Coronary Computed Tomography Angiography for Assessment of Stable Coronary Artery Disease – a Cost-effectiveness Perspective

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ABSTRACT

Patients with chest pain presenting to the emergency room are currently investigated using either invasive coronary angiography (ICA) or noninvasive coronary computed tomography angiography (CCTA). ICA remains an expensive diagnostic tool and exposes patients to a high risk of periprocedural complication. Besides the currently available expansive economic evidence, there is still an important lingering issue: to establish, from the healthcare provider's point of view, which is the most cost-effective investigation tool for the detection of significant coronary artery disease. The aim of this article is to present the latest developments in the field of imaging tools for the detection of coronary atherosclerosis in patients with chest pain, from the perspective of a cost-effectiveness analysis.

Keywords: cost-effectiveness analysis, coronary CT angiography, stable coronary artery disease, stable chest pain, imaging

BACKGROUND

Stable chest pain is still a frequent clinical presentation to medical clinics and emergency departments worldwide.¹ This leads to an increased number of invasive or noninvasive investigations with the primary aim to identify or dismiss the existence of flow-limiting coronary artery disease (CAD).^{2–4} This results in a continuous resource-consuming problem for healthcare providers worldwide, given the fact that CAD continues to represent the most frequent cause of health-related deaths in the European Union (EU)⁵ and contributes to a consistent decrease in the quality of life.^{6,7} In the setting of such extensive charges, the accuracy of CAD diagnosis remains of great importance for the management of these patients.¹ Despite efforts to reduce cardiovascular mor-

tality in acute coronary syndrome (ACS) via advances in the management and implementation of up-to-date effective treatments, stable CAD continues to present high mortality rates. In the current clinical practice, invasive coronary angiography (ICA) has an essential role in the management of CAD subjects, being the current gold-standard for confirming the existence, location, and severity of CAD.⁸ However, ICA remains an expensive diagnostic tool and exposes patients to a high risk of periprocedural complications.^{9–11}

Driven by its ability to provide similar information regarding the coronary tree as conventional coronary angiography, coronary computed tomography angiography (CCTA) presented a widespread diffusion in the imaging field,^{12–20} a fact supported by a substantial weight of clinical evidence.^{21–24} In these terms, CCTA permits the visualization of coronary artery lumen and wall structure at a high image quality, at a low radiation dose,²⁵ but in a non-invasive fashion, with almost 100% accuracy in excluding significant CAD. Being typically performed in outpatient care, it is to be expected to prove less expensive as the conservative ICA, whose status as the gold standard investigation for CAD derives from its 100% diagnostic accuracy.

Currently, healthcare providers allocate significant efforts to provide the most appropriate management for stable CAD, one that is effective from both clinical and cost-effectiveness point of view.²⁶ As a large segment of the population increases in age and develops CAD, the treatment of ischemic heart disease should be sustainable for healthcare providers. This is the basis of the current agenda of cost-effectiveness analysis (CEA). CCTA seems to be the most suitable economic tool, given the differences expected both in terms of costs and outcomes for the common aim: to detect coronary stenosis. CEA investigates different diagnostic tests in order to equally examine costs and outcomes of diagnostic guidelines, with the main aim to optimize health outcomes considering existing resources.²⁷ Thus, CEA has the potential of promoting changes in healthcare systems based on quality-guided research.^{28,29} Another key benefit of CEA is represented by the fact that cost savings are defined in the presence of equivalent outcomes; thus, cost fluctuation does not actually result in a decrease of quality received by the patients.³⁰

Besides the currently available expansive economic evidence, there is still an important lingering issue: to establish, from the healthcare provider's point of view, the cost-efficiency of CCTA compared with the current guideline standard or other imaging techniques for the detection of significant coronary artery disease.³¹

RISK STRATIFICATION, A CORNER MILESTONE

For patients presenting new symptoms of stable chest pain, it is of vital significance to implement a diagnostic workup in order to investigate the presence of CAD.³² The current standard to diagnose functionally significant CAD is ICA. However, since this procedure is costly, invasive, and associated with a high risk for further major adverse events, ICA is recommended as initial test only for subjects with a high probability of CAD, as research has shown that obstructive CAD was identified in only 38–41% of these patients, a fact also clearly highlighted by registry data.^{33–38} These facts are the basis for the necessity of improving screening tools for invasive strategies.^{39–41} From this point of view emerges the need for a better previous risk stratification, a fact underlined by previous decision analysis indicating that the optimal diagnostic strategy in this segment of patients depends primarily on the prior probability for CAD.^{42–44} Moreover, there is a need to implement the concept of gatekeepers for ICA, among which CCTA has gained an increasing popularity in recent research trials.

