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Coronary risk stratification of patients with newly diagnosed heart failure

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ABSTRACT

Objective Coronary artery disease (CAD) is frequent in patients with newly diagnosed heart failure (HF). Multislice CT (MSCT) is a non-invasive alternative to coronary angiography (CAG) suggested for patients with a low-to-intermediate risk of CAD. No established definition of such patients exists. Our purpose was to develop a simple score to identify as large a group as possible with a suitable pretest risk of CAD.

Methods Retrospective study of patients in Denmark undergoing CAG due to newly diagnosed HF from 2010 to 2014. All Danish patients were registered in two databases according to geographical location. We used data from one registry and multiple logistic regression with backwards elimination to find predictors of CAD and used the derived OR to develop a clinical risk score called the CT-HF score, which was subsequently validated in the other database.

Results The main cohort consisted of 2171 patients and the validation cohort consisted of 2795 patients with 24% and 27% of patients having significant CAD, respectively. Among significant predictor, the strongest was extracardiac arteriopathy (OR 2.84). Other significant factors were male sex, smoking, hyperlipidaemia, diabetes mellitus, angina and age. A proposed cut-off of 9 points identified 61% of patients with a 15% risk of having CAD, resulting in an estimated savings of 15% of the cost and 21% of the radiation.

Conclusions A simple score based on clinical risk factors could identify HF patients with a low risk of CAD; these patients may have benefitted from MSCT as a gatekeeper for CAG.

Key questions

What is already known about this subject?
► Coronary artery disease (CAD) is the aetiology of about 65% of all cases of heart failure (HF). Multislice CT (MSCT) is an alternative to invasive coronary angiography for patients with a low risk of CAD, but there is no established way of predicting this risk.

What does this study add?
► In this study, we calculate the CT-HF score, a simple clinical score designed to identify as large a population as possible with a suitable risk for MSCT.

How might this impact on clinical practice?
► We estimate that using the CT-HF score could save about 15% of the cost and 21% of the radiation of evaluating HF patients for coronary disease.

INTRODUCTION

With the ageing population and improved survival after myocardial infarction, heart failure (HF) is an increasing public health concern.[1] Coronary artery disease (CAD) is the largest contributor among men in the development of HF[2] and maybe an aetiological factor in as many as 65% of all cases.[1] CAD also represents a treatable, if not reversible, factor.[3] However, new data suggest that testing for CAD among patients recently diagnosed with HF remains underused.[4] This could be leaving a treatable disease underdiagnosed and undertreated.[3]

The gold standard for diagnosing CAD is invasive coronary angiography (CAG). However, this test is expensive and associated with a small risk of serious adverse outcomes.[5] Multislice CT (MSCT) is a non-invasive, low-radiation and less-expensive alternative with a high sensitivity and negative predictive value, but positive tests still need confirmation with CAG.[6] Thus, MSCT is a possible gatekeeper for the use of CAG and a Class IIb recommendation in the latest European Society of Cardiology guidelines for patients with a low-to-intermediate risk of CAD. However, there is currently no established way of reliably estimating this risk and risk profiles may be different among patients with HF.[7]

Recently, a new coronary risk score has been developed for patients with valvular heart disease undergoing surgery.[8] Our aim is to develop a similar score for patients with newly diagnosed HF.

METHODS

All patients undergoing CAG in Denmark are registered either in the Web-PATS database (for patients from the Capital Region and the Region of Zealand) or the Western Denmark Heart Registry. We obtain data from 2010 to 2014 of patients who underwent a CAG with the primary indication of newly diagnosed HF.

These databases included the details of the procedure as well as any history of ischaemic heart disease (IHD), such as prior percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or acute myocardial infarction (AMI). Significant CAD was defined as a stenosis>70% (>50% for the left main coronary artery) or with a fractional flow reserve<0.80. For these analyses, we chose to exclude all patients with a history of CAD (defined as prior PCI, CABG or AMI) or chronic kidney disease (defined as an estimated glomerular filtration rate<$30\,mL/min/1.73\,m^2$). Additionally, known predictors of CAD were registered, including age, sex, left ventricular ejection fraction (LVEF), diabetes mellitus (DM), family history of IHD, smoking, hypertension and hyperlipidaemia.

