Can Coronary Computed Tomography Angiography Replace Invasive Angiography?

Yes: It is All About Finding the Right Test for the Right Person at the Right Time

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Can stents replace coronary artery bypass surgery? Certainly not. There are some patients with coronary artery lesions that are not amenable to stent placement, there are some patients where stent placement is prognostically inferior to bypass surgery, and there are some situations in which bypass surgery must be used when the attempt to treat a lesion by stent placement failed or resulted in a complication. Does this mean that coronary stents are useless? Certainly not—coronary stents have saved lives and relieved symptoms and continue to do so. They are an alternative to coronary artery bypass surgery in many situations, and they provide a less invasive and economically favorable alternative to open heart surgery. Could we do completely without stenting? Probably we could,[1] but the most reasonable approach is to use them when it makes sense.

Can coronary computed tomography angiography (coronary CTA) replace invasive angiography? Based on the short introduction, it is probably rather evident what I consider the obvious answer to be: No, coronary CTA cannot entirely replace invasive coronary angiography, but it does not have to to be useful. Could we do completely without coronary CT angiography? Probably we could, but why keep the noninvasive alternative to cardiac catheterization from our patients if there are situations in which a well-performed coronary CTA clearly obviates the need for an invasive angiogram?

Response by Stefanini and Windecker on p 417

Let's take the situation of a 57-year-old female patient I'll refer to as Betty (even though her true name is different). She reported some rather typical-sounding chest pain on exercise and occasionally at rest. Bicycle stress ECG testing was performed and led to ST–segment depression in the inferior leads (see Figure 1), reproducible on 2 occasions. Her treating cardiologist discussed invasive coronary angiography as the next diagnostic step, with the option for stent placement, but Betty, having some second thoughts about invasive cardiac catheterization, was happy to accept the alternative offer of a noninvasive coronary CTA examination. Coronary CTA clearly ruled out the presence of coronary stenoses (see Figure 1), and invasive cardiac catheterization was never performed. Of interest, this occurred in the year 2005, nearly 10 years ago. Coronary CTA was performed with a 64-slice system (which were high-end back then but are widely available today), and I have been able to follow the patient ever since: her chest pain eventually resolved and she never developed any further cardiac problems.

A case example never constitutes convincing evidence, but there are ample data to support the fact that coronary CTA permits to accurately rule out coronary artery stenoses and that it has tremendously high prognostic value. Four multi-center trials with independent core laboratory evaluation of reference coronary angiograms have evaluated the accuracy of coronary CT angiography.[2–5] Two of them were performed in patients with suspected coronary artery disease[2,3] and revealed negative predictive values of 97% and 99% to rule out coronary artery stenoses in comparison with invasive coronary angiography (see Table 1). The positive predictive values of these trials were not quite as high, because overestimation of coronary

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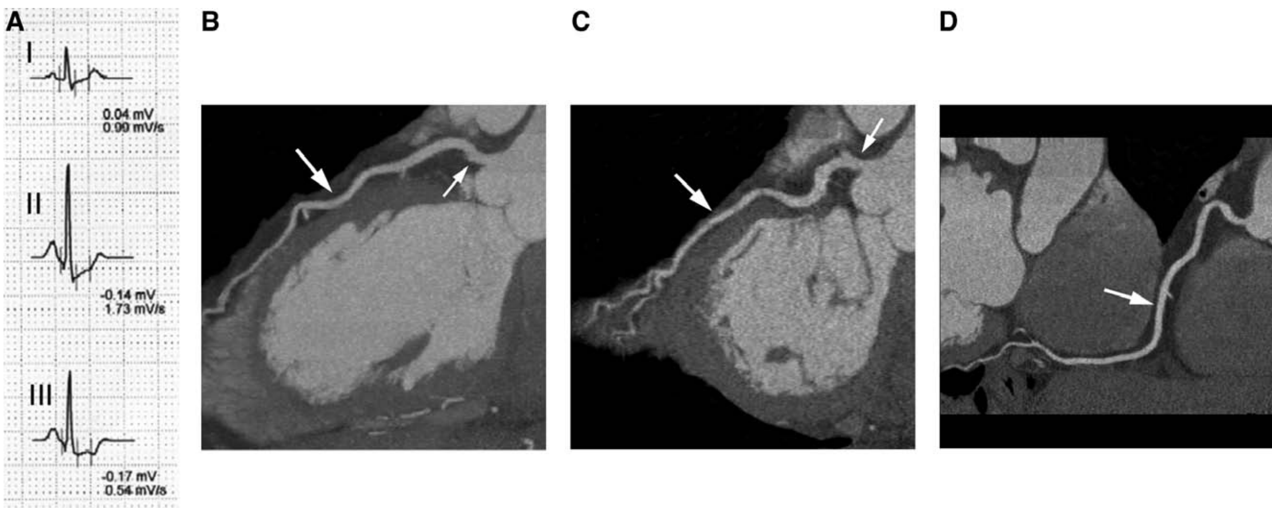

