Asymptomatic Coronary Artery Disease in Adults with Familial Hypercholesterolemia and use of Coronary Artery Imaging as a Screening Tool

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Abstract

Background: Heterozygous Familial Hypercholesterolemia (heFH) is an autosomal dominant disorder caused by a defect in a low-density lipoprotein (LDL) receptor gene and results in drastically elevated serum LDL levels. These patients have a decreased life expectancy secondary to sudden death and myocardial infarction. The clinical course of heFH patients is variable and not directly related to serum LDL levels. Recent studies have also shown that many heFH patients with coronary artery disease (CAD) present asymptptomatically. Computed tomography coronary angiography (CTCA) is one means of detecting subclinical CAD. However, CTCA screening has yet to be proven to improve outcomes in those with asymptomatic CAD, but outcomes of heFH patients have yet to be studied specifically. The purpose of this systematic review is to compile research that compares asymptomatic heFH populations with healthy adults, and determine if CTCA could be warranted in asymptomatic heFH patients. Method: A search of Medline-OVID, Web of Science, and CINAHL with Full Text was conducted using key words: CT angiography/angiography/coronary angiography, familial hypercholesterolemia and asymptomatic/subclinical. Studies were reviewed and included based on relevant criteria. Those relevant articles were assessed using the GRADE system for quality. Results: Three observational studies met inclusion criteria and were included in this systematic review. All three studies showed a significant increase in the number of heFH participants with subclinical CAD as seen on CTCA, with almost one quarter of heFH patients demonstrating severe vessel occlusion. Conclusion: These studies indicate the heFH patient are more likely to have subclinical coronary atherosclerosis. In order to justify the use of CTCA in asymptomatic heFH patients, further research looking at outcomes of heFH patients diagnosed with early CAD is needed. While CTCA does have the ability to detect which heFH patients have CAD, whether or not this information, when applied to treatment strategies, can reduce risk of CAD and mortality has yet to be determined.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
Familial hypercholesterolemia, coronary artery disease, subclinical, asymptomatic, computed tomography coronary angiography, atherosclerosis

Subject Categories
Medicine and Health Sciences

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Asymptomatic Coronary Artery Disease in Adults with Familial Hypercholesterolemia and use of Coronary Artery Imaging as a Screening Tool

Dania Marie Arguello

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 08, 2014

Faculty Advisor: James Ferguson, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

**Background:** Heterozygous Familial Hypercholesterolemia (heFH) is an autosomal dominant disorder caused by a defect in a low-density lipoprotein (LDL) receptor gene and results in drastically elevated serum LDL levels. These patients have a decreased life expectancy secondary to sudden death and myocardial infarction. The clinical course of heFH patients is variable and not directly related to serum LDL levels. Recent studies have also shown that many heFH patients with coronary artery disease (CAD) present asymptomatically. Computed tomography coronary angiography (CTCA) is one means of detecting subclinical CAD. However, CTCA screening has yet to be proven to improve outcomes in those with asymptomatic CAD, but outcomes of heFH patients have yet to be studied specifically. The purpose of this systematic review is to compile research that compares asymptomatic heFH populations with healthy adults, and determine if CTCA could be warranted in asymptomatic heFH patients.

**Method:** A search of Medline-OVID, Web of Science, and CINAHL with Full Text was conducted using key words: CT angiography/angiography/coronary angiography, familial hypercholesterolemia and asymptomatic/subclinical. Studies were reviewed and included based on relevant criteria. Those relevant articles were assessed using the GRADE system for quality.

**Results:** Three observational studies met inclusion criteria and were included in this systematic review. All three studies showed a significant increase in the number of heFH participants with subclinical CAD as seen on CTCA, with almost one quarter of heFH patients demonstrating severe vessel occlusion.

**Conclusion:** These studies indicate the heFH patient are more likely to have subclinical coronary atherosclerosis. In order to justify the use of CTCA in asymptomatic heFH patients, further research looking at outcomes of heFH patients diagnosed with early CAD is needed. While CTCA does have the ability to detect which heFH patients have CAD, whether or not this information, when applied to treatment strategies, can reduce risk of CAD and mortality has yet to be determined.

