



Improvement in the estimation of cardiovascular risk by carotid intima-medial thickness: A report from the Dublin Cardiohealth station study

Maeve Cooney, Marie -Therese Cooney, Vincent Maher, Barket Khan, Tora Leong, Ian Graham *

Adelaide Meath Hospital, Tallaght, Dublin 24, Ireland

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ABSTRACT

Background. The 5th Joint Task Force European guidelines on cardiovascular disease (CVD) prevention recommend the measurement of carotid intima-media thickness (CIMT) in asymptomatic individuals at moderate risk (Class IIa). We aimed to evaluate the ability of CIMT to further risk stratify patients. **Design.** Cross-sectional study. **Methods.** Patients aged over 18 years free of known CVD at moderate, high, or very high risk of CVD were included. The Panasonic Cardiohealth station, a semi-automated ultrasound system, was used to detect carotid plaque and measure CIMT. Elevated CIMT was defined as ≥ 0.9 mm. We analyzed the percentage of those at moderate risk reclassified after addition of CIMT. **Results.** Two hundred patients were included (55% women, mean age 57 years, 12% diabetic); 64%, 23% and 13% were classified as moderate, high, and very high risk, respectively. Across these risk categories, 17%, 33%, and 46% had elevated IMT, p for trend < 0.001 . With the addition of CIMT, 13.9% (95% CI: 5.7% to 22.1%) of women and 20.4% (95% CI: 8.7% to 32.1%) of men initially moderate risk were reclassified. **Conclusions.** CIMT measurement reclassifies a considerable percentage of those at moderate risk based on traditional risk factors alone.

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Introduction

Cardiovascular disease (CVD), which includes coronary heart disease, stroke, and peripheral vascular disease, is the most important cause of death in the developed world. Rates of CVD in the developing world are rapidly increasing (The Global Burden of Disease, 2008). The atherosclerosis which causes CVD often develops early in life and progresses insidiously. It may be advanced by the time of presentation with clinical symptoms, and the first presentation may be a fatal myocardial infarction or highly disabling stroke. This highlights the importance of a preventive strategy for CVD since medical treatments, while effective, in these circumstances may be either inapplicable or palliative (Graham et al., 2007). Two complementary approaches to CVD prevention are required. The population strategy attempts to reduce the risk factor burden in the entire population, thereby reducing the incidence of disease (Rose, 1991). In the high-risk strategy, asymptomatic individuals at an increased risk of future development of CVD are identified and the most intensive risk factor modifications are directed towards these individuals as they will gain most (Graham et al., 2007; Perk et al., 2012).

At present, those at high risk are detected on the basis of the risk caused by the combination of their risk factors. This is calculated using

risk estimation systems, for example, SCORE (Systematic Coronary Risk Evaluation) or Framingham (Conroy et al., 2003; McGorrian et al., 2008). Another approach to detecting those at high risk is to look for the presence of subclinical atherosclerosis. Examples include computerized tomography (CT) scanning for the presence of coronary calcium, which is indicative of the presence of coronary atherosclerosis, and ultrasound scanning of the carotid vessels for the presence of atherosclerosis. Advantages of carotid scanning are that it is relatively inexpensive, non-invasive, and involves no exposure to radiation.

Carotid intima-media thickness (CIMT) and the presence of carotid plaques are the two most commonly used indices of carotid atherosclerosis. The CIMT is defined as the measurement of the thickness of the tunica intima and the tunica media, the innermost two layers of the arterial wall.

Several prospective studies have shown the relationship between CIMT and future development of CVD. In 15,792 healthy subjects aged 45–65 years in the Atherosclerosis Risk in Communities Study (ARIC) who were followed prospectively for 4–7 years, increased CIMT was associated with increased risk of CHD, HR of 1.13 for MI per 0.1 mm difference in CCA (common carotid artery) IMT, adjusted for age and gender (Chambless et al., 1997). In the Rotterdam Study of 7,983 subjects, the HR was 1.19 for the same measurement (Bots et al., 1997).

The 5th Joint Task Force (JTF) European guidelines on CVD prevention recommend that the measurement of carotid intima-media thickness and/or screening for atherosclerotic plaques by carotid artery scanning should be considered for cardiovascular risk assessment in asymptomatic adults at moderate risk (Perk et al., 2012).

* Corresponding author at: Hermitage Consultants Clinic, Old Lucan Road, Dublin 20, Ireland. Fax: + 353 1 6459714.

E-mail address: ian@grahams.net (I. Graham).