The data from the Web-PATS registry were used to develop a risk score which was then validated on the patients registered in the Western Denmark Heart Registry. The goal was to identify as large a group of patients as possible while remaining cost-effective.

Though similar in composition, there were differences between the two databases as the Western Danish Heart Registry did not register symptoms of angina or shortness of breath (eg, New York Heart Association class), patient body mass index (BMI), history of prior stroke or extracardiac arteriopathy (intermittent claudication, aortic aneurysm or dissection, confirmed >50% carotid stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids). As some of these factors were generally thought to be strong predictors of CAD, we choose to include them in the calculations of the score. Thus, all calculations on the validation cohort were made without these factors.

To estimate the expected savings of using MSCT as a gate-keeper for CAG, we reviewed the literature and national agencies and found prices for MSCT and CAG in seven countries—the USA,[9] the UK,[10] Germany,[11] Australia,[12] South Korea,[6] Denmark,[13] and Sweden.[14] From these resources, we saw that the cost of both CAG and MSCT varies significantly between countries. CAG had a mean cost of €1129 ranging from €1973 in Australia[12] to €560 in South Korea.[6] For MSCT, the mean cost was €396, or about a third of the cost of a CAG, ranging from €663 in Australia to €99 in Germany.[11] In all countries surveyed, the cost of a CAG was at least double the cost of an MSCT, with the highest price difference in the UK,[10] where the cost of a CAG (€1424) amounted to around six times the price of an MSCT (€240).

To estimate radiation dosage, we used data from a recent head-to-head comparison of MSCT and CAG.[15]

Using these, we calculated the difference in expenses and radiation if MSCT was used as a gatekeeper for CAG compared with the routine use of CAG.

MSCT only provided anatomical information and thus, the physiological significance of a potential stenosis still needed to be re-evaluated by CAG. Based on a previous study of MSCT in patients with HF,[16] we estimated the re-evaluation rate to be three times the number of patients with significant CAD on CAG. We divided patients into groups according to their score and calculated the cost-effectiveness of the score. This was done by calculating how much money and radiation could be saved per 100 patients in each group factoring in the cost of the initial MSCT as well as the expected number of re-evaluations. The cost-effectiveness of different cut-off values was visualised in a cumulative graph showing the combined savings of different cut-off values factoring in expected re-evaluations, the number of patients in each group and the costs of the procedures.

Statistics

Suspected risk factors of CAD collected in the Web-PATS database were tested with univariate logistic regression for an association with significant CAD. We separated the patients into four age groups from a visual reading of a receiver operating characteristics (ROC) curve of age as a factor for CAD.

All risk factors univariately associated with CAD were entered into a multiple logistic regression with backwards elimination. Statistically non-significant risk factors were eliminated from the regression and the risk estimates were derived from the OR of each factor rounded to the nearest integer. We further used ROC to calculate the area under the curve (AUC) as a measure of the predictive ability of the score. The Youden index was calculated to explore the cut-off with the highest combined sensitivity and specificity. We used a double-sided level of significance of 5%. The calculations were performed using SPSS statistics V.22 for Windows and R V.3.5.2 using RStudio V.1.0.136.[17]

The subsequently developed score was then recalculated for the patients of the Western Denmark Heart Registry to determine its effectiveness. The effectiveness of the score was judged by the number of patients the score classified as low-to-intermediate risk, who on examination turned out to have significant CAD.

RESULTS

From January 2010 to December 2014, a total of 3537 and 4551 patients with newly diagnosed HF were registered in the Web-PATS and the Western Danish Heart Registry, respectively. Excluding patients with a prior history of CAD or chronic kidney disease, as well as patients with missing data, the two databases included 2171 and 2795 patients, respectively (figure 1).