**Keywords:** Familial hypercholesterolemia, coronary artery disease, subclinical, asymptomatic, computed tomography coronary angiography, atherosclerosis
List of Tables

Table 1: GRADE Quality of Assessment
Table 2: Summary of Findings
Table 3: Associated characteristics with CAD

List of Abbreviations

heFH       Heterozygous Familial Hypercholesterolemia
LDL        Low-Density Lipoprotein
CAD        Coronary Artery Disease
CTCA       Computed Tomography Coronary Angiography
GRADE      Grading of Recommendations, Assessment, Development and Evaluations
FH         Familial Hypercholesterolemia
LDL-c      LDL-Cholesterol
CHD        Coronary Heart Disease
CT         Computed Tomography
CAC        Coronary Artery Calcification
AHA        American Heart Association
HDL        High Density Lipoprotein
PCI        Percutaneous Coronary Intervention
Asymptomatic Coronary Artery Disease in Adults with Familial Hypercholesterolemia and use of Coronary Artery Imaging as a Screening Tool

BACKGROUND

Familial hypercholesterolemia (FH) is a genetic disorder affecting 1 in 500 people.¹ Life expectancy in those with FH is shortened with mortality resulting from sudden death and myocardial infarction.² Heterozygous familial hypercholesterolemia (heFH) is a disease that results from autosomal dominant inheritance of a mutated low-density lipoprotein receptor gene causing lifelong elevation of LDL-cholesterol (LDL-c), which may build up in arteries resulting in early onset of coronary artery disease (CAD) and excess mortality.³

Despite elevated cholesterol levels, the clinical course of atherosclerotic manifestations in heFH subjects is variable. One study⁴ of 526 heFH patients found that coronary heart disease (CHD) mortality rates were higher in the age group 20-29 years, suggesting that some FH subjects will have early coronary events, while others will develop these very late or not at all.

Since the 1990s and in part due to increased use of statin medication, rates of coronary and total mortality in FH patients have decreased, though they continue to have higher risk for premature CAD.⁵ Most heFH patients require max dose statin therapy in order to reduce LDL levels at least 50%, which most do not achieve.⁶ Currently, there are other drugs on the market that are being used to treat hypercholesterolemia: niacin, fibrates, bile acid sequesterants, ezetimibe and omega-3 fatty acids. Mechanical removal of LDL-c by apheresis is also an effective option, though very expensive and usually reserved for the most severe forms of heFH.⁷ However, markers for indicating which heFH patients are a candidate for more extensive therapy are limited.
Recent studies suggest that a large number of heFH patients have obstructive CAD, but remain asymptomatic.\textsuperscript{8,9} This stresses the need for markers to detect the presence of obstructive CAD and the risk of developing CAD, in order to direct treatments strategies of heFH patients.

One suggested means of detecting subclinical coronary atherosclerosis is by non-invasive computed tomography (CT). CT can be used to assess atherosclerosis in one of two ways: coronary artery calcification (CAC) scoring and CT coronary angiography (CTCA). Coronary artery calcification is determined using CT without radiologic contrast and then scored using the Agatston score method. The Agatston calcium score is a rule-based system for scoring the CAC. However, the amount of coronary calcium has only a weak association with the extent of obstruction in the vessel; with the exception of Agatston scores $\geq 400$, which was associated with an increased frequency of perfusion ischemia and obstructive CAD.\textsuperscript{10,11,12}

CT coronary angiography is a non-invasive means to assess the lumen and walls of coronary arteries. It is performed after injection of radiological contrast in a peripheral vein and a CT scanner obtains imaging. CTCA has high diagnostic accuracy.\textsuperscript{13,14} However, there is limited data on prognostic implication of CT angiography, and it also exposes the patient to higher radiation exposure than CAC scoring methods. Thus, CTCA is not recommended as a screening tool in asymptomatic patients by the American Heart Association (AHA).\textsuperscript{11}