In patients with a low associated probability of CAD, a series of studies and trials (FAME 2, COURAGE, DIAD, FACTOR 46) showed the reduction of cardiac events as very unlikely, regardless of the test used, appropriate risk factor modification, and optimal medical therapy,^{45–48} with no available randomized clinical trials to date to support an initial invasive strategy in order to reduce major cardiovascular end-points.^{49–51}

A large body of evidence sustains the superiority of CCTA in low-to-intermediate risk patients, demonstrating that CCTA, either as the first or as a layering test, may represent a cost-effective initial strategy for patients with CAD prevalence of 10–50% for both near-term and long-term diagnostic periods.^{52,53} The decision model tree of Dewey *et al.* proved CCTA as the most cost-effective approach to be implemented for the 10–50% pretest likelihood of CAD, while CCTA and ICA proved to be equally effective at a 60% likelihood. ICA proved to be the most cost-effective diagnostic tool only for a pretest likelihood greater than 70%.⁵² The decision analytic model of Halpern *et al.* showed a cost reduction with CCTA depending on the prevalence of CAD, with overall costs reduced as long as the prevalence is under 85%.⁵³ However, in low-to-intermediate prior probability of significant CAD, the optimal diagnostic imaging test remains unclear, as a series of variables, such as costs, diagnostic test characteristics, prior calculated probability, local willingness-to-pay threshold, optimization criteria, availability, patient preference, or local team expertise, must be taken into consideration.³²

Regarding patients with very high probability of CAD presenting stable chest pain, there is a large body of clinical trials suggesting diagnostic strategies involving ICA as the most cost-effective initial strategy for the diagnosis of stable chest pain, with a concomitant lack of clinical and health economic data in a large body of clinical trials (PROMISE, SCOT-HEART, EVINCI) to support the implementation of CCTA in subjects at high risk of CAD in real-world settings.^{31,53–55} However, the same studies have shown that clinical estimates of prior probability are in fact grossly overinflated in real-world implementation. Therefore, in terms of real life, this group of subjects for whom direct ICA proved to be cost-effective compared to CCTA may not actually exist. Thus, these results should only be seen as a stimulus for further required research rather than furnishing definitive conclusions.

UP-TO-DATE RESEARCH

If CCTA is to be considered a gatekeeper for ICA, correct CEAs are of great importance in the field of evidence-based science. Up to date, more than 10 large randomized clinical trials (including ACCURACY, Meijboom, CORE 64, EVINCI, PICTURE, Dewey, and the CONFIRM Registry) have compared CCTA with invasive angiography.^{56–66}

The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry performed a direct comparison between CCTA and ICA. The results revealed that the use of CCTA, as a gatekeeper to ICA, resulted in lower rates of follow-up catheterization for subjects presenting no or mild CAD.⁶⁷

In a study conducted by Budoff *et al.*, a 63.4% cost-saving was obtained when comparing ICA-confirmed CAD diagnosis costs with CCTA. In a similar manner, Halpern *et al.* obtained an overall reduction of costs when performing CCTA before ICA, at a prevalence of CAD below 85%. This trend persisted for the cases of CAD with a 50% prevalence as well.⁶⁸

Another series of studies compared the cost-effectiveness of CCTA prior to ICA with direct ICA. Five studies were cost-utility analyses reporting beneficial measures in terms of gained QALYs, two of them scoring relatively high using the Drummond checklist.^{69–73} The most important parameter driving the cost-effectiveness of CCTA is the probability test of CAD. In low-to-intermediate probability of CAD, CCTA proved to be more effective and less costly compared to the direct invasive approach. Conversely, in patients with higher probability of CAD, the direct invasive approach proved to be more effective and also associated with higher incremental cost-effectiveness

ratios that were above the thresholds typically considered good value for money.^{69,73}

EVASCAN is one of the first large cost-effectiveness trials that included the largest population used for studying diagnostic accuracy in subjects with stable or suspected CAD to date. The trial included 705 patients from 40 centers and provided robust results, concluding what would become the cornerstone of further studies and guidelines.³¹ The main conclusion of the trial stated that in patients with intermediate risk, CCTA is the best option to rule out CAD, especially in subjects who, for different reasons, cannot undergo ICA or present uncertain results from other diagnostic procedures.^{74–76} The trial also assessed the benefits of CCTA triage for intermediate-risk as a cost-saving strategy compared with the conservative “ICA for all” approach. The trade-off for these potential monetary savings is the slight reduction in accuracy and a small increase in radiation dose.⁷⁴