This is considered a level IIb recommendation, GRADE strong with level of evidence B. The American (ACC/AHA) guidelines recommend assessment for carotid atherosclerosis in the intermediate risk group, with the same grade of recommendation and level of evidence (Greenland et al., 2010).

The Cardiohealth Station is a newly developed automated onscreen carotid ultrasonography device, which allows detection of carotid plaques and automated measurement of carotid IM (http://www.panasonic.com/business/medicalvideo/CardioHealth/, n.a.). The measurements are made at the common carotid artery.

Our objective was to measure CIMT and to assess for the presence of carotid plaques in asymptomatic patients attending a CVD risk clinic and answer two key questions:

1. Does CIMT measurement and presence of carotid plaques relate to total CV risk category as determined using clinical risk factors, based on the new four categories of risk recommended by the 5th European guidelines on CVD prevention?
2. What percentage of those at moderate risk based on clinical factors is reclassified to a high-risk category after the measurement of CIMT and assessment for the presence of carotid plaques?

Methods

Study population

Patients attending the outpatient clinic at the Adelaide Meath Hospital for assessment and management of cardiovascular disease risk, without prior evidence of cardiovascular disease, were screened for eligibility for inclusion in the study. Individuals with and without diabetes were included. Patients aged 18 years or over were included if they were categorized as moderate, high, or very high-risk categories, as defined by the 5th JTF European guidelines on CVD prevention (see Box 1). The main exclusion criterion was the presence of established CVD. This was defined as coronary disease, including previous revascularization, acute coronary syndrome or stable angina, stroke or transient ischemic attack, previously detected carotid disease, peripheral vascular disease, or abdominal aortic aneurysm. Those who were unable to give consent and pregnant women were also excluded. All eligible patients attending the clinic were invited to participate. The enrolment period was from November 2012 to February 2014.

Measurements

Using the Cardiohealth Station, three measurements of right and left carotid intima-media thickness (CIMT) at the common carotid artery were taken. Participants also had assessment for the presence of carotid plaques bilaterally.

Other clinical measurements were undertaken on the day of investigation, including blood pressure, heart rate, waist circumference, and body mass index. The most recent available laboratory measurements, including lipid measurements (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), fasting glucose measurement, and cholesterol measurements were undertaken using the enzymatic method. Information on other risk factors was also obtained as part of the clinical history, including smoking status, physical activity level, family history of premature CVD, and medication usage. Smoking status was based on self-report, and patients were considered former smokers if they quit smoking greater than 6 months prior to the examination. Diabetic status was based on self-report and review of medical chart and medication list for a previous diagnosis of diabetes. Physical activity level was based on self-report of physical activity category based on the European guideline definition. Patients were asked "Would you undertake more, less of equal to the following amount of physical activity: 2.5 to 5 h of moderately vigorous physical activity weekly (Perk et al., 2012)? Using this information, the

Box 1

Individuals eligible for inclusion in the study, subdivided by risk category as defined by the 5th JTF European guidelines on CVD prevention.

Very high risk	Subjects with any of the following: <ul style="list-style-type: none"> ● Diabetes (type 1 or type 2) with one other CV risk factor or target organ damage ● Patients with to severe CKD (GFR <30 ml/min/1.73 m²) ● SCORE ≥ 10%
High risk	Subjects with <ul style="list-style-type: none"> ● Diabetes (type 1 or type 2) without other CV risk factors or target organ damage ● Patients with moderate CKD (GFR <60 ml/min/1.73 m²) ● Markedly elevated single risk factors such as: <ul style="list-style-type: none"> ▣ Familial dyslipidemias ▣ Severe hypertension ● SCORE of ≥ 5% and <10%
Moderate risk	SCORE is ≥ 1 and <5% at 10 years, further modulated by <ul style="list-style-type: none"> ● Family history of premature CAD ● Abdominal obesity ● Physical Activity pattern ● TG ● hsCRP ● Social class ● HDL-C

SCORE risk was calculated on all participants. SCORE (systematic coronary risk valuation) estimates the 10-year risk of CVD mortality. Using the combination of SCORE and other risk factors, all patients were assigned to a risk category according to the recommendations of the 5th European guidelines on CVD prevention (see Box 1). The full data collection sheet is included in the supplementary material.

Written consent was obtained from all participants. The investigators received ethics approval for this study through the Adelaide Meath hospital ethics committee. All patient information, including personal identifiers, was stored on an excel spreadsheet in an encrypted volume on a laptop hard disk. After the collection of all patient data and once recruitment of patients was complete, patient identifiers were removed, and the data were permanently anonymized.