Figure 1. A 57-year-old female patient with exercise-induced chest pain and ST-segment depression in the inferior leads on bicycle stress exercise ECG. Coronary CT angiography performed by 64-slice CT rules out the presence of coronary artery stenoses. **A**, ST-segment depression in exercise ECG. **B**, Contrast-enhanced coronary CT angiography, curved multiplanar reconstruction of the left main (small arrow) and left anterior descending coronary artery (large arrow). **C**, Contrast-enhanced coronary CT angiography, curved multiplanar reconstruction of the left main (small arrow) and left circumflex coronary artery. **D**, Contrast-enhanced coronary CT angiography, curved multiplanar reconstruction of the right coronary artery (arrow).

stenoses can occur (see Table 1), but this does not limit the method's clinical value: If used to avoid cardiac catheterization in patients considered for invasive coronary angiography, it is the negative predictive value that counts. Not only in these 2 multicenter trials, but also in numerous meta-analyses, the negative predictive value has consistently been found to be extremely high. One of the most representative meta-analyses, incorporating data obtained by CT systems that had at least 64 slices, reported a per-patient sensitivity of 98% specificity of 82% and negative predictive value of 99%[6] (see Table 2).

One of the 3 available multicenter trials yielded lower accuracy values, with a sensitivity of only 85% and a specificity of 90%.[4] This trial is often cited by those who are somewhat more critical about coronary CTA. However, a look at the receiver operating characteristics curve of that trial demonstrates that it is the weighting between sensitivity and specificity done by the operators which shifted this trial's performance toward specificity and away from sensitivity. In addition, this study included a substantial number of patients with previous myocardial infarction and percutaneous coronary intervention and the overall pretest likelihood of disease was high, a cohort in which the clinical application of coronary CT angiography would not usually be considered. Finally, the fourth multicenter trial also included a large number of patients with previous infarction or stent placement and used a combined reference of angiographic stenosis plus ischemia in single photon emission computed tomography, which explains the lower positive predictive value. All the same, the negative predictive value was high (92%).[5]

It is not only accuracy data but also outcome data that support the use of coronary CTA to rule out coronary artery stenoses, avoid normal invasive coronary angiograms, and in this way replace an invasive test by a noninvasive one. In stable patients, numerous single-center trials followed patients after coronary CTA and investigated the occurrence of coronary

Table 1. Multicenter Studies That Investigated the Accuracy of Coronary Artery Stenosis Detection by Contrast-Enhanced 64-Slice Coronary CT Angiography in Comparison With Invasive Coronary Angiography

