Title
Cardiac computed tomography imaging in familial hypercholesterolaemia

Journal
Current Opinion in Lipidology, 26(6)

ISSN
0957-9672

Authors
Sijbrands, Eric JG
Nieman, Koen
Budoff, Matthew J

Publication Date
2015-12-01

DOI
10.1097/mol.0000000000000249

Peer reviewed

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

Eric J.G. Sijbrands,[1] Koen Nieman, [2] and Matthew J. Budoff[3] for the FH CTA consortium.

[1]Dept. of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands;

[2]Dept. of Cardiology, Erasmus MC, Rotterdam, the Netherlands;

[3]Los Angeles Biomedical Research Institute, 1124 West Carson Street, Torrance, CA 90502.

Corresponding author: Prof. E.J.G. Sijbrands

Erasmus Medical Center - office D435

Department of Internal Medicine

PO-box 2040

3000 CA Rotterdam, The Netherlands

Tel: +31.10.7033283

Fax: +31.10.7033639

e-mail: e.sijbrands@erasmusmc.nl

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.[9-12] A number of registries have been used to analyze short-term and long-term prognosis of CTA findings in asymptomatic patients.[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.[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.[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 leasions.[27] In another study with similarly young FH patients, a substantial proportion had CAC.[28] 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.[29] CTA findings may improve the clinical efficacy directly by personalizing 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 trails. 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)

- ;
- ;
-

Acknowledgements

Financial support and sponsorship

This work was supported by the Erasmus Medical Center, Rotterdam, the Netherlands, and by the Los Angeles Biomedical Research Institute, California, United States of America.

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

(1) Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol 2014;171:309-25.

(2) Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2423.

(3) Neefjes LA, Ten Kate GJ, Rossi A, et al. CT coronary plaque burden in asymptomatic patients with familial hypercholesterolaemia. Heart 2011;97:1151-7.

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

(4) Neefjes LA, Ten Kate GJ, Alexia R, et al. Accelerated subclinical coronary atherosclerosis in patients with familial hypercholesterolemia. Atherosclerosis 2011;219:721-7.

(5) ten Kate GL, ten Kate GJ, van den Oord SC, et al. Carotid plaque burden as a measure of subclinical coronary artery disease in patients with heterozygous familial hypercholesterolemia. Am J Cardiol 2013;111:1305-10.

(6) Ten Kate GJ, Neefjes LA, Dedic A, et al. The effect of LDLR-negative genotype on CT coronary atherosclerosis in asymptomatic statin treated patients with heterozygous familial hypercholesterolemia. Atherosclerosis. 2013;227:334-41.

(7) Miname MH, Ribeiro MS 2nd, Parga Filho J, et al. Evaluation of subclinical atherosclerosis by computed tomography coronary angiography and its

association with risk factors in familial hypercholesterolemia. Atherosclerosis 2010;213:486-91.
(8) Viladés Medel D, Leta Petracca R, Carreras Costa F, et al. Coronary computed tomographic angiographic findings in asymptomatic patients with heterozygous familial hypercholesterolemia and null allele low-density lipoprotein receptor mutations. Am J Cardiol 2013;111:955-61.
(9) Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010;122:e584-636.
(10) Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA. 2010;303:1610-6.
(11) Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol 2004;43:1663-9.
(12) Shaw LJ, Raggi P, Callister TQ, Berman DS. Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers. Eur Heart J. 2006;27:968-75.
(13) Shaw LJ, Giambrone AE, Blaha MJ, et al. Long-Term Prognosis After Coronary Artery Calcification Testing in Asymptomatic Patients: A Cohort Study. Ann Intern Med 2015;163:14-21.

• this prediction study was performed in asymptomatic patients.

(14) Chow BJ, Small G, Yam Y, et al. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry) registry. Arterioscler Thromb Vasc Biol 2015;35:981-9.

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

(15) Ratchford EV, Carson KA, Jones SR, Ashen MD. Usefulness of coronary and carotid imaging rather than traditional atherosclerotic risk factors to identify firefighters at increased risk for cardiovascular disease. Am J Cardiol 2014;113:1499-1504.

(16) Hoeg JM, Feuerstein IM, Tucker EE. Detection and quantitation of calcific atherosclerosis by ultrafast computed tomography in children and young adults with homozygous familial hypercholesterolemia. Arterioscler Thromb 1994;14:1066-74.

(17) Kolansky DM, Cuchel M, Clark BJ, et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. Am J Cardiol 2008;102:1438-43.

(18) Santos RD, Miname MH, Martinez LR, et al. Non-invasive detection of aortic and coronary atherosclerosis in homozygous familial hypercholesterolemia by 64 slice multi-detector row computed tomography angiography. Atherosclerosis 2008;197:910-5.

(19) Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in The Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. Eur Heart J 2015;36:560-5.

(20) Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 2013;381:40-46.

(21) Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel

on familial hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014;35:2146-57.
(22) Sijbrands EJ, Westendorp RG, Defesche JC, et al. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. BMJ 2001;322:1019-23.
(23) Tada H, Kawashiri M-A, Okada H, et al. Assessment of coronary atherosclerosis in patients with familial hypercholesterolemia by coronary computed tomography angiography. Am J Cardiol 2015;115:724-729.
(24) Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8:342e358.
(25) Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol 2015;65:1273-82.
(26) Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008;29:2625-33.
(27) Hoffmann U, Dirisamer A, Heher S, Kostner K, Widhalm K, Neunteufl T. Relation of peripheral flow-mediated vasodilatation and coronary arterial calcium in young patients with heterozygous familial hypercholesterolemia. Am J Cardiol 2002;90:70-3.
(28) Gidding SS, Bookstein LC, Chomka EV. Usefulness of electron beam tomography in adolescents and young adults with heterozygous familial hypercholesterolemia. Circulation 1998;98:2580-3.
(29) Mols RE, Jensen JM, Sand NP, et al. Visualization of coronary artery calcification: influence on risk modification. Am J Med. 2015: in press.

Rozanski A, Gransar H, Shaw LJ, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol 2011;57:1622-32.