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Cardiac CT imaging in familial hypercholesterolemia: implications for therapy and clinical trials.

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Abstract (200 words max.):

Purpose of review:
The purpose of the present review is to summarize the potential clinical applications of computed tomographic angiography (CTA) based on the limited CTA findings in FH so far and recent advances of CTA research in other high-risk patients.

Recent findings:
Long-term aggressively statin treated, asymptomatic FH patients can have dramatic coronary artery disease (CAD). A clear association between the presence and the extent of non-obstructive CAD and all cause mortality was found in the international multicenter coronary CTA evaluation for clinical outcomes (CONFIRM) registry. Notably, baseline statin therapy was associated with a significant lower mortality for individuals and less CAD but not for individuals with normal coronary arteries in CONFIRM.

Summary:
CTA imaging has made clear that an increased plaque burden is present even among asymptomatic, long-term aggressively statin treated FH patients. In the CONFIRM registry, nonobstructive CAD predicted all cause mortality and statin treatment reduced CAD and improved the life span. Clinical trials with CTA are required to develop and test identification of CAD and personalized treatment strategies for FH.

Keywords:
cholesterol-lowering, coronary atherosclerosis, computed tomographic angiography, familial hypercholesterolemia, surrogate endpoint
**Abbreviations:**

CAC  coronary artery calcification  
CAD  coronary artery disease  
CTA  computed tomographic angiography  
FH  familial hypercholesterolemia  
LDL  low-density lipoprotein
Introduction (word count 1913; max 2500)

All facets of familial hypercholesterolemia (FH), molecular background including modifier genes, cardiovascular endpoints, mortality, treatment, novel treatments, etc. have been studied extensively.\(^1\) Still it is very hard to predict the individual residual risk of treated FH patients. The type of referral seems a strong predictor: FH patients, who were identified in a cascade screening program and put on moderate dosages of statins, had a substantially reduced cardiovascular disease risk,\(^2\) whereas asymptomatic FH patients at a lipid clinic on long-term aggressive statin therapy had dramatic coronary atherosclerosis.\(^3-6\)

Remarkably, not much attention has been paid to atherosclerosis of the coronary arteries of treated FH patients. A number of small series of FH patients with computed tomographic angiography (CTA) scan images have been published.\(^3-8\) The availability of the ultrafast CT scans has reduced the average radiation exposure significantly and this imaging technique is more and more applied to evaluate patients with symptoms as well as asymptomatic FH patients.

The purpose of the present review is to summarize the potential clinical applications of CTA based on the limited CTA findings in FH so far and recent advances of CTA research in other high-risk patients.

Coronary computed tomographic angiography (CTA)

CTA is a rapid noninvasive angiographic modality that is widely applied to evaluate chest pain. Coronary artery calcification (CAC) has been tested most extensively for its use in estimating the cardiovascular prognosis. CAC clearly provides additive information, above and beyond traditional cardiovascular disease risk evaluations.\(^9,10\)
In asymptomatic groups of patients with a high cardiovascular disease risk, a strong association between the extent of CAC and clinical outcomes has been observed.\textsuperscript{9-12} A number of registries have been used to analyze short-term and long-term prognosis of CTA findings in asymptomatic patients.\textsuperscript{7-14} It has been argued that CTA also yielded difficult to interpret findings: non-obstructive coronary artery disease (CAD). Recently, a clear association between non-obstructive CAD and all cause mortality was found in the international multicenter coronary CTA evaluation for clinical outcomes (CONFIRM) registry.\textsuperscript{14} A total of 5712 had normal coronary arteries and 4706 had nonobstructive CAD. These consecutive patients were followed up for a median of 27 months after CTA for all-cause mortality. The presence and the extent of nonobstructive CAD predicted mortality. Moreover, baseline statin therapy was associated with a significant reduction in mortality for individuals with nonobstructive CAD but not for individuals with normal coronary arteries. Whereas treatment with aspirin had no influence on all cause mortality. The findings of CONFIRM suggest that CTA screening of high risk groups is feasible. Interestingly, a small study in another high-risk group, firefighters, showed that coronary calcification predicted increased risk better than traditional cardiovascular disease risk evaluation.\textsuperscript{15} These firefighters were relatively young (mean age was 46 years) similar to FH patients who often seek medical attention at relatively young age.