Baseline characteristics of the two databases can be seen in table 1. There was a slightly higher prevalence
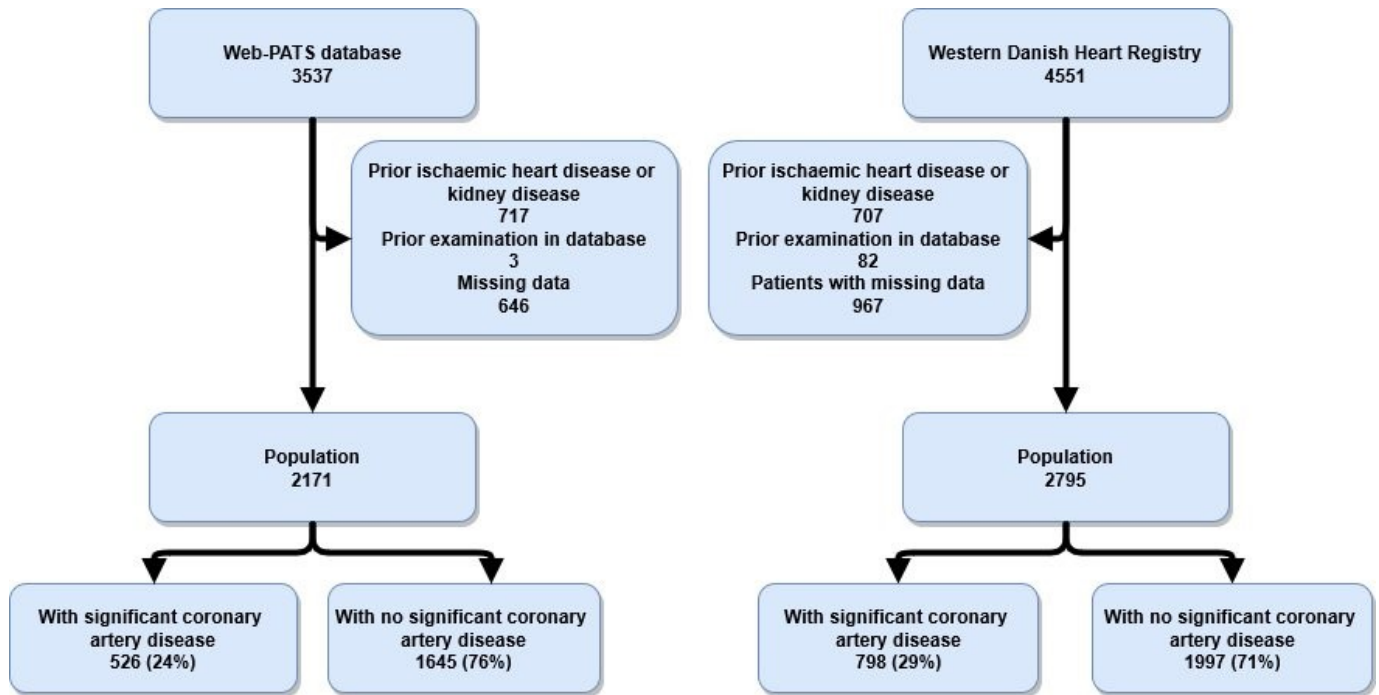
Figure 1 Consort diagram of the two databases: the original cohort (Web-PATS) and the validation cohort (the Western Denmark Heart Registry).

Table 1	Baseline characteristics			
Risk factors		**Web-PATS database, n=2171**	**The Western Denmark Heart Registry, n=2795**	**P value**
Female, n (%)		617 (28)	774 (28)	0.59
Hyperlipidemia, n (%)		1046 (48)	1132 (41)	<0.001
Hypertension, n (%)		1135 (52)	1511 (54)	0.15
Diabetes mellitus, n (%)		445 (21)	541 (19)	0.33
Family history of CAD, n (%)		523 (24)	813 (29)	<0.001
Previous stroke, n (%)		207 (10)	NA	
Smoking, n (%)		1465 (68)	1949 (70)	0.09
Extracardial arteriopathy, n (%)		133 (6)	NA	
BMI>30 kg/m^2, n (%)		575 (27)	NA	
LVEF<30%, n (%)		994 (46)	971 (35)	<0.001
Angina, n (%)		401 (19)	NA	
NYHA classification, n (%)	I	359 (17)		
	II	993 (46)		
	III	575 (27)		
	IV	67 (3)	NA	
Age, years, n (%)	<51	264 (12)	341 (12)	
	51–60	453 (21)	605 (22)	
	61–70	781 (36)	930 (33)	
	>71	673 (31)	919 (33)	0.23

Risk factors at baseline in both databases.
Smoking defined as active or prior smoker.
BMI, body mass index; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NA, not available in the database; NYHA, New York Heart Association Functional Classification.

