One million patients undergo invasive coronary angiography (CA) in the United States every year.¹ In view of its invasive nature and related costs, noninvasive imaging of coronary imaging has the theoretical appeal to improve comfort for patients, reduce cost, and refine patient selection to limit invasive procedures to patients requiring treatment for ischemic coronary artery disease (CAD). Coronary computer tomography angiography (CCTA) has been introduced as a noninvasive method for CAD assessment >15 years ago,² but was limited by insufficient temporal and spatial resolution of early multi-detector computed tomography (CT) scanners. The advent of 64-slice and dual-source CT scanners has improved the clinical utility of CCTA by shortening the breath-hold duration and improving resolution.³ More recently, 320-slice CT scanners were introduced further, improving on the performance of earlier generation scanners.⁴ Despite these technological advances, the development of CCTA has reached its limits and remains inferior to coronary angiography. In this article, we aim to clarify that although CCTA is a valuable noninvasive tool in the diagnostic work-up of patients with low to intermediate likelihood for CAD, it has no role in high-risk patients and should therefore be considered complementary rather than competing with invasive CA.

Response by Achenbach on p 426

Diagnostic Performance of CCTA
The temporal and spatial resolution of CCTA with contemporary 64-slice CT multidetector scanners remains considerably lower compared with invasive CA (temporal: 80–190 ms versus 10 ms; spatial: 300–400 μm versus 150–200 μm). As a result, invasive CA remains the only method to allow for real-time assessment of coronary anatomy, whereas CCTA, despite short acquisition times, requires labor- and time-intensive image processing before arriving at the diagnosis. Moreover, the accuracy of CCTA to determine stenosis severity is inferior compared with invasive CA as determined by quantitative coronary angiography (Figure 1), which in turn results in a frequent overestimation of stenosis severity by CCTA. Along this line, only ≈50% of significant coronary stenoses (≥70%) identified by CCTA are associated with ischemia after further evaluation.⁵,⁶

As summarized in Table 1, several multicenter studies applying this technology have shown a sensitivity ranging from 81% to 99%, a specificity ranging from 64% to 93%, a positive predictive value ranging from 64% to 92%, and a negative predictive value ranging from 83% to 99% in a per-patient analysis.⁶⁻⁹ Of note, a prospective multicenter study conducted in Ontario, Canada, with CCTA images analyzed by local expert observers instead of core-laboratories, showed a high variability in terms of diagnostic accuracy across the 4 participating centers.⁹ The sensitivity, specificity, positive predictive value, and negative predictive value ranged from 50% to 93%, 92% to 100%, 85% to 100%, and 43% to 95%, respectively, across the centers, calling into question the diagnostic reproducibility of CCTA. In addition, 2 recent studies comparing a novel methodology for...
Noninvasive fractional flow reserve assessment with CCTA versus conventional CCTA showed a lower than expected sensitivity (84% to 94%), specificity (25% to 42%), positive predictive value (58% to 61%), and negative predictive value (72% to 80%) with the latter.\(^10,11\) These findings indicate that the accuracy of CCTA varies widely across institutions and observers owing to differences in acquisition protocols, local expertise, and interpretation, and lacks the robustness of diagnostic reliability required when applied in routine clinical practice. Even experts argue that only high-quality CCTA scans can be interpreted reliably and accurately, whereas poorly performed scans interpreted by nonexpert readers often lead to false-positive findings offsetting the potential advantages of this noninvasive diagnostic tool.\(^12\)