The variability of risk of CHD in adults with heFH stresses the importance of asymptomatic CAD detection in order to determine which heFH patients are most likely to progress to CHD, and to indicate the need for more aggressive prophylactic measures in such patients. The first step is to determine if there is a significant difference between asymptomatic healthy adults and those with heFH. The purpose of this systematic review is to compile research that compares asymptomatic heFH populations with healthy adults, and to determine if
CTCA is warranted in asymptomatic heFH patients. The answer to this question could pave the way to determining if early detection and treatment of asymptomatic CAD could reduce lifetime risk of CHD, which could warrant use of CTCA or CAC scoring in asymptomatic heFH patients.

**METHODS**

An exhaustive search using both Medline-OVID, Web of Science, and CINAHL search engines was performed. For all of these databases, three individual searches were conducted and then combined. The first search included keywords “CT angiography” or “Angiography” or “Coronary angiography.” The second search was for the term “Familial Hypercholesterolemia.” The third search was for key words “asymptomatic” or “subclinical.” These three searches were then combined using AND to find articles that contained all three of the searched keyword categories.

This review included study populations of adults between the ages of 30 and 70. In all included studies the diagnosis of heFH was determined by published standardized clinical diagnostic criteria and/or genetic testing. Patients diagnosed with heFH, as well as control groups, had to have no previous diagnosis or symptoms of cardiovascular disease and had to be currently asymptomatic for CAD. Control group participants were excluded if they had LDL-c ≥ 130 or were currently on lipid lowering therapy. Other exclusion criteria for both heFH and control groups included: allergy to iodine contrast, renal disease, and irregular heart rhythm. Studies performed before December 2003 were excluded.

Study imaging for all included studies was performed by both non-contrast CT to analyze CAC score as determined using the Agatston criteria, as well as CT coronary angiography, using iodine contrast. CTCA was interpreted by at least two independent and blinded observers.
Relevant articles were critically appraised using a standardized form and then assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)\textsuperscript{15} as displayed in Table 1.

RESULTS

The Medline-OVID search produced 17 results, Web of Science searches produced 18, and CINAHL search produced 4. In total 28 individual papers were produced from the Medline-OVID, Web of Science and CINAHL search strategies. Of the published works produced, three studies met the criteria based on study demographics and eligibility criteria of the database searches: Neefjes et al,\textsuperscript{16} Vilades et al,\textsuperscript{17} and Miname et al.\textsuperscript{18} These three studies\textsuperscript{16,17,18} were similar in design and methodology, with a few variations.

Each study\textsuperscript{16,17,18} looked at CAD in asymptomatic heFH patients by means of Agatston calcium score as well as CTCA. Neefjes et al,\textsuperscript{16} did not compare heFH patients to healthy controls, though it provided more specific results, such as Agatston calcium score stratification and had the largest population size (140) of heFH patients. The types of coronary artery plaques present in heFH patients was measured in both Neefjes et al,\textsuperscript{16} and Miname et al.\textsuperscript{18} Significant obstruction was defined by Neefjes et al,\textsuperscript{16} and Miname et al,\textsuperscript{18} as obstruction >50%; while Vilades et al,\textsuperscript{17} defined significant obstruction as >70% occlusion. Coronary artery findings detected on CT imaging for heFH patients and control groups from the studies\textsuperscript{16,17,18} were compared (see Table 2). Other variables were also measured in relationship with CAD in asymptomatic heFH patients in all three studies,\textsuperscript{16,17,18} as displayed in Table 3.