Table 2 The CT-HF score

Risk factor	Point
Male	2
Angina	1
Smoking	2
Hyperlipidaemia	2
Diabetes mellitus	2
Extracardiac arteriopathy	3
Age 51–60 years	2
Age 61–70 years	4
Age≥71 years	6

Smoking defined as prior or active smoker.
HF, heart failure.

of hyperlipidaemia, family history of heart disease and LVEF<30% among the patients of the Western Danish Heart Registry (all p<0.001).

All inserted risk factors were significantly associated with CAD on the univariate logistic regressions except LVEF<30%, BMI>30 kg/m^2 and NYHA classification (online supplementary table 1). Multivariate regressions showed no significant association between CAD and family history of CAD, prior stroke or hypertension. The final score included the risk factors: sex, hyperlipidaemia, DM, smoking, extracardiac arteriopathy, angina and age (table 2). ROC was performed on the primary cohort (AUC 0.72; 95% CI 0.69 to 0.74), as well as on the validation cohort (AUC 0.67; 95% CI 0.65 to 0.70) (online supplementary figure 1).

Using the CT-HF score, patients receive a score of 0–18. Figure 2A,B shows the CT-HF score of the patients in our two cohorts and the number of patients who had significant CAD on their CAG. From this, different possible cut-offs values can be evaluated. Using the Youden index, the optimal cut-off was 8. Further, visual estimation suggests the ideal cut-offs be about 6–9 points. Exploration of the results of different cut-offs from 6 to 9 points calculated on the Web-PATS cohort and the Western Denmark Heart Registry can be seen in online supplementary tables 2 and 3.

To examine the cost-effectiveness of using MSCT for patients at each step of the CT-HF score, we calculate the potential savings in cost and radiation dosage per 100 patients, estimating a re-evaluation rate of three for each positive MSCT. The result is seen in online
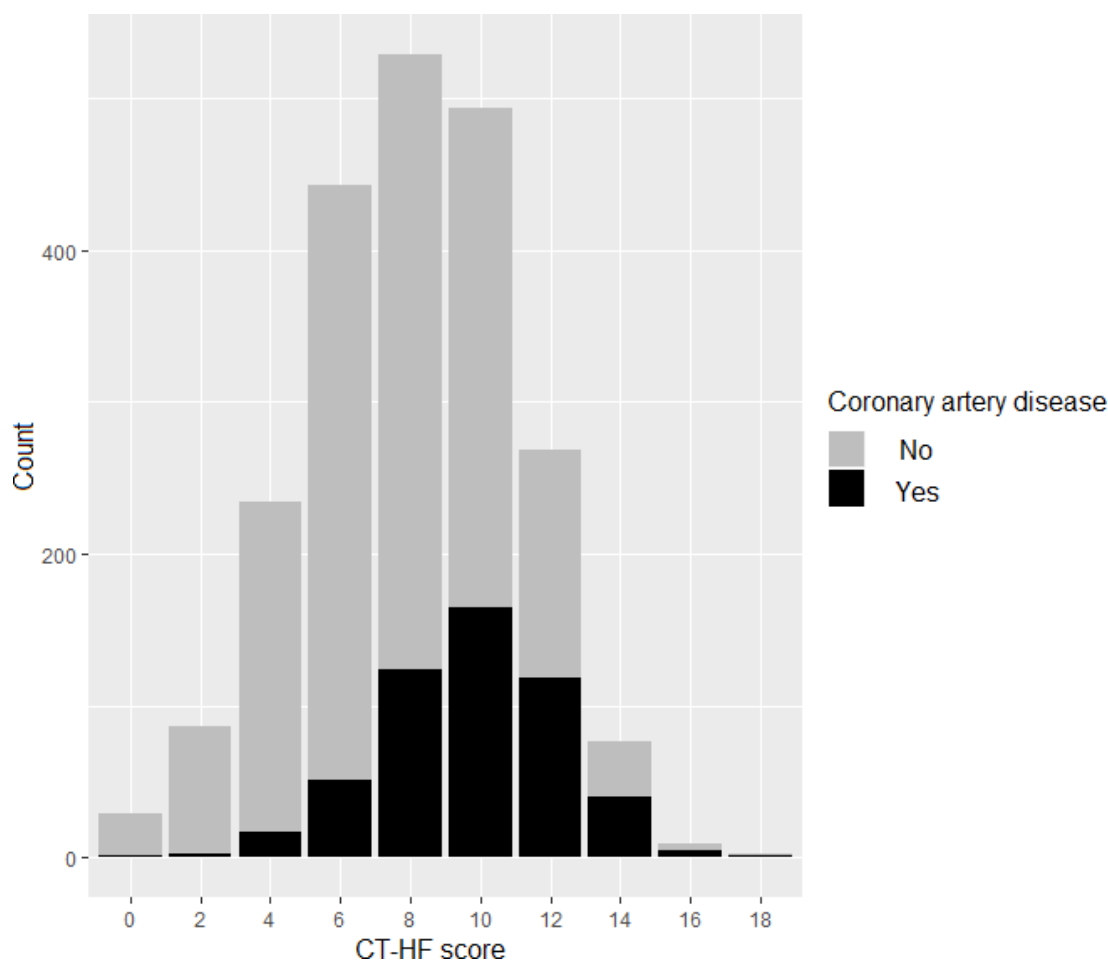