**Patients not Suitable for CCTA**

An important consideration in the overall appraisal of diagnostic entities is the issue of patient selection and the suitability for CCTA. It is widely acknowledged that morbidly obese patients as well as patients with intolerance to β-blockers cannot be studied by CCTA.\(^6\) Moreover, CCTA is not useful in the presence of heavy coronary calcifications and previous coronary revascularization, particularly after previously implanted metallic stents.\(^13\) Of note, heart rate and rhythm play an important role in patient selection for CCTA because there is a direct correlation between heart rate and the ability to evaluate coronary segments. In general, >95% of coronary segments are evaluable among patients with a heart rate ≤60 beats per minute. Conversely, the proportion of evaluable segments decreases to 80% among patients with heart rates in the range of 60 to 65 beats per minute, and to 70% among patients with heart rates in the range of 65 to 80 beats per minute. In patients with heart rates >80 beats per minute, it becomes increasingly difficult to evaluate coronary segments reliably.\(^13\) Accordingly, patients with atrial fibrillation, frequent premature atrial or ventricular ectopy, and uncontrolled tachyarrhythmias cannot be studied by CCTA. Overall, >25% of patients cannot adequately be studied by CCTA at this stage. In view of the increasing life expectancy, the proportion of elderly patients with CAD is expected to grow.\(^1,14\) However, elderly patients with CAD often present with coronary calcifications,\(^15\) atrial fibrillation,\(^16\) and chronic kidney disease,\(^17\) which makes them rarely evaluable by CCTA. It is therefore predictable that the proportion of patients who are evaluable by CCTA will further decline in the next decade.

**Patients With Stable CAD**

Low- or Intermediate-Risk Patients
In view of its negative predictive value, CCTA plays a role in patients with low and intermediate pretest probability of CAD. According to the European Society of Cardiology (ESC) guidelines, CCTA has a Class IIa, Level of evidence C recommendation—under the prerequisite that a good image quality can be expected (see paragraph above)—in patients within the lower range of intermediate pretest probability (15% to 50%) of CAD as an alternative to stress imaging techniques or after a nonconclusive exercise ECG or stress imaging.\(^18\) The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines on stable ischemic heart disease introduce a differentiation between patients able to exercise and patients unable to exercise.\(^19\) Among the former group, recommendation for CCTA ranges from Class III, Level of evidence C to Class IIb, Level of evidence B according to the interpretability of

### Table 1. Diagnostic Performance of 64-Slice CCTA for the Detection of Coronary Diameter Stenosis >50% (per Patient Analysis) in Multicenter Studies

<table>
<thead>
<tr>
<th>CAD</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al(^6)</td>
<td>291</td>
<td>56%</td>
<td>85%</td>
<td>90%</td>
</tr>
<tr>
<td>Budoff et al(^7)</td>
<td>227</td>
<td>23%</td>
<td>95%</td>
<td>83%</td>
</tr>
<tr>
<td>Meijboom et al(^8)</td>
<td>360</td>
<td>68%</td>
<td>99%</td>
<td>64%</td>
</tr>
<tr>
<td>Chow et al(^9)</td>
<td>169</td>
<td>42%</td>
<td>81%</td>
<td>93%</td>
</tr>
</tbody>
</table>

**Performance in multicenter studies using CCTA as comparator**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CAD</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koo et al(^11)</td>
<td>103</td>
<td>37%</td>
<td>94%</td>
<td>25%</td>
<td>58%</td>
<td>80%</td>
</tr>
<tr>
<td>Min et al(^10)</td>
<td>252</td>
<td>47%</td>
<td>84%</td>
<td>42%</td>
<td>61%</td>
<td>72%</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; NPV, negative predictive value; and PPV, positive predictive value.
ECG, whereas CCTA assumes a Class Ia, Level of evidence C for patients unable to exercise. Noteworthy, the document states that there is no prospectively established evidence demonstrating that CCTA leads to better patient selection for medical therapy, and revascularization procedures or more importantly improved clinical outcomes at this point in time.19 An important consideration for the use of CCTA is that the diagnostic performance of CCTA is inversely related to the patient’s pretest probability (Table 2). In other words, it performs well in patients at low pretest probability of CAD, but its specificity and negative predictive value are lower as soon as the patient risk increases.

Of note, there is consensus that pretest probability for CAD and diagnostic performance of a specific test are interdependent.18,20 As a matter of fact, the use of a diagnostic method is considered acceptable if the number of false-negative results after the test has been performed is lower than the number of the false-negative results based on the pretest probability of disease, and if the number of false-positive results is lower than the pretest probability of disease. Accordingly, the usefulness of CCTA among low-risk patients needs to be carefully considered. Indeed, provided the specificity of CCTA is approximately 80% based on multicenter registries (Table 1), the use of CCTA in patients with a pretest probability for CAD <20% would cause more harm than benefit because it would lead to a number of false-positive results in excess of the pretest probability for CAD. Conversely, patients with intermediate pretest probability (ie, >20%) of CAD appear to be ideal candidates for further risk stratification with CCTA. Diagnostic strategies according to pretest probability of CAD are summarized in Figure 2.