Author	Number of Sites	Number of Patients	Prevalence of Obstructive CAD*	Sensitivity (95% CI)	Specificity (95% CI)	Negative Predictive Value (95% CI)	Positive Predictive Value (95% CI)
Budoff et al[2]	16	230	25%	95 (85% to 99%)	83% (76% to 88%)	99% (96% to 100%)	64% (53% to 75%)
Meijboom et al[3]	3	360	68%	99% (98% to 100%)	64% (55% to 73%)	97% (94% to 100%)	86% (82% to 90%)
Miller et al[4]	9	291*	56%	85% (79% to 90%)	90% (83% to 94%)	83% (75% to 89%)	91% (86% to 95%)
Rochitte et al[5]	16	381†	38%	92%‡ (87% to 96%)	51%‡ (44% to 57%)	92%‡ (86% to 96%)	53%‡ (47% to 60%)

The last of the cited studies (Rochitte et al) used a combined reference standard of "at least 50% stenosis in coronary angiography plus perfusion defect in SPECT." All values are based on per-patient analyses.

*This trial included 58 patients with previous myocardial infarction and 28 patients with previously percutaneous coronary intervention.

†This trial included 104 patients with previous myocardial infarction and 109 patients with previously placed coronary stents.

‡Combined reference standard of angiographic stenosis plus perfusion defect

Table 2. Results of a Meta-Analysis That Investigated the Accuracy of Coronary Artery Stenosis Detection by Computed Tomography Angiography in Comparison With Invasive Coronary Angiography[6]

	Number of Trials	Sensitivity (95% CI)	Specificity (95% CI)	Negative Predictive Value (Range)	Positive Predictive Value (Range)
Per-patient analysis	18	98.2% (97.4% to 98.8%)	81.6% (79.0% to 84% to 0%)	99.0% (88% to 100%)	90.5% (75% to 100%)
Per-artery analysis	17	94.9% (93.9% to 95.8%)	89.5% (88.8% to 90.2%)	99.0% (93% to 100%)	75.0% (53% to 95%)
Per-segment analysis	17	91.3% (90.2% to 92.2%)	94% (93.7% to 94.2%)	99.0% (98% to 100%)	69.0% (44% to 86%)

CI indicates confidence interval.

artery disease events, either limiting analysis to hard events such as myocardial infarction and death, or carefully blinding analysis to early revascularization which may have been triggered by the results of coronary CTA (eg, a stenosis prompting stent placement or bypass surgery).

An early landmark outcome trial was published by Min et al[7] in 2007, reporting on the 15-month follow-up of 1127 symptomatic patients >40 years of age who had undergone 16-slice coronary CTA. Patients without any stenosis >50% had a survival rate of 99.7%, indicating excellent prognosis after a normal CT examination.

Hadamitzky et al[8] included 1265 individuals in their analysis of patients investigated by 64-slice CT, and over a follow-up of 18 months, only 0.5% percent of 802 patients in whom coronary artery stenoses had been ruled out by CT developed an event, whereas 4.8% of patients with obstructive lesions in coronary CTA developed an event. The same authors reported a 5-year follow-up of 1584 patients (with only 36 individuals lost to follow-up). Only hard events were analyzed; 48 patients died (36 cardiac and 12 noncardiac deaths) and 13 patients experienced nonfatal infarction. Among 1217 patients in whom coronary artery stenoses had been ruled out, only 41 developed a hard event (3.3%), as compared with 33 of 316 patients with ≥1 stenosis (10.4%). Notably, if coronary CTA not only showed absence of stenosis, but also absence of any coronary atherosclerotic plaque, the annual event rate was only 0.2%.[9] In a meta-analysis of 18 single-center trials with a total of 9592 patients who underwent 64-slice CT, Hulten et al[10] reported a pooled negative likelihood ratio of 0.008 for hard events if coronary CTA was completely normal—making it very safe to avoid any further treatment or diagnostic testing after a normal coronary CTA.