Figure 2 (A and B) CT-HF score calculated on patients in both databases and their risk of coronary artery disease. The patients are divided in to groups for each two points of the score. (A) Shows the patients of the Web-PATS database. (B) Shows the patients of the Western Denmark Heart Registry. HF, heart failure.
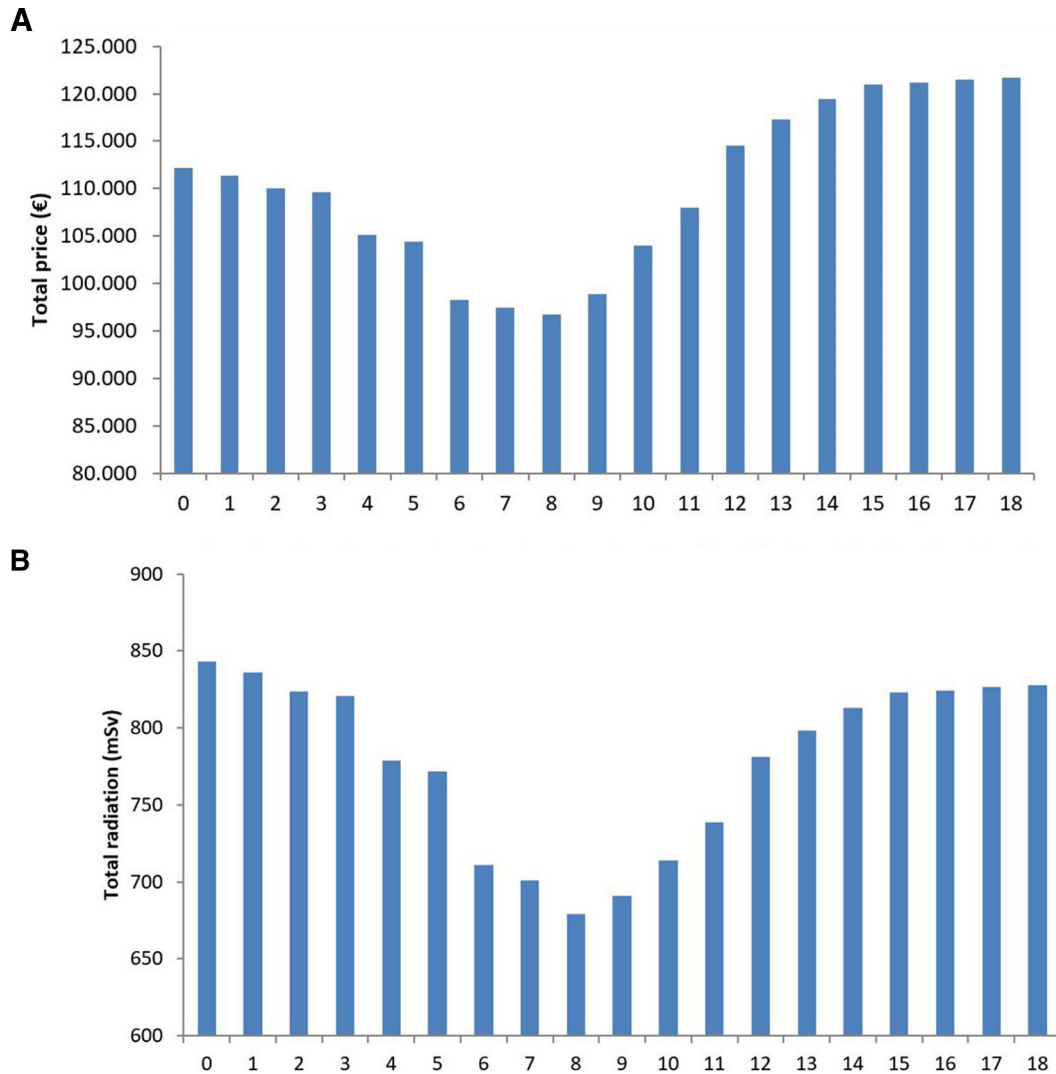
Figure 3 (A and B) A cumulative graph of price (€) calculated for a mean price of €1129.3 for CAG and €395.74 for MSCT and radiation dosage (MSV) calculated for a mean dosage of 8.5 mSv for CAG and 2.1 mSv for MSCT. CAG, coronary angiography; MSCT, multislice CT.

