0.62–1.14), p = 0.26, I_2 0%] although numerically, CT was favoured, as shown in Fig. 2.

Similarly, with rates of death (Fig. 3) [0.3% v 0.6%, fixed-effect model, OR: 0.55 (0.24–1.25), p = 0.56, I^2 0%], MI (Fig. 4)[0.94% v 0.84%, fixed-effect model, OR: 1.13 (0.64–2.00), p = 0.67, I^2=0%] and stroke (Fig. 5)[0.43% v 0.87%, fixed-effect model, OR: 0.51 (0,26–1.03), p = 0.06, I^2 0%] no statistically significant difference was shown although stroke is close to statistically favouring CT.

The rates of revascularisation (Fig. 6) (either PCI or CABG) during the initial diagnostic period were statistically significantly higher in the ICA arm [12.6% v 18.3%, fixed-effects model, OR: 0.64 (0.55–0.75), p<0.00001, I^2 =0%].

Procedural complications were only reported in two studies.[9,11] These complications were death (0%), MI (0.2% v 0.5%), stroke (0% v 0.05%), cardiac arrhythmia (VT/VF) (0% v 0.3%), complication prolonging hospital stay by > 24 h (0.2% v 0.6%), dissection of coronary artery or aorta (0.1% v 0.1%), cardiac arrest (0% v 0.1%) and cardiac tamponade (0% v 0.05%) comparing CTCA with ICA respectively. These were procedure related complications reported during the initial management. Any complication numerically favoured CT but did not reach statistical significance [0.5% v 1.72%, random effects model, OR: 0.52 (0.06–4.38), p = 0.55, I^2 52%]as shown in Fig. 7.

Revascularisation rates, as shown in Fig. 8, were assessed in two studies and this showed no statistical difference between the two groups [13.3% v 12.1%, fixed effects model, OR: 1.11 (0.92–1.34), p = 0.28, I^2 0%].

The number of coronary angiograms with unobstructed coronary arteries was lower in the CTCA arm compared to the ICA arm (Fig. 9), [36.9% v 70.0%, random effects model, OR: 0.17 (0.09–0.32), I^2 81%,

Table 2
Classification of chest pain symptoms at clinic assessment.

Study ID	Typical angina	Atypical angina	Non-cardiac chest pain	Other
Dewey et al		144 (43.8)	177 (53.8)	8 (2.4)
Chang et al	459 (30.5)	593 (39.5)	28 (1.9)	166 (11.0)
Maurovich-Horvat et al	507 (14.2)	1648 (46.3)	1311 (36.8)	95 (2.7)

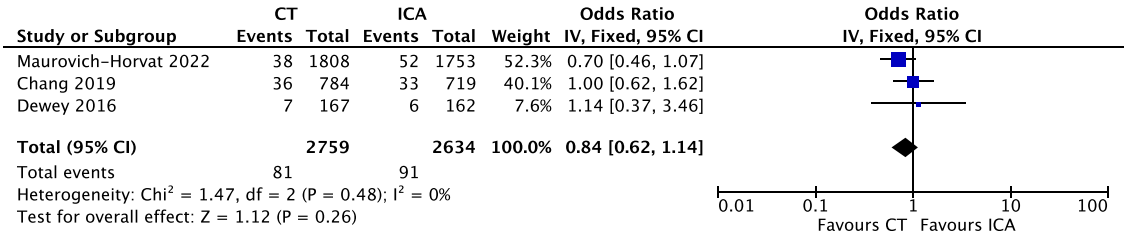

Fig. 2. Forest plot showing MACE comparing CTCA with ICA.