Large-scale multi-center international registries support the extremely good prognosis of symptomatic patients after a normal coronary CTA examination. Most prominently, the CONFIRM registry[11] collected data from 12 centers in 6 countries between 2005 and 2009. Min et al analyzed 24 775 of these patients, with follow-up obtained in 23 854, of which 5594 patients had obstructive coronary artery disease and 18 260 did not. Over a mean period of 2.3 years, 404 deaths were recorded. The mean annualized death rate in patients with a normal coronary CTA examination was only 0.28%.[12]

The same registry yields interesting data on the ability of coronary CTA to identify individuals who may profit from revascularization. Shaw et al[13] analyzed the relationship between coronary CTA results, invasive coronary angiography, and subsequent mortality. They found that in patients without any obstructive stenosis in coronary CTA, invasive coronary angiography was associated with a relative hazard for death of 2.2 (P=0.011), whereas in patients with obstructive stenoses in coronary CTA, invasive angiography was associated with a relative hazard for death of 0.61 (P=0.047). Finally, Min at al used the CONFIRM registry to analyze the survival benefit of coronary revascularization and found that such a benefit was only present in patients with high-risk anatomy in coronary CTA (at least 2-vessel coronary artery disease with involvement of the left anterior descending coronary artery, 3-vessel coronary disease, or left main stenosis).[14] Revascularization was associated with a hazard ratio for death of 0.38 (95% confidence interval [CI], 0.18–0.83) in patients with high-risk CAD in coronary CTA, but there was no survival difference in patients without high-risk CAD in coronary CTA (hazard ratio, 3.24; 95% CI, 0.76–13.89).

Notably, a very good prognosis of patients with a normal coronary CTA examination was not only shown for stable chest pain, but also for individuals presenting to the emergency room with acute chest pain and low-to-intermediate likelihood of an acute coronary syndrome. Several investigators reported extremely low event rates during follow-up after patients were discharged secondary to a normal coronary CTA.[15–21] For example, there were no coronary events within 30 days in 640 patients discharged after a normal coronary CTA study (of a total of 908 patients who received coronary CTA),[20] and 1 death of unknown cause, but no definite cardiac event, no myocardial infarction, and no clinically driven revascularization after 1 year in 481 discharged patients based on coronary CTA.[18] These trials can justifiably be criticized for including very-low-risk patients,[22] but they are a start and they do prove that the use of coronary CTA is a safe strategy in acute chest pain without troponin and ECG changes.

All in all, these and other prognostic trials in patients who underwent coronary CTA[23] unanimously demonstrate a very good prognosis if coronary CTA ruled out the presence of coronary artery stenoses, thus supporting its clinical utility if used in patients with suspected coronary artery disease.

Finally, evidence that coronary CTA may in fact replace at least some catheter-based coronary angiograms comes from invasive coronary angiography itself. Analysis of 398 978 patients in the American College of Cardiology National Cardiovascular Data Registry revealed that obstructive coronary stenoses were found in only 37.6% of patients.[24] Even if noninvasive testing was reported as positive, only 41.0% of patients had obstructive stenoses. Clearly, if a noninvasive test used instead of invasive coronary angiography could avoid a substantial number of these normal coronary angiograms, there would be tremendous potential. Coronary CTA can do just that—avoid invasive testing when CTA is normal, proven to be associated with an excellent prognosis.

Why then the controversy about coronary CTA? Why is it not readily accepted, and are the obstacles to widespread use such that its application should be entirely avoided? Some of the arguments used against coronary CTA stem from the fact that it requires the use of contrast agent and exposes the patient to radiation. Indeed, radiation exposure was substantial several years ago, with a landmark study demonstrating that in individual centers, the average estimated effective radiation exposure was as high as 30 mSv (it should be mentioned that in the same study, sites at the lower end of the spectrum performed coronary CTA with an average exposure of only 4–5 mSv).[25] Since then, tremendous progress has been achieved regarding radiation exposure, with the introduction of dose-sparing protocols for ECG synchronization, the widespread use of lower tube voltages, and the development of iterative reconstruction algorithms. The use of rather straightforward, standardized protocols in widespread organizations has been shown to permit reductions in radiation exposure that easily reach 50%.[26] In the most recent multicenter trial, the average effective dose for coronary CT angiography was 3.2 mSv (as compared with 9.75 mSv for single photon emission computed tomography and 12.0 mSv for invasive angiography).[5] If heart rate is low (<60 beats/min) and stable, coronary CTA with prospectively ECG-triggered image acquisition and a tube voltage of 100 kV yields very stable image quality at effective doses around 1.5 mSv (see Figure 2). Under certain prerequisites, doses slightly <1.0 mSv are achievable with preserved high accuracy for stenosis detection.[27,28] By combining various techniques for dose reduction, acquisitions can be performed with even lower radiation exposure[29] (see Figure 3). There have even been some series reporting doses below 0.1 mSv in selected individuals.[+++] This is clearly not possible in all patients, but it demonstrates the potential for dose-effective coronary CTA.