supplementary figure 2A,B for expenses and radiation dosage, respectively. Further exploring ideal cut-off point for testing with MSCT, we construct a cumulative graph showing the estimated total cost, factoring in the number of expected re-evaluations for each hypothetical cut-off, shown in figure 3A,B.

The cost-effectiveness of different potential cut-off points varies from country to country with the difference in cost of the tests. For all countries, however, an MSCT-first approach would be cost-effective at below 7 points, while patients with more than 9 points have too high a risk of CAD. At a mean price of €1129 for a CAG and €396 for an MSCT, the most cost-effective cut-off would be 8 points, where the savings would be about 14% of the total price. For radiation dosage, the relatively high radiation dose of a CAG (around 8 mSv) compared with an MSCT (around 2 mSv) results in an optimal cut-off at 8 points. At this cut-off, about 20% of the total radiation would be spared.

DISCUSSION

We have developed a simple clinical score based on known risk factors of CAD that can predict the risk of CAD in patients with newly diagnosed HF. Patients with a low score may benefit from an MSCT-first approach, potentially saving money, radiation as well as complications.

There are several limitations to our findings. First, while the two databases are similar in many respects, unfortunately, the Western Danish Heart Registry include no classification of symptoms of angina or extracardiac arteriopathy, both factors included in our score. We have chosen to include these factors in our analysis since they are both strong predictors of CAD in the Web-PATS registry. Another limitation is the possible information bias as not all patients diagnosed with HF receive CAG or, in fact, any sort of evaluation of possible CAD. Whereas the patient population in this study is already subject to a clinical judgement that they are at risk of having CAD.

Thus, our findings might not be generalisable to all patients with HF. However, as these patients were evaluated, they probably represent a higher risk of CAD than a complete population of HF patients. Thus, if calculated on all patients, we would expect a lower average CT-HF score as well as a lower average prevalence of CAD. All patients in this study received a CAG and therefore, we do not know the true re-evaluation rate with CAG if an MSCT-first approach was implemented.

MSCT is a Class IIb recommendation in the latest European Society of Cardiology guidelines for patients with a low-to-intermediate risk of CAD.[7] However, not all patients with HF are suitable for an MSCT-first approach. Patients with a history of CAD were excluded from this analysis. Further, we chose to exclude patients with a history of chronic kidney disease. This was done mainly because of the risk of contrast-induced nephropathy associated with the increased use of contrast in MSCT and in eventual re-evaluation. Additionally, patients with chronic kidney disease have a higher risk of coronary calcifications and were, thus, more likely to have blooming artefacts, potentially leaving the procedure inconclusive. Clinically unstable patients should be spared the possible extra waiting time of an MSCT and instead be sent directly to CAG where acute revascularisation is available. Also, though recent studies have shown the ability of MSCT to exclude CAD in patients with atrial fibrillation,[18] this is not routinely done in all centres due to technical issues. Some of the specific clinical characteristics of HF patients may in itself limit the accuracy and reproducibility of MSCT, such as inability to hold their breath as well as difficulties controlling the heart rate. HF patients also represent a population at a higher risk of contrast-induced nephropathy,[19] something to keep in mind when sending patients to an MSCT that in general uses more contrast than a CAG. This underscores the importance of patient selection as unnecessary examinations with MSCT could lead to additional cases of contrast-induced nephropathy.

