Computed tomography to replace invasive coronary angiography? The DISCHARGE trial

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Ongoing advancements of coronary computed tomographic angiography (CTA) continue to challenge the role of invasive coronary angiography (ICA) as the gold standard for the evaluation of coronary artery disease (CAD). To investigate the comparative effectiveness of ICA when compared with CTA as an initial diagnostic imaging strategy the DISCHARGE Trial enrolled 3561 patients with stable chest pain and an intermediate pre-test probability of obstructive CAD. The study showed no difference between CTA and ICA in the incidence of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke during 3.5 years of follow up. As with many trials that advance a field, this trial raises several additional questions of interest that will be discussed. Furthermore, recent studies focused on the discrepancies of CTA vs. ICA indicate that the status of CTA remains unchanged in its ability to rule out disease but at present cannot be considered a substitute for ICA when coronary lesions are documented. Thus, a change in clinical practice patterns likely requires evidence from clinical studies demonstrating equivalence of CT to ICA for guiding medical management. Developments, however, are swift, and CT technology is catching up on its invasive counterpart.

To diagnose obstructive coronary artery disease (CAD) and consequently determine appropriate treatment is not a trivial task. Invasive coronary angiography (ICA) is considered the reference standard, particularly when combined with haemodynamic interrogation by fractional flow reserve (FFR) in the presence of an intermediate coronary lesion. This effective invasive procedure, however, carries inherent risks of potential serious complications and is accompanied by considerable costs, relatively high radiation exposure, and patient discomfort. Furthermore, this strategy has not been without challenges since a substantial percentage of patients (~60%) who are referred for angiography have no haemodynamically significant coronary artery stenosis. Over the past 20 years, coronary computed tomography angiography (CTA) has undergone rapid growth from a technique that can estimate the amount and severity of CAD, to a test that provides important prognostic information and has a direct impact on subsequent patient management decisions. Moreover, as the yield of ICA to detect CAD is low, CTA has become a gatekeeper to the catheterization laboratory as a negative CTA of sufficient quality virtually rules out obstructive CAD and significantly reduces unnecessary invasive procedures. Consequently, 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes now include coronary CTA among the routine testing options for evaluating patients with stable chest pain when there is a low-to-intermediate likelihood of CAD (Class I/Level of Evidence B).

Recently, two large randomized clinical trials among patients with stable symptoms demonstrated that, compared with functional testing, the use of computer CTA was associated with an increase in the use of coronary revascularization procedures. Although no significant...
changes in outcomes were seen in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, the Scottish Computed Tomography of the Heart (SCOT-HEART) study enrolled a higher risk population and found a 50% relative risk reduction in hard events when coronary CTA was added to traditional care. The Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) trial complements the rationale and findings of these studies.

The DISCHARGE trial

The DISCHARGE trial is a multicentre, pragmatic, randomized, parallel-group, superiority trial aiming to compare CTA with ICA as initial diagnostic imaging strategy to guide the treatment of patients with stable chest pain. The primary hypothesis was that using CTA would determine a reduction in the annual risk of major adverse cardiovascular events (MACEs) from 1.4 to 0.8%, when compared with ICA. In 26 European certified centres, 3667 patients with stable chest pain and intermediate (i.e. 10-60%) pre-test probability of obstructive CAD referred for ICA were enrolled and randomly assigned in a 1:1 ratio to undergo either CTA (n=1833) or ICA (n=1834). The primary outcome was MACE (defined as a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) over a median follow up of 3.5 years. Secondary outcomes included major procedure-related complications occurring during or within 48 h after CTA, ICA or related tests, or revascularization procedures, and patient-reported outcomes, including angina pectoris.

In the modified intention-to-treat analysis, 3561 patients (mean age, 60 years; 56% females) were included. The median time from enrolment to the initial diagnostic procedure was 3 days in the CTA group and 12 days in the ICA group [hazard ratio (HR), 1.54; 95% confidence interval (CI), 1.44-1.65]. The primary outcome of MACE occurred in 38 of 1808 patients (2.1%) in the CTA group and in 52 of 1753 (3.0%) in the ICA group (HR, 0.70; 95% CI, 0.46-1.07; P=0.10). The annual rate of MACE was 0.61% in the CT group and 0.86% in the ICA group.

Major procedure-related complications occurred in 9 patients (0.5%) in the CT group and in 33 (1.9%) in the ICA group (HR, 0.26; 95% CI, 0.13-0.55). During the last 4 weeks of follow up, angina was reported in 8.8% of the patients in the CT group and in 7.5% of those in the ICA group (odds ratio, 1.17; 95% CI, 0.92-1.48).

The authors conclude that a strategy of initial CT is safe and results in no significant difference in the incidence of MACE when compared with ICA.

Limitations of the DISCHARGE trial

Although the high adherence to the group assignments (98% of patients), the completeness of follow up (99% of patients), the elevated proportion of female gender (56% of patients) and the pragmatic design are clear strengths of the trial which enhance external validity, there are several potential limitations of the study.

