Long-term application of vitamin K antagonists, more harm than good? The additional value of imaging

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This editorial refers to ‘Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk atrial fibrillation patients’, by B. Weijs et al., on page 2555

As Weijs et al. have described, most patients diagnosed with paroxysmal atrium fibrillation (AF) are currently treated by prescribing life-long use of vitamin K antagonists (VKAs) to prevent thrombo-embolic complications. By applying minimal invasive multislice computed tomography (MSCT) imaging, the authors found a possible adverse treatment effect in patients who were receiving VKAs for relatively longer, showing significant higher levels of calcium in their coronary arteries compared with patients with a shorter time on VKAs. This could have serious consequences for current clinical practice.

In contrast to many other patient populations with cardiovascular diseases, a subgroup of patients exist in which AF is diagnosed at a relatively young age. With this in mind, the long-term safety of the pharmaceutical treatment (in this case prevention) is therefore of great importance. Until recently, the effects of long-term treatment strategies on coronary vessel wall morphology, whose primary objective is not to be used to treat coronary artery disease (CAD), were impossible to study in humans other than by using invasive coronary imaging techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT). These modalities can only be used in conjunction with invasive coronary angiography, which obviously will not be performed unless there is an indication for the presence of CAD. Furthermore, it would be necessary to image the complete coronary artery tree, which is not an easy task for catheter-based imaging modalities, and consequently a challenging and tedious analysis is required. A good example is the study design of the PROSPECT trial. Fortunately, there is also currently the possibility to image these patients by applying minimally invasive coronary MSCT, elegantly described by Weijs et al. It entails, within its limitations, imaging the complete coronary artery tree in a rapid fashion. In contrast to invasive coronary angiography, there is only the need to administer a small amount of contrast medium intravenously to visualize the coronary artery lumen, and naturally radiation exposure is a factor, and is not completely negligible.

Applying minimally invasive coronary MSCT imaging, within a population of AF patients with low cardiovascular risk, Weijs et al. observed that patients who are receiving VKAs for relatively longer have significantly more coronary calcification compared with patients who are receiving this treatment over a shorter time span (Figure 1). Corroborating experimental data suggest that VKAs may decrease the activity of matrix Gla-protein, a strong inhibitor of soft tissue calcification. The authors concluded that the patient population of low risk AF who are on VKAs needs to be studied more in depth to judge if the current treatment strategy needs to be adapted to other possible options. The authors’ finding requires and justifies a randomized long-term study to corroborate their data and to evaluate if a change in treatment strategy would be warranted by, for example, a change to one of the new anticoagulants as suggested by the authors.

Rapid developments in coronary imaging have made it possible to study a variety of treatment effects as described by the authors. The newer generation of MSCT scanners are able to image the coronary artery tree at high speeds by using more detectors (320-slice scanners), avoiding motion artefacts, and, even more importantly, at much lower radiation levels compared with the scanners of the recent past. One could suggest that those patients who need to undergo treatments which might have an effect, negative or possibly even positive, on the coronary artery vessel wall morphology should be imaged in a standard way by MSCT. When performed prior to the commencement of a treatment this would allow observers to study serial patient-specific changes (Figure 1). Many longitudinal IVUS studies suggest that there might be an improved accuracy to detect treatment effects by applying serial measurements as opposed to being limited to...
only an individual measurement at one single point in time. Unfortunately, the calcium score, known as the Agatston score, applied by Weijs et al. was measured at one single time point only and so differential changes in coronary artery calcification levels in individual patient are lacking (Figure 1). Although the patients were relatively young, it cannot be excluded that they already had significant CAD present at the time of the start of the VKA treatment, as has been shown in the past. A repeated (e.g. differential) measurement would therefore be of utmost importance in future studies investigating the current hypothesis of the suspicion of the effects of VKAs. Although the authors present their findings as an adverse effect, it has been shown in IVUS-driven studies that increased levels of plaque calcification accompanied by negative coronary vessel wall remodelling could be signs of plaque stabilization. These are questions left unanswered in the study of Weijs et al. which need to be addressed in future studies.

Another intriguing aspect arose from the study of Weijs et al.: what is the underlying mechanism here? Although MSCT is very sensitive at picking up coronary calcification, it cannot determine

**Figure 1** (A) A cross-sectional multislice computed tomography (MSCT) image of a calcium score scan. Due to the high attenuation of calcium in MSCT scans it can be detected easily as bright areas within the images, as indicated here by **, of calcium present in the proximal left anterior descending (LAD). This is the examination set-up as described by Weijs et al. (B) A three-dimensional (3D) reconstruction of this calcium score acquisition in a similar projection to the 3D reconstruction of the contrast enhanced scan in (C). Using this contrast-enhanced scan the LAD can be extracted from the MSCT image data and a comprehensive longitudinal reconstruction of the LAD (D) can be computed. Ideally these examinations should be performed longitudinally so that serial changes of the coronary artery vessel wall morphology could be evaluated over time. In such a fashion not only could the changes in the amount of calcium be detected but also serial remodelling of lesser advanced stages of coronary artery disease and its development can be followed. In the case where a patient in this population suffers a coronary event which needs an intervention, then an additional intracoronary imaging examination, such as presented here by applying intravascular ultrasound (IVUS) (E and F), could reveal more details of the location of the calcium and other plaque components. D and E, and F and G are matched, so there is a one-to-one link between these images. The different appearances of the calcium, bright exaggerated areas in MSCT (D and F), and bright rims with shadowing behind in IVUS (E and G), can be appreciated.
the precise location of the calcium within the coronary artery. Due to the high attenuation values of calcium it is visualized as exaggerated very bright areas, making it difficult to determine their exact location in the coronary artery (Figure 1). As the authors describe it could be within coronary plaques, which is atherosclerosis, but it could also be within the media, called Mönckenberg disease. This distinction can only be made by use of intravascular imaging modalities (Figure 1). Therefore, it would be of great importance if patients on long-term VKA therapy who might end up with CAD requiring a coronary intervention should also be additionally imaged by IVUS and/or OCT; the PROSPECT trial\(^1\) was designed in a similar fashion. Although it must be emphasized that these intravascular imaging modalities are not the gold standard, which is still histopathology, when applied as a complementary imaging tool they could be of great added value. However, care must be taken as these intracoronary imaging methods also need specific methods of analyses as they also suffer from calcium-related imaging artefacts\(^1\) (Figure 1). In contrast to MSCT, IVUS shows calcium as bright rims with dark areas behind them (called acoustic shadowing). However, due to the tomographic cross-sectional imaging of the vessel, it allows accurate determination of the location of calcification as compared with MSCT (of course in cases where the vessel is not circumferentially calcified over long lengths).\(^3\)

As long-term randomized controlled trials will take several years, another possibility to investigate the association between long-term use of a VKA and calcification is to use MSCT data from existing hospital databases. By applying propensity analyses, it is feasible to compare patients treated with a VKA with patients not treated with a VKA in larger cohorts of patients compared with the study of Weijs et al., investigating more in depth by increasing the power of the study whether the use of a VKA really induces increased levels of CAD.

The study by Weijs et al. ‘tickles’ scientific curiosity to determine what exactly is taking place in this particular patient population who are on long-term VKAs. However, from a cost–benefit approach we are facing difficult financial times in which it can be authorized the necessary finances for the extra diagnostics for these types of long-term follow-up studies. These studies are needed to learn and study, and, perhaps even more importantly, to prevent a patient’s exposure to possible adverse treatment effects, which were unexpected at the time of the start of the treatment.

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**References**