High-Risk Patients
The role of CCTA in symptomatic patients with high pretest probability is questionable. According to the ACCF/AHA guidelines, CCTA assumes a Class Ib, Level of evidence C recommendation as compared with invasive CA, which has a Class I, Level of evidence C recommendation.19 Similarly, the ESC guidelines indicate that there is no role for CCTA in symptomatic patients at high pretest probability of disease, whereas invasive CA has a Class I, Level of evidence C recommendation with a view toward risk stratification and evaluation for revascularization.18 Noteworthy, symptomatic patients are categorized as being at high risk based on the presence of classic cardiovascular risk factors including advanced age, arterial hypertension, dyslipidemia, diabetes mellitus, smoking habits, and male sex.21 Based on these, more than two thirds of symptomatic patients have at least 2 risk factors and should therefore be considered at high pretest probability for CAD.22 There are multiple reasons why invasive CA but not CCTA is indicated among patients at high pretest probability for CAD. First, invasive CA not only more accurately delineates coronary anatomy but also offers the opportunity for real-time functional assessment of ischemia by use of fractional flow reserve, which has been shown to improve patient and lesion selection for revascularization.23 In addition, invasive CA allows to characterize and semiquantitatively assess coronary flow patterns (TIMI flow and myocardial blush grade), presence of thrombotic material, extent of the collateral circulation, spontaneous dissections, and myocardial bridges. In view of the higher spatial resolution, small vessel disease can be better evaluated with invasive CA, which is also important in the assessment of cardiac transplant vasculopathy. Moreover, invasive CA also allows to reliably quantify the extent and complexity of CAD using the SYNTAX-score, which has been consistently validated as a valuable score to choose between revascularization strategies (coronary artery bypass graft versus percutaneous coronary intervention) and to assess the long-term prognosis of patients undergoing percutaneous coronary interventions.24,25 Last but not least, invasive CA allows for ad hoc interventions in case of obstructive CAD requiring percutaneous coronary intervention, avoiding the need to schedule a second procedure that instead is needed if obstructive CAD would be detected by CCTA. Therefore, invasive CA should be preferred in symptomatic, high-risk

<table>
<thead>
<tr>
<th>Pretest probability of CAD</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>105</td>
<td>98%</td>
<td>74%</td>
<td>93%</td>
<td>89%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>83</td>
<td>100%</td>
<td>84%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Low</td>
<td>66</td>
<td>100%</td>
<td>93%</td>
<td>75%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic Performance of 64-Slice CCTA According to Baseline Patient Risk

CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; NPV, negative predictive value; and PPV, positive predictive value. Adapted from Meijboom et al10 with permission of the publisher. Copyright ©2008, Elsevier.

Figure 2. Diagnostic strategies in stable patients according to pretest probability of disease. CA indicates coronary angiography; CAD, coronary artery disease; and CCTA, coronary computed tomography angiography.
patients as recommended by the American and European guidelines on the management of stable CAD, whereas CCTA is not useful in this patient population.\textsuperscript{18,19,26} Also in view of the exceedingly low rates of complications associated with invasive CA (Table 3), it is unlikely that these recommendations will change in the future.