In the light of the lower-than-expected annual risk of the primary outcome in the control group (0.86 vs. 1.4%) and a smaller-than-expected difference between the two groups (30 vs. 43% relative risk reduction), the trial was largely underpowered to test a realistic superiority hypothesis.

The low event rate along with the fact that only approximately one quarter of the patients in each group had obstructive CAD is not surprising and raises doubts about the correct identification of the pre-test probability. Several studies have indicated that the prevalence of obstructive disease among patients with suspected CAD is nowadays lower than in the past. A pooled analysis of three contemporary study cohorts, including patients evaluated for suspected CAD, has indicated that the pre-test probability (PTP) based on age, sex, and symptoms is approximately one-third of that predicted by the model used in previous trials including the DISCHARGE study. These trial design features suggest that the overall trial population had a low risk of obstructive CAD rather than an intermediate risk. The most recent guidelines for the evaluation and diagnosis of chest pain recommend no testing and intensification of goal-directed medical therapy in very low-risk patients.

Finally, some potential selection bias must be acknowledged. A large number of patients with non-anginal chest pain (>35%) were included in the trial. Whether the exclusion of these patients would have led to different trial outcomes remains uncertain. In addition, patients had already been referred for ICA at the time of randomization, may represent another potential selection bias.

Can computed tomographic angiography replace invasive coronary angiography? The issue of contemporary discrepancies of stenosis assessment by computed tomographic angiography and invasive coronary angiography

During the last decade, CTA has emerged as a viable alternative to its invasive counterpart. Moreover, as the yield of ICA to detect CAD is low, coronary CTA has become a gatekeeper to the catheterization laboratory as a negative CTA of sufficient quality virtually rules out obstructive CAD and significantly reduces unnecessary invasive procedures. Nonetheless, CTA is considered a screening tool for ICA rather than its replacement owing to poorer image quality because of lower spatial and temporal resolution, motion and blooming artefacts, as well as the dependency on a low and stable heart rate for adequate image acquisition. In a post-hoc analysis of the ISCHEMIA trial, in which the concordance between CTA and ICA was studied among 1728 patients with moderate or severe ischaemia on stress testing, a 92.2% concordance rate was found between CTA and ICA with respect to having at least a 50% stenosis in 1 or more coronary arteries and excluding left main
coronary artery (LMCA) stenosis of at least 50%. In 4.9% of cases, there was a 30% or greater stenosis on CTA not evident on ICA, and in 2.9% of cases, there was significant LMCA on ICA not seen on CTA. Of note, the rate of underestimation of LMCA stenosis by CTA was highest among patients with a 25–49% LMCA stenosis (7.0%), ostial left circumflex stenosis (5.4%), or ostial left anterior descending stenosis (8.9%) on CTA. Also, there was only modest concordance (54.5%) with respect to the number of diseased vessels, with underestimation in 20.2% and overestimation in 25.3%.

Ongoing advancements of CTA continue to challenge the role of ICA as the gold standard for the evaluation of CAD. In the CORE320 study, Coronary Artery Evaluation Using 320-row Multidetector Computed Tomography Angiography and Myocardial Perfusion), the diagnostic accuracy of 320-slice CTA for detecting obstructive CAD in reference to ICA was assessed in 381 patients with known or suspected CAD. Diagnostic accuracy of CTA at a per-patient level was good with a C statistic of 0.90 and marked by excellent sensitivity (92%) and moderate specificity (74%). Accuracy of CTA progressively declined when analysis was performed at a vessel and segment level, with a positive predictive value of 68 and 49%, respectively. Thus, agreement between CTA and ICA on a per-vessel- and per-segment-based analysis remains modest despite advanced CT technology.

In an attempt to overcome the shortcomings of eyeballing lesion severity, computational fluid dynamics has been applied to CTA images to derive functional information and now allow to fairly accurately calculate FFR values non-invasively throughout the coronary tree (FFRCT). The addition of FFRCT to CTA alone has proved to improve the diagnostic accuracy to detect obstructive CAD. The potential advantages are obvious as such functional information is readily available without the need of an additional test. Nonetheless, recent studies have highlighted that specificity of FFRCT at the per-patient level still remains low. In addition, FFRCT suffers from a relatively high rejection rate because of insufficient image quality that generally runs into the double digits.

The findings of ISCHEMIA trial post-hoc analysis and CORE320 study are in line with the results of the recent SYNTAX trial. The diagnostic accuracy of SYNTAX score calculated from both modalities suffers from a relatively high rejection rate because of insufficient image quality that generally runs into the double digits.

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Conclusions

Coronary CTA is the preferred test in patients with a lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality. Unfortunately, CTA examinations of optimal quality with experienced interpretations are not a universal guarantee.

The main take-home message of the DICARGE trial is that CTA may represent an effective gatekeeper in enriching the low-risk population of patients referred for ICA. However, it is not currently ready to be utilized for final therapeutic decision-making instead of coronary angiography, but developments are swift, and CT technology is catching up on its invasive counterpart.

Conflict of interest: None declared.

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