**Identifying severe familial hypercholesterolemia**

Whether the use of coronary CTA to identify asymptomatic CAD offers a feasible method by which at-risk FH patients can be identified and effectively treated remains unknown. Remarkably, a clear indication for statins, i.e. dyslipidemia, was associated
with low mortality risk in CONFIRM. Within treated dyslipidemias, only a number of small studies have been performed.

**Homozygous familial hypercholesterolemia**

Homozygous FH is strongly associated with calcifications of the coronary arteries, the aortic valves as well as the ascending aorta.\(^{16-18}\) The modern multimodal treatment with statins and other cholesterol-lowering drugs has improved the survival of these patients, especially when there is some residual LDL receptor function.\(^{19}\) The patients with a complete deficiency of LDL receptor function require LDL apheresis and in the near future they may profit from lomitapide (microsomal transport protein inhibitor).\(^{20}\) LDL cholesterol is an important surrogate marker for studies and full cardiologic follow-up is indicated in this rare extreme FH.\(^{21}\)

**Heterozygous familial hypercholesterolemia**

In the quite frequent heterozygous FH, this is completely different. In untreated heterozygous FH, a large variation of mortality has been observed, even among carriers of an identical mutation.\(^{22}\) In statin-treated heterozygous FH, normalization of CAD risk, severe but asymptomatic CAD as well as myocardial infarction has been observed. So far, a promising biomarker to predict CAD among these treated FH patients has not been identified. Recently, an interesting study was performed in 104 Japanese FH patients, who had signs and symptoms of cardiovascular disease and had relatively often other traditional risk factors of cardiovascular disease.\(^{23}\) CTA information (coronary plaque burden score based on a 17-segment American Heart Association classification)\(^{24}\) predicted major adverse cardiac events during a modest median follow-up period of 2.5 year. In 140 asymptomatic, Dutch FH patients, who underwent CTA, only 5 maces were observed during 5 years. This Dutch group of FH
patients clearly had fewer other risk factors and less affected coronary arteries than
the Japanese group. The Japanese study is, however, very promising as it suggests that
it is feasible to identify FH patients, whose residual CAD risk during statin treatment
is very high, by CTA.

Severely calcified coronary arteries were observed in asymptomatic FH patients, who
were on long-term aggressive statin treatment. These patients had often a high
stenosis score as well. Moreover, these coronary disorders were strongly associated
with age. The findings of these studies suggest that – if your heterozygous FH patients
were not identified early in a screening program but were referred to a lipid clinic –
statin treatment is started too late. An indication for cardiologic follow-up including
CTA is probably present as well in these heterozygous FH: perhaps we should
consider a context of secondary prevention to treat such patients with asymptomatic
CAD. Ideally, research with long-term follow-up and repeated CTA’s are required to
optimize and personalize the treatment of these patients. Immediate CTA’s in statin-
naïve patient and during statin treatment are needed to examine the effect of long-term
aggressive statin treatment on coronary calcification. On might hypothesize that
statins increase calcification of plaques as part of the process of stabilizing the
plaques.\(^{25}\)

Heterozygous FH patients, who required CTA to evaluate symptoms, clearly had
diffuse CAD.\(^{23}\) In these FH patients at very high CAD risk, the clinical efficacy of
statin treatment may be disappointingly small as in secondary prevention.\(^{26}\) Research
with CTA is required to test the effect of novel additional treatment modalities, like
PCSK9 inhibitors, in these statin treated FH patients who have a large residual CAD
risk. In heterozygous FH, we might need to redefine severe and refractory FH from solely based on LDL cholesterol levels to including information about the CAD state as well. The present-day ultrafast CTA scanner cause limited radiation exposure that enables scanning of relatively young NH patients. Notably, CAC was absent in young FH patients with a mean age below 23 years, whereas the peripheral flow-mediated vasodilatation was already impaired suggesting that CTA detects more advanced lesions. In another study with similarly young FH patients, a substantial proportion had CAC. In the latter study more additional risk factors were present. The ideal age to start screening with ultrafast CTA is unknown and future research is required to develop an optimal cost-effective strategy.

Implications of CTA for therapy

The CTA findings may be of use to intensify lifestyle interventions and to develop strategies that stimulate adherence to therapy. CTA findings may improve the clinical efficacy directly bypersonalizing the treatment strategies. Especially, severe FH will be deviated from a metabolic surrogate to a potentially more meaningful coronary disease phenotype. This might shift the indication for the novel PCSK9 inhibitors from an LDL cholesterol level to persons with coronary atherosclerotic disease.