Another frequent point mentioned against the use of coronary CTA is the fact that CT, being a purely anatomic imaging modality, cannot establish the hemodynamic relevance of coronary artery lesions, and therefore has similar limitations as invasive angiography. This is absolutely true, but again does not prevent coronary CTA from being clinically useful. If the aim is to rule out coronary artery stenoses, demonstrating the absence of stenosis is enough to avoid further testing. This does not mean that it would not be desirable to assess the hemodynamic relevance of coronary atherosclerotic lesions by cardiac CT (and such efforts are underway in the form of CT myocardial perfusion[5,30–36] and CT-derived fractional flow reserve).[37–40] However, in just the same way as invasive coronary angiography does not require fractional flow reserve measurements in every single case, coronary CTA can be of

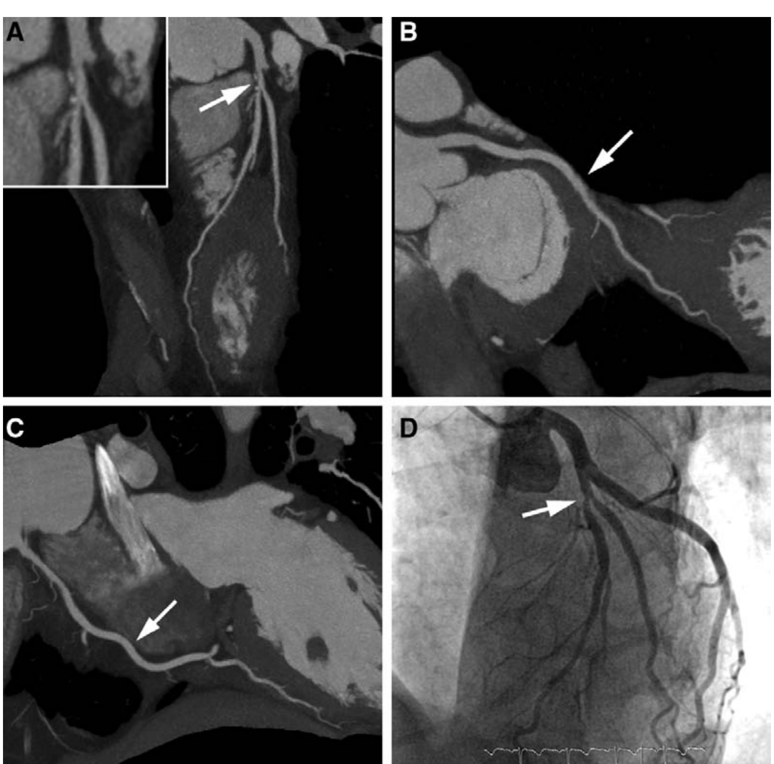

Figure 2. Prospectively ECG-triggered coronary CT angiography with a tube voltage of 100 kV. Effective dose 1.5 mSv. A coronary artery stenosis is present in the left anterior descending coronary artery, confirmed by invasive coronary angiography. **A**, Coronary CT angiography, curved multiplanar reconstruction of the left main and left anterior descending coronary artery. The arrow indicates a bifurcation stenosis of the left anterior descending coronary artery and large first diagonal branch, caused by partly calcified atherosclerotic plaque (see inset). **B**, Contrast-enhanced coronary CT angiography, curved multiplanar reconstruction of the left main and left circumflex coronary artery (arrow). **C**, Contrast-enhanced coronary CT angiography, curved multiplanar reconstruction of the right coronary artery (arrow). **D**, Invasive angiography of the left coronary artery, confirming the presence of a high-grade stenosis at the bifurcation of the left anterior descending coronary artery and diagonal branch.