Statistical analysis

All statistical analyses were completed using Stata version 9. The percentage in each risk category with elevated IMT in either the right or left carotid artery was assessed. Additionally, the percentage with elevated IMT on either side or the presence of plaque in either carotid artery was assessed. The χ^2 test for trend (Stata's p_{trend} command) was used to assess for statistical significance of the differences in percentages across the three groups. In all cases, elevated IMT was defined as ≥ 0.9 mm, as per European guidelines (Perk et al., 2012).

The number of patients with elevated IMT demonstrated in either the left or right carotid artery as a percentage of the total number in the moderate risk category was calculated. The number with either elevated IMT or presence of carotid plaque was also calculated. The 95% confidence intervals for these percentages were calculated. These patients were considered reclassified to a higher risk category through the addition of the carotid measurements to their risk assessment.

Results

Cardiohealth station examinations were performed on 201 individuals (54% women). Full data required for risk categorization was available

Table 1
Baseline characteristics.

Variable	Women	Men
Age	58.0 (8.1)	55.5 (7.9)
Total Cholesterol (mmol/l)	5.2 (1.3)	5.0 (1.9)
Systolic blood pressure (mmHg)	140.2 (21.7)	143.6 (17.9)
Current smokers	14%	14%
Former smokers	1.8%	3.3%
Family history	46%	38%
Waist circumference (cm)	96.6 (15.2)	104.1 (12.6)
BMI	31.9 (8.4)	32.5 (9.7)
HDL cholesterol (mmol/l)	1.7 (0.7)	1.3 (0.6)
LDL cholesterol (mmol/l)	2.9 (1.1)	2.8 (1.6)
Triglycerides	1.7 (1.5)	2.2 (2.4)
Less than recommended activity	41.3%	41.3%
Recommended activity	21.1%	19.6%
More than recommended	36.7%	32.6%
Individuals with diabetes	6.6%	12.2%

for 193 (96%) of the group. The baseline characteristics for the entire group and subdivided by gender are shown in Table 1. Table 1 also shows the proportions of the group in each risk category.

Fig. 1 shows the distribution of the carotid IMT (highest value of right or left IMT) in the full group. Table 2 shows the mean right, left, and average IMT values as well as the proportion with elevated IMT (either left or right) and elevated IMT or carotid plaque visible.

Table 3 shows the CIMT measures in each risk category and the percentages of each risk category with elevated IMT. This is represented graphically in Figs. 2 and 3, respectively.

Looking at the moderate risk group alone, 16.5% (95% CI: 9.8%–23.2%) had elevated IMT meaning they were reclassified to a higher risk group. This included 13.9% (95% CI: 5.7%–22.1%) of women and 20.4% (95% CI: 8.7% to 32.1%) of men in the moderate risk group being reclassified.

Fig. 4 shows a scatterplot and linear regression of highest measured IMT versus estimated 10-year risk of fatal CVD calculated using SCORE. This also provides a graphical representation of those who are reclassified from the moderate (points shown in brown) risk category when CIMT is included in the risk assessment.

Table 2
Carotid intima-media thickness (mean and standard deviation) and carotid plaque in men and women.

	Women	Men
Right IMT	0.73 (0.15)	0.73 (0.16)
Left IMT	0.72 (0.14)	0.81 (0.22)
average IMT	0.72 (0.13)	0.77 (0.18)
Left plaque	31%	29%
Right plaque	38%	36%
Any plaque	51%	45%
Elevated IMT	18%	30%
Plaque or elevated IMT	60%	58%

Discussion

In common with previous studies, it was shown here that a significant proportion of those identified as moderate risk by clinical risk factors alone actually have significant carotid atherosclerosis. This reclassification is particularly important in the moderate risk group because it may signal the need for more intensive risk factor modification. This supports the recommendation in the European guidelines that assessment for carotid atherosclerosis be considered to further risk stratify those at moderate risk (Perk et al., 2012). One of the limitations of this study is that only cross-sectional data are available. Therefore, although we have calculated the percentage of individuals reclassified, we do not definitely know that these reclassifications are uniformly in the correct direction. However, a number of previous large prospective studies have shown that carotid atherosclerosis is related to the future development of CVD (Chambless et al., 1997; Bots et al., 1997). In the Rotterdam study, it was shown that in older women, the net reclassification index for the addition of CIMT to a model containing Framingham variables was 8.0% (Elias-Smale et al., 2012).