There are a number of potential limitations for the use of CTA information in clinical care: CTA measures may not provide unequivocal cut-off values, and the CTA measures may be very variable resulting in wide confidence intervals of the subgroups of patients, who might be at a specific level of CAD risk. Moreover, clinical trials with CTA on which health economic evaluations can be based need to be performed first before implementing CTA based treatment approaches. Nonetheless, the fact that
efficacy of statins could be linked to the subtle forms of CAD in the CONFIRM registry suggest that these CTA trials are feasible.

**Implications of CTA for clinical trials**

We propose to merge CTA data and set up biobanks for drug reposition and target discovery research. Subsequently, the new drugs can be tested in clinical trials with CTA. The United States Food and Drug Administration (FDA) may grant marketing approval for a new drug on the basis of adequate and well-controlled clinical trials, which establish that the drug has an effect on a validated surrogate endpoint. A validated surrogate endpoint predicts clinical benefit of a drug. The analysis of the CONFIRM registry, established that statins were associated with less CAD resulting in better survival. This study validated subtle CTA-based findings as surrogate endpoint for predicting the most undisputable endpoint all cause mortality.

For the new drugs that have been developed recently CTA might offer a better surrogate endpoint, which is closer to the cardiovascular disease endpoints than LDL cholesterol levels. Moreover, CTA may be used to select patients for clinical studies, i.e. to exclude patients with normal coronary arteries. A specific characteristic of trials with CTA is that the endpoints are continues traits, i.e. change of coronary calcification and coronary plaque or stenosis scores, rather than the dichotomous CAD endpoint. Taken together, trial with CTA based endpoints will require smaller sample sizes, shorter duration and lower costs compared to randomized clinical trials with hard endpoints. Such smaller and shorter trials may make head to head comparison of drugs more feasible.
Conclusion

Research with CTA imaging has made clear that an increased plaque burden and increased CAC are present even among asymptomatic and long-term aggressively statin treated FH patients. Clinical trials with CTA are required to develop and test identification of CAD and personalized treatment strategies. If these trials are successful, the definitions of severe and refractory FH should be extended with information about the disease state of the coronary arteries. FH patients with symptoms of CAD, a history of CAD, extremely high LDL cholesterol levels, or patients who do not respond to statin therapy are at very high risk for CAD and should receive additional preventive therapy an their LDL cholesterol should be reduced to the target level. However, restricting more extensive treatment to these groups neglects the asymptomatic CAD of a substantial proportion of FH patients who started statin treatment too late, i.e. all FH patients who did not start treatment during young adulthood.

The recent findings in the CONFIRM registry are important, because nonobstructive CAD predicted all cause mortality and statin treatment reduced CAD and improved the life span. First, this study shows that detection of nonobstructive CAD is clinically relevant instead of a difficult to interpret finding. Secondly, the beneficial effect of statin treatment on coronary atherosclerosis was observed and implicitly the residual risk of treated patients. These findings support the use of CTA in high-risk groups to detect CAD and start preventive measures early. Thirdly, these findings further validate CTA measures as important surrogate endpoints for clinical trials. Trials with CTA will not fully remove the need for clinical outcome trials, but they offer multiple
opportunities to speed up the development and reduce the costs of bringing new drugs to the market. Fourthly, head to head comparisons of different preventive strategies may become more feasible. Fifthly, trials with CTA may bring a higher level of evidence to treatment of the rare homozygous FH patients. Finally, if CTA data are merged and combined with biobanks, novel drugs may be discovered that specifically target atherosclerosis.
Key points:

(3-5 key points/sentences that summarize your article)

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Conflicts of interest

Dr. Sijbrands has received funding of research in the past from Merck, Sharp and Dome, the Netherlands, Pfizer. Nieman… Dr. Budoff has received research grants from General Electric Healthcare. The research grants were not related to the topic of this review article (CTA in FH).
References and recommended reading:

Papers of particular interest have been highlighted as:

• of special interest

•• of outstanding interest

• this is the first study from which it became apparent that aggressively statin treated FH can be refractory at the CAD level.


• this prediction study was performed in asymptomatic patients.

this study linked nonobstructive CAD to excess mortality and showed that statins were associated with less CAD and a longer life span.