**Patients With Acute Coronary Syndromes**

CCTA has been proposed for risk stratification and early discharge planning of patients with suspected acute coronary syndromes in the emergency room setting.\textsuperscript{27–31} Recently, 2 multicenter randomized clinical trials have prospectively evaluated the use of CCTA in patients with possible acute coronary syndromes.\textsuperscript{32,33} In the Rule Out Myocardial Ischemia/Infarction by Computer Assisted Tomography (ROMICAT-II) trial,\textsuperscript{32} 1000 patients with symptoms suggestive of acute coronary syndromes but without ischemic electrocardiographic changes and negative initial troponin test were randomly allocated to early CCTA or standard evaluation. This trial showed that the incorporation of CCTA into an emergency room protocol among these low-risk patients reduces the length of hospital stay by \(\approx 8\) hours at the cost of increased downstream healthcare utilization and radiation exposure without overall cost saving compared with standard evaluation. In another randomized trial,\textsuperscript{31} Litt and colleagues randomly allocated 1370 low-to-intermediate risk patients with suspected acute coronary syndromes to CCTA or standard evaluation. At 30 days, none of the patients discharged with negative CCTA died or had a myocardial infarction. Moreover, the use of CCTA increased the rate of direct discharge from the emergency room department (50\% versus 23\%) and reduced the length of stay (18 hours versus 25 hours) compared with standard evaluation. In synthesis, the findings of these 2 randomized trials indicate that CCTA for triage of low-risk patients with suspected acute coronary syndromes in the emergency room department reduces the length of stay and allows expedited discharge of patients with negative findings. However, it needs to be pointed out that patients included in these 2 trials were at very low risk, with negative troponin and absence of electrocardiographic changes at baseline.\textsuperscript{32,33} Indeed, the proportion of patients with a final diagnosis of acute coronary syndrome was <8\% in both trials. It is therefore disputable whether the use of CCTA portends any clinical benefit beyond a reduction of a few hours in the length of hospital stay, at the cost of a higher cumulative radiation exposure and downstream procedures.

Application of CCTA among higher risk patients with acute coronary syndromes is contraindicated in view of well-established clinical risk stratification algorithms based on risk scores, electrocardiography and cardiac biomarkers.\textsuperscript{34–38} It has been shown that even patients with small increases in cardiac troponin have a higher risk of death or myocardial infarction compared with troponin-negative patients.\textsuperscript{36,39} Patients with \(\geq 1\) primary high-risk criterion (positive troponin, ST-segment changes, GRACE score > 140) in the setting of suspected acute coronary syndrome derive prognostic benefit from a routine early invasive strategy,\textsuperscript{34,35} rendering CCTA superfluous for further risk stratification. Moreover, the advent of high-sensitivity troponin assays\textsuperscript{37,38} further minimizes the number of troponin-negative patients, thereby limiting the window of opportunity for CCTA. Finally, patients with acute coronary syndromes typically present with increased heart rates, a high prevalence of arrhythmias,
hemodynamic instability, pulmonary edema, and inability for breath holds for >10 seconds, limiting any eventual suitability for CCTA.

**Triple Rule Out Protocols**

The discrimination between acute coronary syndromes and other causes of acute chest pain is a frequent question in emergency room departments. Specifically, aortic dissection and pulmonary embolism are 2 acute conditions that may mimic the symptoms of acute coronary syndromes and are associated with a high risk of mortality. Triple rule out protocols based on CT scan may allow to discriminate between acute coronary syndromes, aortic dissection, and pulmonary embolism within a single examination. Nevertheless, there are some technical issues that limit the development and implementation of such protocols. A triple rule out protocol requires a higher volume of contrast material and an accurate timing of its injection to visualize all 3 vascular areas of interest. This leads to a prolonged CT acquisition time and subsequently higher radiation exposure compared with CCTA alone. Of note, even by applying the latest technology the mean radiation dose is reported to be in the range of 8 to 16 mSv. At this point in time, a large number of small investigations have been conducted on triple rule out protocols. However, the applicability of this strategy in routine clinical practice remains controversial and raises concerns over healthcare expenditure. Based on currently available evidence, the use of triple rule out protocols is considered of uncertain value.

**Patients With ST–Segment Elevation Myocardial Infarction**

The diagnosis of ST–segment elevation myocardial infarction (STEMI) is based on clinical symptoms and acute electrocardiographic changes without any diagnostic role for CCTA. In patients with an established diagnosis of STEMI, timely implementation of reperfusion therapy is recommended in all patients with symptom onset of <12 hours duration with a Class I, Level of evidence A recommendation according to ESC and ACCF/AHA guidelines. 