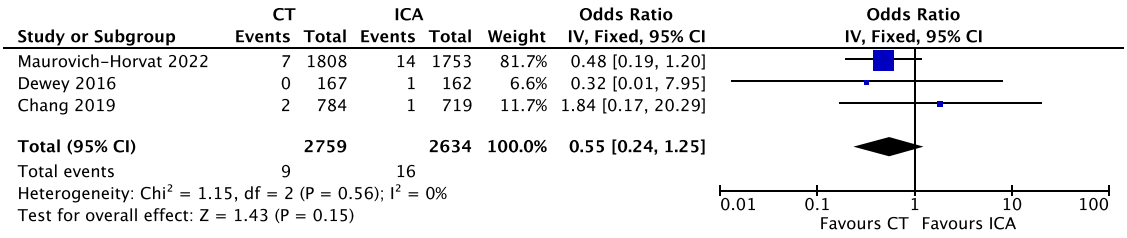

Fig. 3. Forest plot showing death comparing CTCA with ICA.

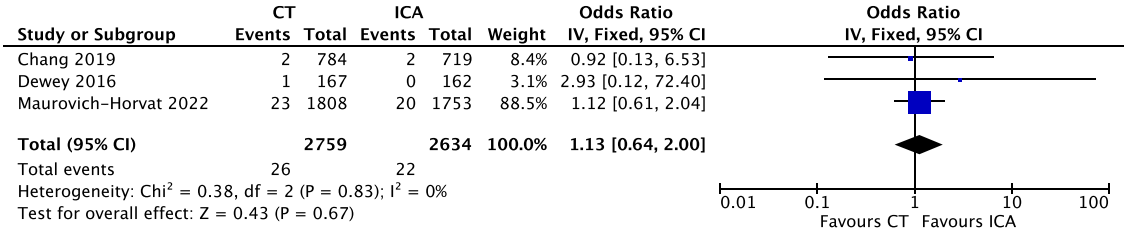

Fig. 4. Forest plot showing MI comparing CTCA with ICA.

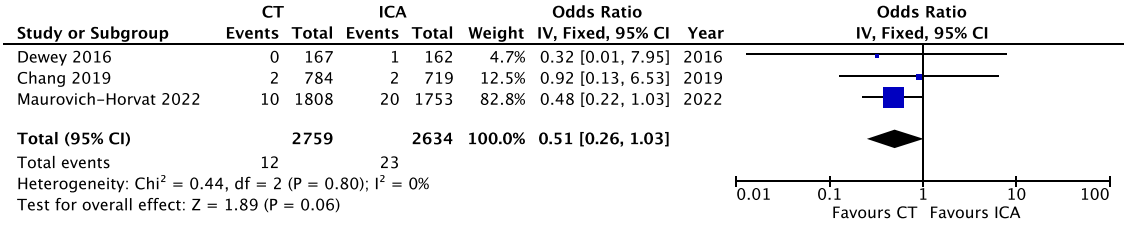

Fig. 5. Forest plot showing stroke comparing CTCA with ICA.

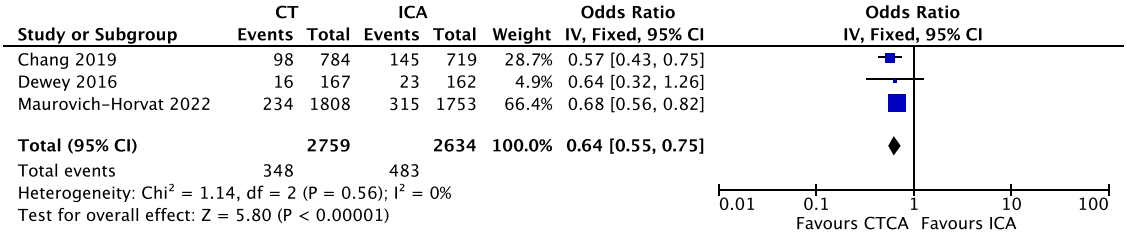

Fig. 6. Forest plot showing rates of revascularisation comparing CTCA with ICA.