The most common complications of a CAG are vascular (about 4%–7% of procedures).[5] Most of these are minor bleedings, but some are larger or more complicated (eg, pseudoaneurysm or arteriovenous fistula) and may even result in the patient needing a transfusion and prolonging the hospital stay. More serious complications are rare, such as stroke (0.07%), myocardial infarction (<0.05%) and death (<0.08%), though they may be more frequent in patients with congestive HF.[5] MSCT is non-invasive, making it less expensive[20] and associated with a lower mean radiation dose.[15]

Large systematic reviews have shown MSCT to be a highly sensitive test for the exclusion of CAD, with a sensitivity of >98%.[21 22] However, MSCT still only provide anatomical information and physiological significance, and obstructiveness cannot be routinely assessed from the scan. For this reason, positive findings still have to be confirmed with a conventional invasive CAG. With the addition of fractional flow reserve, MSCT accuracy may improve further limiting the number of re-evaluations with CAG needed. Though still primarily used as a test of CAD, MSCT does provide additional data among patients with HF regarding morphology (eg, hypertrophic cardiomyopathy or dilated cardiomyopathy) as well as aetiology (eg, sarcoidosis).[23] Functional imaging tests, such as Rubidium-82 positron emission tomography imaging, is a possible alternative to MSCT as a gatekeeper for CAG. However, MSCT is generally viewed as the most cost-effective gatekeeper.[24]

An advantage of MSCT is higher availability since the procedure is more easily implemented at centres than invasive procedures. Another potential advantage is the ability to visualise and diagnose significant extracardiac pathology in surrounding structures, mostly mediastinum and lungs. The prevalence of such findings varies in the literature from about 14% up to 28%.[25 26]

The newly developed score, the CT-HF score, is an easily calculated clinical score that stratifies HF patients according to their risk of CAD. What constitutes low to intermediate on the score remains to be determined. A cut-off of 9 points identifies about 56%–64% of patients with a risk of 13%–21% of CAD, while a lower cut-off of 7 points yields 36%–38% of patients with a risk of 9%–14%. Using the mean price of CAG and MSCT across the seven countries, a cut-off of 8 would save about 14% of the cost and 20% of the radiation. At 7 points, this drops to 14% of the cost and 18% of the radiation.

With the improved survival after AMI and improved treatment of patients with HF, the prevalence of HF is only expected to rise in the coming decades.[1 2] CAD is among the most common causes of HF contributing in as many as 65% among male HF patients.[1] With the publishing of the STICH trial 10-year follow-up, we now have data for patients with HF and CAD treated with CABG showing a robust long-term benefit.[3] Further, HF patients with concomitant CAD have an indication for implantable cardioverter-defibrillator,[27] which have shown a clear prognostic benefit unlike patients with non-ischaemic HF for whom the benefit seems to be limited to younger patients.[28] This underscores the importance of identifying patients with HF and CAD for whom treatment is clinically relevant.

A possible alternate approach for low-risk patients could be the evaluation of coronary artery calcium (CAC) as the first step before MSCT. Though cut-offs for different levels of risk of CAD varies in the literature, a CAC of 0 is universally associated with a low risk of events[29 30] even among patients with HF,[31] with long-term follow-up studies finding a low risk of mortality as far as 12 years ahead of a measurement.[32] Thus, patients with a low CT-HF score (<4) may avoid a full MSCT in the presence of a CAC of 0.

CONCLUSION

A simple clinical risk score can identify a subgroup of patients with newly diagnosed HF with a low risk of CAD. These patients may benefit from an MSCT-first approach,

reducing radiation dosage, the risk of complications as well as the price of the procedures.

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