**Radiation Exposure**

An important consideration with respect to the use of CCTA is unnecessary exposure of patients to additional ionizing radiation. With the newest scanners and sophisticated acquisition techniques, CCTA can be performed with a lower radiation dose than the 12 to 18 mSv of conventional 64-slice CT scanners. Indeed, the implementation of prospective ECG-triggered modulation, reduced tube voltage, and novel acquisition modalities and the use of 320-slice detectors allow to reduce the radiation dose to as low as 2 to 6 mSv. However, this is achievable only in selected institutions and under supervision of experienced readers. Beyond the radiation dose administered by a single CCTA, it is noteworthy that in the ROMICAT-II trial the use of CCTA translated into a higher use of invasive CA with a significantly higher, cumulative radiation exposure among patients allocated to evaluation with CCTA compared with patients allocated to standard evaluation (Figure 3). The increased radiation exposure represents a matter of concern particularly when this diagnostic tool is applied to young and low-risk patients.

**Plaque Characterization**

A potential advantage of CCTA over invasive CA may be the possibility to visualize and characterize not only the vessel lumen but also underlying plaques. Plaque imaging with CCTA—based on plaque density in Hounsfield units—has been proposed in several studies, particularly after the introduction of 64-slice CT scanners with high spatial resolution. CCTA can be used for the assessment of positive remodeling, spotty calcifications, and low attenuation plaque. A refined plaque characterization may allow to improve risk stratification and to explore novel therapeutic strategies in the future. This may be of particular interest if the morphological characteristics assessed by CCTA are complemented by a functional evaluation...
of plaque activation by the use of positron emission tomography. However, identification of plaques responsible for future ischemic events (ie, vulnerable plaques) is not possible at this point in time. In addition, the resolution of CCTA is inferior to intracoronary invasive techniques such as intravascular ultrasound and optical coherence tomography, which can be easily performed during invasive CA (Figure 4 and Table 4).

Conclusions

Although there has been important technological progress in the development of CCTA, its clinical application remains limited. Owing to well-established risk algorithms, there is no role for CCTA in patients with acute coronary syndromes and STEMI, which constitute the most frequent indication for invasive CA in routine clinical practice today. Similarly, CCTA has no role in symptomatic patients with high pretest probability for CAD. CCTA is a valuable diagnostic modality in symptomatic patients with low to intermediate risk for CAD (15% to 50%), where invasive CA should not routinely be applied. Conversely, stable patients at low pretest probability (<15%) and asymptomatic patients should not be evaluated by CCTA, because the latter may lead to more frequent false-positive results compared with the pretest risk. In conclusion, CCTA does not compete but rather complements invasive CA when applied in appropriately selected patients.

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References


Response to Stefanini and Windecker

Stephan Achenbach, MD

It is comforting to see that 2 authors in a debate, approaching the same issue from opposing ends, reach a similar conclusion: Coronary computed tomography angiography (CTA) can be used in some—but not all—patients to detect and rule out coronary stenoses and therefore constitutes an alternative to invasive angiography. Whether this means a smaller or a larger percentage of patients lies in the eye of the beholder. Naturally, a writer with a CT background and intimate knowledge of the method’s capabilities prefers a somewhat broader approach than 2 interventionalists.

However, subtle bias is present in the points put forward by Stefanini and Windecker. Some examples: They boldly claim that “the development of coronary CTA has reached its limits” or that it “…requires labor- and time-intensive image processing before arriving at the diagnosis.” Neither is true. Table 4 lists “10 minutes” as the duration of both coronary CTA and invasive angiography—I have yet need to see the cath laboratory that turns around 6 patients per hour, although this is very possible for CT. They state that recent coronary CTA trials showed lower accuracy than expected—but readers must be aware that this was in comparison with fractional flow reserve, where invasive coronary angiography is also notoriously poor. They criticize CT for limitations of the triple rule out or the difficulties of characterizing plaque—hardly fair when invasive angiography has absolutely nothing to offer but the coronary lumen.

The role of coronary CTA is, therefore, larger than they try to make us believe; but then again, a cautiously positive approach is much better than outright rejection of its possibilities (or zealous overuse).
Can Coronary Computed Tomography Angiography Replace Invasive Angiography?: Coronary Computed Tomography Angiography Cannot Replace Invasive Angiography

Giulio G. Stefanini and Stephan Windecker

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