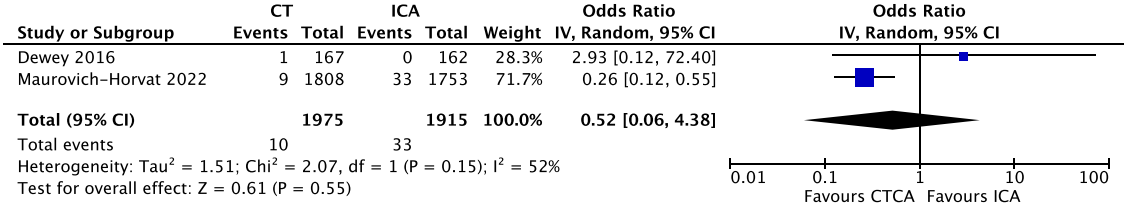

Fig. 7. Forest plot showing major procedural complications comparing CTCA with ICA.

$p<0.001$], which is in keeping with the higher sensitivity associated with CTCA.[13]

There was a significant increase in the requirement of additional functional stress testing in the CTCA arm at follow-up compared to ICA with the two studies that reported outcomes for this (Fig. 10)[9][12] [17.2% v 12.4%, fixed effects model, OR: 1.47 (1.26–1.72), I^2 0%, $p<0.001$].

Finally, angina burden at follow-up was analysed in two studies[9][12]. There was a marked difference in reported angina between the two studies but no significant difference was found between the two investigation strategies (Fig. 11); 18.5% v 16.7%, fixed effects model, OR: 1.13 (0.96–1.32), I^2 0%, $p = 0.14$.

Sensitivity analysis showed that no single study changed the non-significant findings for MACE, MI and death. Maurovich-Horvat et al. and Dewey et al. combined achieved statistical significance for stroke ($p = 0.05$). No study changed the findings of the analysis on revascularisation.

Discussion

This meta-analysis confirms that there is no statistically significant difference in MACE when comparing an initial non-invasive CT approach to an invasive diagnostic angiography strategy in investigating patients with chronic coronary syndrome. This study did

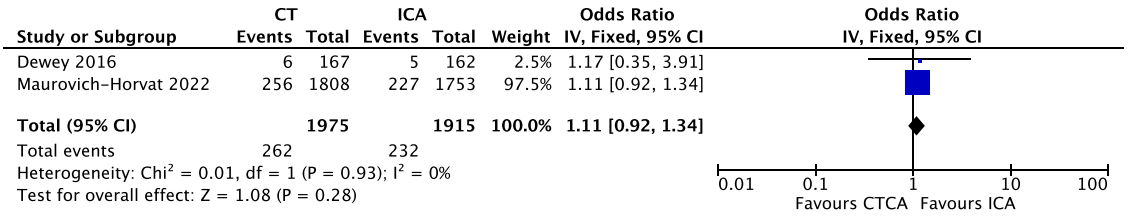

Fig. 8. Forest plot showing revascularisation rates comparing CTCA with ICA.

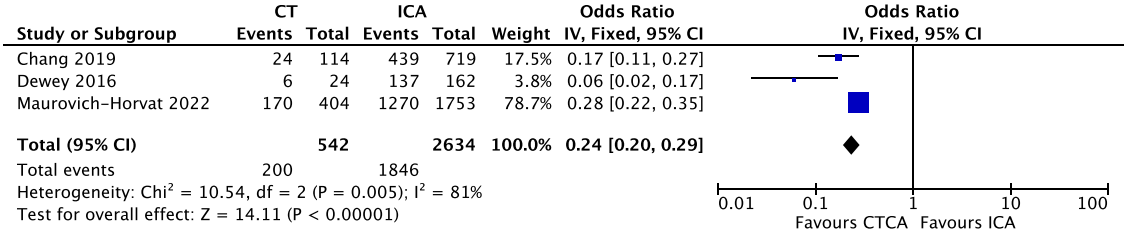

Fig. 9. Forest plot showing the number of coronary angiograms with normal findings comparing CTCA with ICA.

