

# Images beyond clinical presentation? Promising, but not confirmed in ESRD transplant candidates

Maciej Sosnowski

Unit of Noninvasive Cardiovascular Diagnostics, 3<sup>rd</sup> Chair of Cardiology,  
Medical University of Silesia, Katowice, Poland

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### Introduction

Recent advances in noninvasive cardiac imaging have opened new opportunities for detecting clinically silent coronary artery disease (CAD). Coronary computed tomography angiography (CCTA) is an excellent example. Many authors stress its high negative predictive value, making this noninvasive method especially valuable for excluding significant coronary lesions in very high-risk asymptomatic persons and in symptomatic subjects with a low or moderate CAD probability [1]. As the efficacy of CCTA for risk assessment in pre-renal transplant patients is uncertain, the study of Mao et al. [2] refers to an important contemporary clinical issue. Seeking a noninvasive method for excluding CAD in these patients is of great value, since other noninvasive modalities have been shown to be neither specific nor sensitive [3]. As silent CAD confers a higher procedural risk (transplantation) and increases the risk for post-transplant cardiovascular complications, at present selective invasive coronary angiography remains the only reliable approach [4]. However, some key questions should be addressed for a balanced understanding of the results of Mao et al. [2] in terms of the applicability of novel imaging modality in dialyzed end-stage renal disease patients awaiting renal transplantation.

### What do different current guidelines say?

Risk evaluation of cardiovascular outcome in patients with end-stage renal disease referred for renal transplantation is a matter of discordant indi-

cations, regarding various guidelines authors' expertise in the field of cardiology, nephrology and radiology.

Recent cardiology guidelines indicate a need to consider at least two issues: overall CV risk and surgical risk [5–7]. Regarding the first, symptomatic status (angina, dyspnea or equivalents) is of utmost importance in terms of CAD probability estimation. In asymptomatic subjects, accumulation of at least four risk factors (including renal impairment) is considered substantial. Even so, a level of evidence is usually low (B or C) due to lack of randomized trials. For instance, a negative recommendation regarding CCTA (class III) in patients with no signs or symptoms suggestive of CAD is given on the basis of experts' consensus (level of evidence C) [5, 6]. The second issue relates to the risk associated with surgical procedures, among which major vascular surgery is graded the highest [7]. In such a setting, invasive coronary angiography (ICA) may be considered (class IIB, level B) [7]. Unfortunately, cardiology guidelines do not refer specifically to patients with end-stage renal disease (ESRD) or renal transplant candidates/recipients.

In contrast to cardiologists, nephrologists consider noninvasive methods, albeit constituents of their opinions, are weaker and conflicting, and they do not come from randomized trials (class B = analogy to class II for cardiology guidelines) [8]. As the main fear of nephrologists relates to the use of contrasting media for invasive coronary angiography, many noninvasive methods have been examined over past decades in a search of the best way of diagnosing CAD and risk prediction in ESRD patients. In general, only high-risk ESRD patients with positive cardiac stress test(s) should undergo ICA for possible revascularization prior to transplantation

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**Address for correspondence:** Maciej Sosnowski, MD, PhD, Unit of the Noninvasive Cardiovascular Diagnostics, School of Medicine, Medical University of Silesia, Ziołowa 47, 40–635 Katowice, Poland, tel: + 48 32 252 86 63, fax: + 48 32 252 39 30, e-mail: maciej.sosnowski@gmail.com

[9]. Also, the risk associated with ICA cannot be ignored in ESRD patients in general, since only a low proportion requires revascularization before renal transplantation in contrast to a relatively high proportion of patients being at high risk as assessed noninvasively (class B) [9]. It is worth pointing out that evidence of significant coronary artery stenosis does not necessarily bear a risk for an unfavorable cardiovascular outcome, as plaque instability, rather than angiographic stenotic lesion, is associated with infarction [9].

Last, but not least, radiologists consider CCTA only in symptomatic patients to be justified depending on CAD probability (low or moderate) [10, 11]. Unfortunately, no solutions for ESRD patients, and for those who are renal-transplant candidates in particular, are provided. However, the risk associated with X-ray exposure is considered as one of the major limiting factors for the wider use of CCTA [12].

Thus, a discrepancy between guidelines leaves many areas open for researchers. However, weaknesses of guidelines should be taken into consideration and should constitute objectives of further investigations.