CCTA Findings
All three studies\textsuperscript{16, 17,18} found that heFH groups had more frequent CAD than the control groups of studies Vilades et al,\textsuperscript{17} and Miname et al.\textsuperscript{18} In all the studies, \textsuperscript{16,17,18} nearly one quarter of heFH participants were found to have vessels that were greater than 50% obstructed. Neefjes et al,\textsuperscript{16} Vilades et al,\textsuperscript{17} and Miname et al,\textsuperscript{18} found significant obstruction in 24%, 26%, and 19% of heFH patients respectively. Which is significantly greater than that of healthy adults, as 5% of Vilades et al,\textsuperscript{17} and 1% of Miname et al,\textsuperscript{18} were found to have significant obstruction. Normal appearing arteries were found in only 16%, 50%, and 52% of heFH participants by Neefjes et al,\textsuperscript{16} Vilades et al,\textsuperscript{17} and Miname et al,\textsuperscript{18} respectively. This is compared to 63% of healthy adults with normal arteries in Vilades et al,\textsuperscript{17} and 86% in Miname et al.\textsuperscript{18}

**Agatston Score**

In the two studies\textsuperscript{17,18} that compared the Agatston scores in heFH populations to that of healthy adults, it was determined that heFH patients had higher CAC scores. Though, there was much variability between the two studies.\textsuperscript{17,18} Studies Neefjes et al,\textsuperscript{17} and Miname et al,\textsuperscript{18} demonstrated a mean Agatston score of 51 and 55 respectively in the heFH participants. However, Vilades et al,\textsuperscript{17} found a mean score of 204 in the heFH population. Only Neefjes et al,\textsuperscript{16} calculated the number of participants in the highest risk category >400, which was 23% of participants. Vilades et al,\textsuperscript{17} also demonstrated a significant correlation of Agatston score with the presence of coronary artery diseases in the heFH group.

**Variables and CAD**

Across all three studies,\textsuperscript{16, 17,18} the only variables that were significantly correlated with CAD as found on CTCA were HDL cholesterol and age. LDL-c as well as total cholesterol levels were significantly correlated with CAD in studies by Neefjes et al,\textsuperscript{16} and Vilades et al.\textsuperscript{18}

**Plaque Composition**
Plaque composition was calculated in studies by Neefjes et al., and Miname et al. Neefjes et al. found that in patients with heFH, most of the plaques detected on CTCA were calcified (54%). Miname et al. also found that the majority of plaques in vessel segments were calcified in heFH participants, while healthy participants were most likely to have mixed plaques in vessel segments and had equal proportion of non-calcified and calcified plaques.

**DISCUSSION**

The studies reviewed do show higher rates of CAD detected in asymptomatic heFH patients. Not only are heFH participants more likely to have CAD, almost one quarter of them demonstrated >50% obstruction in at least one vessel. For symptomatic patients, current AHA recommendations suggest percutaneous coronary intervention (PCI) in patients with obstruction >70%. Though, currently guidelines do not recommend PCI in asymptomatic patients. According to Zhang et al., who studied 419 patients undergoing PCI for coronary stenosis, PCI did not reduce major adverse cardiac events in comparison with outpatient medical therapy in asymptomatic patients. Based on these study findings, CTCA could be used to guide preventative and therapeutic treatment strategies for heFH patients, even though it is not an appropriate diagnostic test to indicate PCI.

These studies do not focus explicitly on Agatston calcium score; however, they did report mean or median calcium scores for their study participants. It is worth noting that Neefjes et al. found that 23% of their heFH population had calcium scores > 400. This is significant because 400 is the CAC score at which CTCA readings become less accurate and tend to underestimate amount of obstruction present. Both studies, Vilades et al. and Miname et al., found a significant correlation between calcium score and presence of CAD. Although, the
presence of coronary plaque has only a weak correlation with the extent of stenosis.\textsuperscript{20,21} Thus limiting the ability of calcium score to report extent and severity of CAD.

Previous studies\textsuperscript{22,23} have shown that non-calcified plaques show the strongest association for being the culprit lesions in acute coronary syndrome, and that calcified plaques are the least associated with ACS. Of the studies\textsuperscript{16,17,18} reviewed, there were no statistically significant findings related to plaque composition when comparing healthy patients and heFH patients.