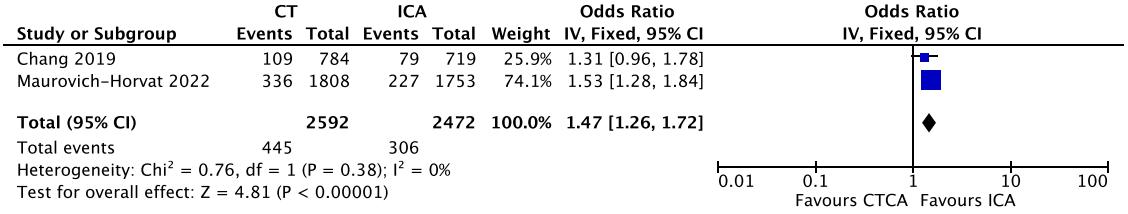

Fig. 10. Forest plot showing additional functional testing at follow-up comparing CTCA with ICA.

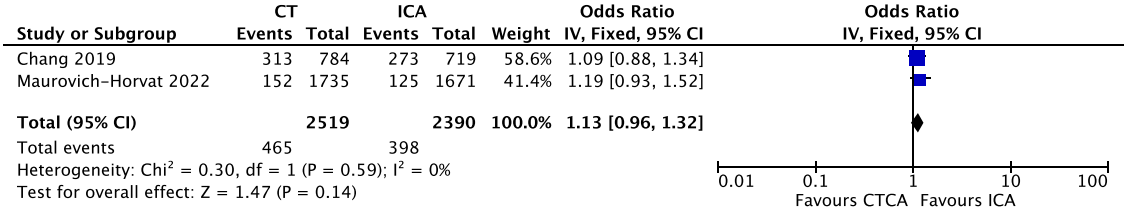

Fig. 11. Forest plot showing angina burden at follow-up comparing CTCA with ICA.

largely include patients with atypical to non-cardiac chest pain, with typical angina accounting for only 17% of patients. With both the PROMISE[6] and Scot-Heart[7] showing CT as an alternative to functional testing for chronic coronary syndromes, the role of CTCA is experiencing an exponential rise as the diagnostic test of choice in patients seen in the chest pain clinic. The development of CT-FFR adds another string to the CT bow, meaning the choice to opt for a CT does not limit the diagnostic test to an anatomical test only. There is also an increasing direction of thought that the detection of atheroma may be more prognostically important than demonstrating ischaemia. In some studies, with >50% of patients with MIs having previously had non-obstructive disease, atheroma is a better predictor of future events than demonstrating ischaemia, with CT angiography outperforming functional testing at predicting events ($p = 0.04$)[14] and in fact, a lower degree of ischaemia in patients with atheroma being associated with a higher rate of myocardial infarction.[15] It is clear that there is a prognostic benefit in identifying the presence of coronary atheroma, be it invasively or via CTCA to prognosticate and address risk factors aggressively, independent of the degree of coronary obstruction. This highlights the importance of comparing invasive angiography and CTCA as the two methods for best assessing plaque burden. However, this meta-analysis did highlight a significant increase in the requesting of functional testing in patients undergoing CTCA compared to angiography at follow-up. This has an impact on both cost and waiting times and may be attributable to a higher degree of diagnostic uncertainty in patients undergoing CTCA only. The addition of CT-FFR may help to address this.

For patients with stable coronary disease, there is now good evidence showing there is a low event rate in patients with stable angina, with no prognostic benefit to revascularisation in severe ischaemia over optimal medical therapy,[16,17] although there was a prognostic benefit in revascularisation in multivessel disease.[15] This further supports the argument that delineation of plaque burden is of utmost importance in guiding management with stable coronary disease.

Interestingly, this meta-analysis has shown significantly increased rates of revascularisation in the patients who underwent invasive angiography compared with those assessed by CT despite no difference in MACE in the two arms. This suggests a degree of performance bias by interventionalists which most likely carries forward into real world practice. However, angina burden prior to revascularisation has not been assessed in these studies, so it may be that patients undergoing invasive angiography with significant lesions opt for revascularisation during the same procedure to reduce anginal symptoms. There was however no difference in angina symptoms between CTCA and ICA at follow-up. This was for all patients and did not include analysis specifically for patients undergoing revascularisation. Given the high number of patients with unobstructive coronary

disease, the high burden of angina in the CONSERVE study (39%)[12] could be attributed to a misperception of cause of symptoms.