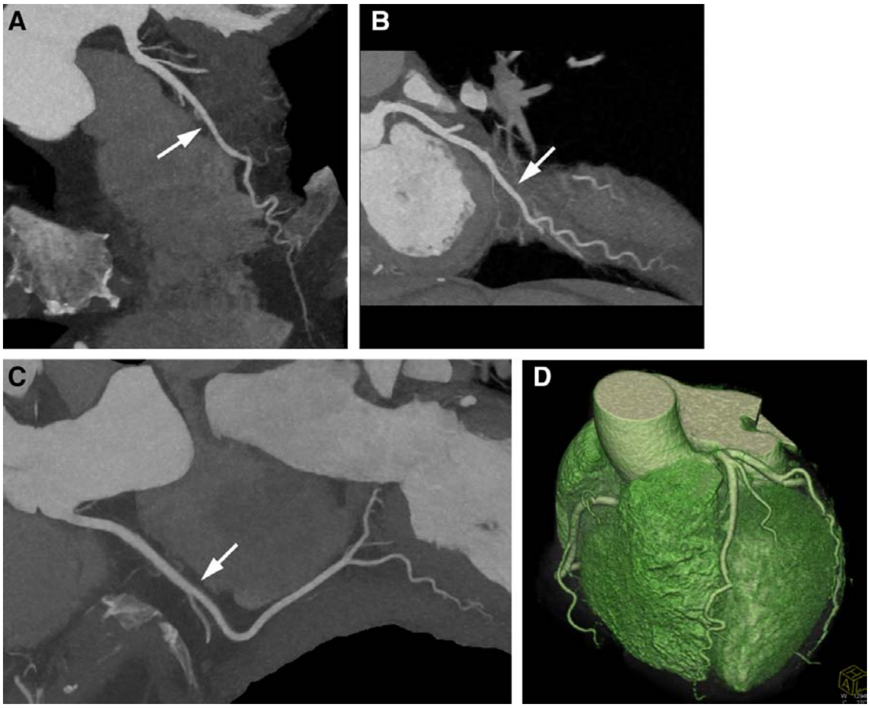

Figure 3. Very-low-dose coronary CT angiography performed by dual source CT at 70 kV tube voltage. Patient weight 68 kg, heart rate 58 beats/min, dose-length product 19.4 mGy*cm (estimated effective dose 0.3 mSv). No coronary artery stenoses are present. **A**, Curved multiplanar reconstruction of the left main and left anterior descending coronary artery (arrow). **B**, Curved multiplanar reconstruction of the left main and left circumflex coronary artery (arrow). **C**, Curved multiplanar reconstruction of the right coronary artery (arrow). **D**, Three-dimensional, surface-weighted volume rendering technique to achieve a 3-dimensional reconstruction of the heart and coronary arteries.

substantial benefit just by displaying normal coronary anatomy and eliminating the need for further testing.