There were some surprising findings as to other variables related to CAD. All three studies\textsuperscript{16,17,18} found that low HDL was significantly correlated to CAD in heFH patients. Neefjes et al,\textsuperscript{16} and Miname et al,\textsuperscript{18} found LDL-c levels and age to be related to CAD. Surprisingly, other variables known for their association with CAD in non-heFH patients, such as smoking and diabetes had no significant correlation.\textsuperscript{11}

The studies examined in this systematic review had several limitations. One limitation that effects all studies is that CTCA tends to overestimate or underestimate severity of CAD in patients with extensive calcified plaques, specifically in those with calcium scores greater that 10, and severely in those >400.\textsuperscript{11} Also, there was variability among participants as to weather or not they had previously or were currently undergoing statin therapy for hyperlipidemia. Though, there is no proven evidence to show that statin therapy modifies CAC evolution.\textsuperscript{7} Each study had limitations in its study population. Population size is small in each of the reviewed studies. Also, Neefjes et al,\textsuperscript{16} did not compare its heFH patients to healthy asymptomatic adult controls. Age is also a limitation. Though, the age range selected is based on known association of CAD and age, it excludes application of these findings to the very young and very old. Lack of extended follow up limits the application of review results, as there were no measurements of adverse outcomes or major cardiac events as they relate to the amount of CAD
found in these asymptomatic patients. Finally, though CTCA is growing in use, coronary
angiogram (cardiac catheterization) remains the gold standard for diagnosis of coronary artery
disease and was not used in any study reviewed in this analysis.

Further research is needed to justify the use of CTCA in asymptomatic heFH patients.
Studies must include longer follow up to determine the associated risk of future major cardiac
events based on CTCA in heFH patients as compared to healthy adults. No studies exist that
specifically target heFH patients that undergo prophylactic PCI, to predict outcomes specific to
that patient population.

CONCLUSION

This systematic review does indicate that there is a future for CTCA in the risk
stratification of heFH patients. CTCA has the ability to accurately tell us the extent of CAD in
heFH patients, whom have been shown in this review as more likely to have asymptomatic CAD.
If this information, when applied to treatment strategies, has the ability to reduce risk of acute
coronary syndrome and mortality, remains to be discovered.
References


**TABLE 1: GRADE of Reviewed Studies**

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
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<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Observational</td>
<td>Serious&lt;sup&gt;a,b,c,d,e&lt;/sup&gt;</td>
<td>Not serious&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not likely</td>
<td>Very low</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Agatson Calcium Score</strong></td>
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<td></td>
<td></td>
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<td>Not serious&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not likely</td>
<td>Very low</td>
<td>Important</td>
</tr>
<tr>
<td><strong>Plaque Composition</strong></td>
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<tr>
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<td>Serious&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not likely</td>
<td>Very low</td>
<td>Important</td>
</tr>
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<sup>a</sup>No healthy adult control group studied in Neefjes et al.
<sup>b</sup>Diabetic participants not excluded in Medel et al.
<sup>c</sup>Variability with what was considered obstruction: >50% in Neefjes et al and Miname et al; and >70% in Medel et al.
<sup>d</sup>Length of current or previous statin use not accounted for
<sup>e</sup>Control group much smaller than heFH group (35 and 102 respectively)
<sup>f</sup>Agatson calcium score reported as mean in Neefjes et al, and median in Miname et al. and Medel et al.
<sup>g</sup>Total sample size in all three studies is lower than optimal
<table>
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<tr>
<th>Study</th>
<th>Neefjes et al,\textsuperscript{16} (heFH (n = 140))</th>
<th>Control (none)</th>
<th>Vilades et al,\textsuperscript{17} (heFH (n = 50))</th>
<th>Control (n = 70)</th>
<th>Miname et al,\textsuperscript{18} (heFH (n = 102))</th>
<th>Control (n = 35)</th>
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<tr>
<td>Normal</td>
<td>23 (16%)</td>
<td>____</td>
<td>25 (50%)</td>
<td>44 (62%)</td>
<td>53 (52%)</td>
<td>35 (86%)</td>
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<tr>
<td>Obstructive Lesions</td>
<td>33 (24%)</td>
<td>____</td>
<td>13 (26%)</td>
<td>4 (5%)</td>
<td>20 (19%)</td>
<td>1 (3%)</td>
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<tr>
<td>Non-Obstructive Lesions</td>
<td>84 (60%)</td>
<td>____</td>
<td>11 (22%)</td>
<td>19 (27%)</td>
<td>29 (28%)</td>
<td>4 (11%)</td>
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<td>Two Obstructive vessels</td>
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<td>____</td>
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<tr>
<td>Three Obstructive Vessels</td>
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<td>____</td>
<td>____</td>
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<td>____</td>
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<tr>
<td><strong>Agatston Score</strong></td>
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<td></td>
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<tr>
<td>&gt;400</td>
<td>51 mean</td>
<td>____</td>
<td>204 (35-450) median</td>
<td>46 (45-76) median</td>
<td>55 +/- 129 (0-748) median</td>
<td>38 +/- 140 (0-666) median</td>
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<tr>
<td>Plaque composition</td>
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<tr>
<td>Non-Calcified</td>
<td>192 (25%)</td>
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<td>0.60</td>
<td>0.11</td>
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<tr>
<td>Calcified</td>
<td>419 (54%)</td>
<td>____</td>
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<td>0.80</td>
<td>0.11</td>
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<tr>
<td>Mixed</td>
<td>163 (21%)</td>
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<td>0.63</td>
<td>0.20</td>
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TABLE 3: Associated heFH participants characteristics with CAD