Whilst not all three studies included procedural complication outcomes, there was evidence that a CTCA initial strategy was associated with a numerically lower rate of peri-procedural major adverse cardiovascular events and that with a larger number, this may demonstrate significance.

The majority of patients in these studies had low to intermediate probability of coronary disease which falls within the guideline recommendations for a CT first strategy. This is supported by the high number of patients in the invasive coronary angiography who had unobstructed coronary arteries. This meta-analysis adds strength to those guidelines recommending a CT first approach. Similar study design in a high risk population would be an interesting study, given the findings of Courage[16] and Ischaemia,[17] which highlight safety of a medical therapy approach in the majority of patients with coronary disease (in the absence of three vessel disease). The studies which reported a time from clinic review to diagnostic test showed a very short initial investigation waiting time,[9,11] which is not truly reflective of real world practice, and may influence day to day decision making.

CTCA has been found to be cost-effective when compared to invasive angiography for investigation of stable coronary disease, across all risk groups.[18] CTCA has also been shown to have had significant uptake in utilisation as a diagnostic test in the UK between 2011 and 2017 and a small increase in rates of diagnostic angiography have also been seen according to British Cardiovascular Interventional Society data across the same time period.[19] This adds strength to the need for expansion of CT services and reduction in listing patients for diagnostic angiography in the absence of high risk features.

Limitations

This study did not include patient level data analysis, rather this was a study level data analysis. We attempted to create a combined Kaplan-Meier curve to overcome this,[20] however this was not possible due to the inadequate resolution of the published curves .

This meta-analysis only included 3 RCTs, but there were over 5000 patients included in these. There was low heterogeneity across the study designs which strengthens our statistical analysis and overall there was a low risk of bias although performance bias was a risk and is likely highlighted in the increased rates of revascularisation in the invasive arm of the analysis.

In Chang et al.,[12] a significant number did not receive the allocated investigation (4.7% in CTCA and 11% in the ICA arm). This was largely due to patient preference which may have introduced performance bias, a limitation highlighted by the lack of blinding in the study design. Furthermore, a very small number in Dewey et al[11] did not undergo the allocated CTCA due to clinician preference. Whilst this is a small number and unlikely to affect the outcome in these intention to treat/ investigative RCTs, it does again highlight the risk of performance bias.

Conclusions

CTCA is a safe and appropriate first investigation strategy for patients being investigated for stable coronary disease, with no difference in MACE compared to an initial revascularisation approach, a reduction in revascularisation rates and a numerical reduction in procedural complications. This meta-analysis reinforces the role of CTCA as the investigation of choice in stable angina.

Statements and declarations

Dr Natasha Corballis and Dr Vasiliki Tsampasian are NIHR Academic Clinical Fellows. Dr Simon Eccleshall received funding for lectures and proctorship from B Braun, Medtronic and MedAlliance and funding for investigator-initiated research unrelated to this work from B Braun. Professor Dweck MRD is supported by the British Heart Foundation (FS/14/78/31020) and is the recipient of a Sir Jules Thorn Award for Biomedical Research 2015 (15/JTA). Professor Vassiliou receives funding for investigator initiated research unrelated to this work from B Braun and Medtronic. This work was partially supported by the Norfolk Heart Trust.

Conflict of interest statement

Dr Natasha Corballis and Dr Vasiliki Tsampasian are NIHR Academic Clinical Fellows. Dr Simon Eccleshall received funding for lectures and proctorship from B Braun, Medtronic and MedAlliance and funding for investigator-initiated research unrelated to this work from B Braun. Professor Dweck MRD is supported by the British Heart Foundation (FS/14/78/31020) and is the recipient of a Sir Jules Thorn Award for Biomedical Research 2015 (15/JTA). Professor Vassiliou receives funding for investigator initiated research unrelated to this work from B Braun and Medtronic. This work was partially supported by the Norfolk Heart Trust.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2022.09.018.

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