### **Did the study of Mao et al. answer the questions?**

Mao et al. [2] carried out a small, one center, study in which hypertensive dialyzed ESRD patients awaiting renal transplantation had a CCTA examination for CAD exclusion. The authors focused on feasibility, quality, reproducibility and safety of CCTA.

The small number of examined subjects is one of the major limitations of the study. As most patients were African-American (89%), any generalization for the entire population, or whites only, should be treated with caution. Additionally, the risk factors evidenced differ from those usually considered and indicated by guidelines. For instance, smoking status was ignored, while studies in normal and symptomatic populations list smoking as the most important factor. In addition, CAD probability based on clinical presentation has been omitted in the study. Being aware of guidelines, symptomatic status plays a crucial role for both indication for CCTA and its interpretation.

The mean age of examined persons represents the usual value for patients referred for renal transplantation. However, in this specific subset of patients, accelerated arterial calcification and its relation to patho-mechanisms somewhat different from atherosclerotic process, has long been ac-

knowledged. In terms of coronary artery calcium values (mean  $684 \pm 1632$  Agatston units), the examined patients can represent 90<sup>th</sup> percentile strata for age or can be compared to 70 year-old asymptomatic subjects. In such cases, the calcium burden has been shown to limit the reliability of CCTA [5, 13].

In the study of Mao et al. [2] poor quality of imaging affected almost 40% of analyzed segments of the coronaries, though only in six patients the coronary artery calcium had been scored above 400 Agatston units. Importantly, in ten (36%) ESRD patients with a 'zero' coronary artery calcium, there were no coronary lesions on CCTA. The proportion of un-interpretable stenoses within main epicardial coronaries varies depending on readers, achieving six and ten patients (respectively), which accounts for 25% and 37% of uncertainties (Table 2 of Mao's study). Thus, in every fourth (or every third by second reader) patient with ESRD, the critical stenosis, which might be an object of coronary intervention, cannot be reliably assessed. The question is whether the glass in this case is seen to be half-empty or half-full? From a clinical viewpoint, X-ray exposition and contrast media use would not be justified if the result can be inconclusive in such a proportion.

### **What does the study add?**

For the first time, it was shown that in asymptomatic ESRD patients referred for renal transplantation, CCTA is feasible, well tolerated and safe. It also documented that in this subset of patients, a 'zero' calcium score strongly advocates against the presence of stenotic atherosclerotic lesions. In addition, the authors found that complementary non-invasive evaluation by means of morphometric and functional methods (dobutamine-stress echocardiography) might be of value [2].

### **What does the study fail to answer?**

Lack of ICA renders a reliable assessment of coronaries impossible. Thus, the statistical performance of CCTA cannot be judged. As the presence of significant stenosis within major coronary arteries on CCTA might not necessarily be confirmed by invasive evaluation, its clinical significance remains unknown [1, 5–7]. Also, a relatively low Kappa statistic at segment level (0.46) indicates a high dependence of stenosis grading according to the individual experience of investigators. In other words, an assessment of coronary lesions seems to be rather subjective, and in some cases inconclusive. It

is important to state that the lack of clinical endpoints is the 'Achilles heel' of Mao's study. A lack of data regarding clinical outcome in ESRD patients and clinical management guided by the results of CCTA does not permit the position of CCTA among non-invasive procedures to be determined.

### What is necessary to confirm or reject the implications of the study?

Noninvasive diagnostic procedures, if they form a basis of medical management, should undergo a path of examination similar to that of drugs. The most obvious method is a randomized study, in part of which a subject's noninvasive modality is examined, and in another part previously used methods are used. In both arms, a 'gold standard' invasive study would be mandatory. Despite the relatively high accuracy of noninvasive coronary computed tomography angiography for excluding significant coronary lesions, evaluating the severity of plaques (either calcified or non-calcified) is less straightforward, especially in the presence of high calcium deposits. An anatomical severity does not necessarily correspond with the functional sequels, i.e. acute ischemia or hibernation. For the results to be valuable, a multi-center study with a greater number of participants would be necessary. For CCTA as an alternative method to ICA, cardiac events (outcome) and management (decision) should be tested in a random fashion. Of course, such an attempt in symptomatic persons might provide an ethical dilemma. However, until answers are given in properly planned and controlled studies, CCTA remains an experimental tool that should not be used routinely, especially in high-risk populations. Clinical presentation should be considered as more important than any impressive images.

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