Critique is also often based on the less-than-perfect positive predictive value of coronary CTA. It is absolutely true that CT has a tendency toward overestimation of stenosis degree, that artifacts can mimic stenoses, and that the positive predictive value is lower than we would want it to be. This is especially true when coronary CT angiography is compared with functional studies such as single photon emission computed tomography myocardial perfusion,[5,41,42] or invasively measured fractional flow reserve[38,39] (a comparison that can hardly be used as an argument against CT and for invasive angiography, because the coronary angiogram has the exact same limitations). All the same, this needs to be taken seriously. Coronary CT angiography is not a test that should be used as a screening method—the respective consensus documents state this very clearly.[43,44] Too many false-positive lesions (given the low prevalence of disease in screening populations) and too many stenoses that do not cause ischemia would be found, potentially resulting in unnecessary treatment. However, the very same holds true for invasive coronary angiography, and what providers have to be careful about is to not lower the threshold for coronary CTA too much. The method is ideally suited to rule out disease in patients at the lower spectrum of pretest likelihood who would otherwise be considered for other forms of testing, including invasive angiography. Application outside this comfort zone may be justified in single cases, but in general should be avoided in order not to generate screening scenarios or to use coronary CTA in high-risk populations where it has little to contribute.

Finally, one might argue that it is not necessary to add coronary CTA to the noninvasive armamentarium that is currently available to assess patients with suspected coronary artery disease. Testing for ischemia with stress imaging tests has a good prognostic value and, if used to its full potential, should be able to eliminate all potential candidates for coronary CTA because only patients with clear evidence of ischemia remain, these in turn would be candidates for invasive angiography and revascularization. This would be true in a perfect world, but ischemia testing has its own limitations. Not all tests can be used in all patients, interpretation can be ambiguous, and the positive predictive value is not 100%. This explains why in the registry mentioned above, even after previous noninvasive testing, 59% of patients undergoing invasive coronary angiography had no relevant coronary artery stenoses.[24] Clearly, there is room for another noninvasive test.

So, can coronary CTA replace the invasive angiogram? Certainly not entirely, and no one would reasonably claim this, want this, or require this. However, coronary CTA can be used in cases where the outcome of invasive angiography is relatively likely to be normal, typically after some form of testing for ischemia. It may also be used as a first diagnostic test for symptomatic patients in some cases, again with the aim to rule out stenoses early and avoid a further sequence of testing. This approach has been incorporated into the recent European guidelines for the management of patients with stable chest pain, with the very wise addition that suitable patient characteristics, adequate equipment, and local expertise have to be present—something that would be considered reasonable for any other diagnostic test.[45] And reasonable, in fact, should probably be the buzz word when considering clinical applications of coronary CTA. Overuse is damaging, but ignoring the possibilities that coronary CTA has to offer is not helpful either. There is no one solution for all situations. No test can entirely replace the invasive coronary angiogram. However, coronary CTA can be a very good solution in many instances, and we'd better be ready to use it at its full potential. In the end, as always, it is about finding the right test for the right person at the right time.

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Key Words: angiography ■ computed tomography ■ coronary artery disease

Response to Achenbach

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We concur with many of the arguments put forward by our colleague Stephan Achenbach. Of note, all points raised relate to the widely accepted notion that coronary computed tomography angiography (CCTA) is a valuable noninvasive diagnostic modality to rule out coronary artery disease in patients with low-to-intermediate risk owing to its high negative predictive value. However, CCTA does not compete with invasive coronary angiography (CA) in this specific patient population, but rather with other noninvasive diagnostic modalities such as stress echocardiography, magnetic resonance, and nuclear and PET perfusion imaging. It is worth mentioning that CCTA unfolds its diagnostic potential only in the hands of appropriately trained experts. CCTA should not be applied to patients who do not derive benefit from this diagnostic modality. In this context, CCTA should be avoided among asymptomatic patients for purposes of screening, which not only exposes patients to inadequate radiation exposure but also triggers superfluous diagnostic procedures resulting from unexpected CCTA findings. Similarly, CA rather than CCTA should be performed among high-risk stable coronary artery disease patients and patients with intermediate-to-high-risk acute coronary syndromes. CCTA is unable to replace CA because the latter technique is much more robust and can be applied to any patient with any clinical condition at any time, providing real-time assessment of coronary anatomy (and function) with better spatial resolution and offering the potential to proceed with percutaneous coronary interventions if needed. Nevertheless, an appropriate use of CCTA in low-to-intermediate-risk patients may increase the number of useful invasive CAs leading to revascularization.

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