CURRENT GUIDELINE RECOMMENDATIONS

With regard to the current recommendations of the guidelines of the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA) in the setting of chronic coronary syndromes (CCS), the latest ESC guideline from 2019 recommends the use of CCTA in the diagnostic and risk stratification of obstructive CAD amongst patients with stable chest pain on the basis of the pretest CAD probability, local team expertise and availability, and anticipated quality of the examination (I to IIa, B to C).⁷⁷ Less prioritized by the outdated 2012 ACC/AHA guideline, the use of CT angiography for CCS diagnosis is disadvantaged to the detriment of functional imaging tests as the choice to be made.⁷⁸ Current guidelines regarding the use of CCTA in patients with stable chest pain are predominantly derived from the results of the initial diagnostic accuracy studies.⁷⁸ In this setting, the main application of CCTA consists in acting as a gatekeeper for ICA and further revascularization, with further reduction in diagnostic work-up costs. On the other hand, in its 2016 guideline, the National Health Service (NHS) of the United Kingdom controversially recommended CCTA as the first-line investigation for all patients with angina and no prior CAD.⁷⁹ Also, previous pretest probability of obstructive CAD was no longer advised. The NHS recommendation is based on a surveillance review which included each imaging modality, on the basis of which a cost-effectiveness analysis was undertaken. CCTA emerged as having a very high diagnostic sensitivity as well as a lower cost in comparison with other

imagistic investigations, particularly ICA.⁷⁹ Therefore, the analysis concluded that as a first-line investigation, CCTA offered a lower cost per correct diagnosis than any of the alternative strategies in all three risk groups of patients.

FURTHER QUESTIONS

As the most developed European countries lined up in implementing guidelines and country-specific organization recommendations, given the large grade of heterogeneity in the availability of CT scanners in other countries, the applicability of current recommendations in various healthcare systems may differ and remains to be explored. The implementation of these general indications for the assessment of stable CAD was estimated to be associated with a near 700% increase in the number of performed CCTA.⁸⁰ However, the utilization of CCTA remains sub-optimal related to the evidence proving its clinical efficiency, compared with other imaging techniques.⁸¹ Thus, the potential implementation of these latest recommendations for the diagnostic management of stable CAD may involve a substantial investment in CCTA infrastructure and training. Besides the field of research or large clinical trials, the use of CCTA in routine clinical practice will inevitably generate a series of equivocal CCTA scans. Consequently, attending physicians may require further imaging tests in the diagnostic work-up in order to solve the doubt generated by the equivocal results, increasing the economic burden.²⁵

64-slice CCTA has also been proven accurate for CAD diagnosis in most patients.^{82–85} However, specific groups of patients may have low-quality images as a result of a difficult scanning process.⁸⁶ These groups of patients include those with tachycardic rhythm >65 bpm, arrhythmias, obesity, coronary calcium score (CCS) >400, previous percutaneous coronary interventions with stent implantation, intolerance to beta-blockers, or previous coronary artery bypass graft. Up-to-date ICA may be indicated in these difficult-to-image subjects. However, newer generation CCTA instruments may provide an alternative for these cases. According to a study conducted by Burgers *et al.*, the use of new-generation dual-source CCTA in case of difficult-to-image patients with CAD is equal in terms of effectiveness with ICA but at a cost-saving for both suspected and known CAD patients.⁸⁵ Therefore, this alternative is recommended to be implemented for the assessment of patients who prove to be difficult to assess using earlier CT scanners.

There are still great expectations from future research in order to more definitively apply cost data to healthcare policy decision-making.

CONCLUSIONS

Given the current competitive economic environment, it is of great importance to understand expenditures correctly, as the increased costs of healthcare further lay the grounds for a necessary understanding of good value in healthcare.

Available economic analyses suggest the fact that with a high negative predictive value and a high diagnostic accuracy, CCTA seems to be an excellent cost-effective approach as a rule-out-test for CAD, prior to ICA, when applied to the appropriate population. However, further multicenter randomized trials are needed in order to determine the degree by which CCTA may improve clinical outcomes in patients with chest pain.

Finally, the implementation of CCTA for the evaluation of new-onset chest pain in the real world essentially depends on newly implemented health strategies, grounded on the reconfiguration of currently available assets and staffing levels.

Therefore, it becomes clear that CCTA is a definitely cost-effective imaging tool for the diagnosis of chest pain, confirming its key role in identifying the best clinical pathways that should be adopted to guarantee the optimal clinical outcome of CAD patients.

CONFLICT OF INTEREST

Nothing to declare.

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