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<tr>
<th>Study</th>
<th>Neefjes et al,16</th>
<th>Vilades et al,17</th>
<th>Miname et al,18</th>
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<tbody>
<tr>
<td></td>
<td>heFH (n = 140)</td>
<td>heFH (n = 50)</td>
<td>heFH (n = 102)</td>
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<tr>
<td></td>
<td>Control (none)</td>
<td>Control (n = 70)</td>
<td>Control (n = 35)</td>
</tr>
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</table>

Variables related to presence of CAD (Univariate analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neefjes et al,16</th>
<th>Vilades et al,17</th>
<th>Miname et al,18</th>
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<tr>
<td>Age</td>
<td>p= .000</td>
<td>0.01</td>
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<td>Gender</td>
<td>p= .003</td>
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<td>0.43</td>
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<tr>
<td>CI = (-7.14 to -1.45)</td>
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<td>Smoker</td>
<td>p= .532</td>
<td>0.535</td>
<td>0.24</td>
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<tr>
<td>CI = (-2.12 to 4.10)</td>
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<tr>
<td>Diabetes</td>
<td>p= 0.822</td>
<td>0.527 (multivariate)</td>
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<td>CI= (-5.08 to 6.39)</td>
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<tr>
<td>Hypertension</td>
<td>p= 0.125</td>
<td>0.497</td>
<td>0.55</td>
</tr>
<tr>
<td>CI = (-0.69 to 5.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>p= 0.038</td>
<td>0.434</td>
<td></td>
</tr>
<tr>
<td>CI = (0.02 to 0.78)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>p= 0.029</td>
<td>0.467</td>
<td>0.0055</td>
</tr>
<tr>
<td>CI = (0.13 to 2.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>p= 0.004</td>
<td>0.050</td>
<td>0.005</td>
</tr>
<tr>
<td>CI = (-9.12 to -1.82)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>p= 0.467</td>
<td>0.365</td>
<td>0.13</td>
</tr>
<tr>
<td>CI = (0.60 to 1.29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendon Xanthoma</td>
<td>p= 0.077</td>
<td>0.488</td>
<td>Achilles 0.026</td>
</tr>
<tr>
<td>CI = (-0.34 to 6.38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>p= 0.001</td>
<td>0.193</td>
<td>0.0003</td>
</tr>
<tr>
<td>CI = (0.01 to 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bold = statistically significant findings