The CIMT measurements were better correlated with guideline-defined risk category as opposed to SCORE. This is likely to be due to the number of risk factor not included in the SCORE calculation, most notably diabetes. It is interesting to note that based on the regression line relating SCORE risk and CIMT (see Fig. 4), a SCORE of

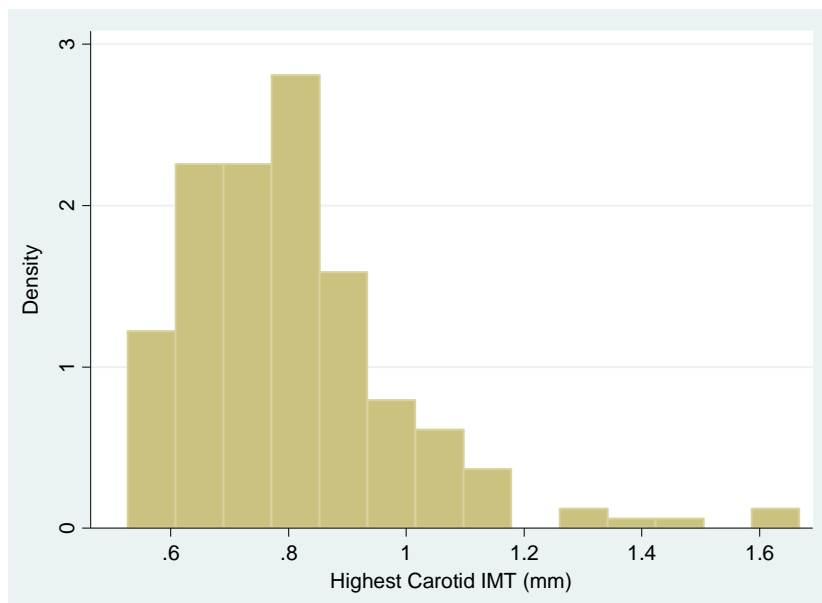


Fig. 1. Distribution of highest carotid intima-media thickness (mm).

Table 3
CIMT measurements and percentage with elevated IMT or presence of plaque in each risk category (CI: confidence interval).

	Very high risk		High risk		Moderate risk		p for trend
	N	Mean (95% CI)	n	Mean (95% CI)	N	Mean (95% CI)	
Left IMT	24	0.84 (0.77–0.92)	43	0.82 (0.75–0.88)	121	0.71 (0.69–0.74)	<0.001
Right IMT	24	0.80 (0.73–0.87)	43	0.73 (0.68–0.78)	120	0.71 (0.69–0.74)	<0.001
Average IMT	24	0.82 (0.76–0.88)	43	0.77 (0.72–0.82)	121	0.71 (0.69–0.74)	<0.001
Elevated IMT (%)	24	46 (24–67)	43	33 (18–47)	121	17 (10–23)	<0.001
Carotid disease (%)	24	83 (67–99)	43	63 (48–78)	121	53 (44–62)	<0.001

5% was associated with a CIMT of 0.9 mm, which has been defined by the European guidelines as the cut point for high risk (Perk et al., 2012).

One of the advantages of using a risk estimation system that relies only on conventional risk factors is the ease and speed of use, which facilitates implementation of risk assessment in routine clinical practice. A system such as SCORE or HeartScore requires no additional risk factor measurements and takes only seconds to calculate. Furthermore, systems have been developed to integrate these risk calculators with electronic health records providing an automatic estimation of CVD risk (Wells et al., 2008).

The extra time required may be an obstacle to implementation of assessment for carotid atherosclerosis in routine clinical practice. The ease of use of the Cardiohealth station may assist with this. The system can be operated by a technician with limited training and in a significantly shorter timeframe than when measured using conventional ultrasonography. During this study, the measurements could be made within a 30-min time period, and it proved feasible to assess carotid measurements during a routine outpatient clinic visit. Additionally, patients tolerated the procedure without difficulty and many were interested in viewing and discussing their results. Whether the measurement of carotid atherosclerosis on the day of clinic would translate into increased success with risk factor control deserves further study in the setting of a study with longitudinal follow-up, ideally with participants randomised to have the carotid assessment or usual care alone. It is possible that the increased awareness of risk may encourage favorable lifestyle changes and improvements in adherence to medication.

A validation study has evaluated the performance of this new system in comparison to the conventional manual system for carotid scanning (Vanoli et al.). The comparative coefficients of variation for inter- and intra-operator variability were 8.2% and 6.4%, respectively, for automated measurement and the inter-operator

variability was 8.7% for manual measurement (Vanoli et al.). There was no clinically relevant difference between measurements obtained by the two systems (coefficient of variation 4.6%) (Vanoli et al.). The acquisition time of the automated system was significantly shorter than the conventional system (70 ± 32 vs. 121 ± 57 s, $p < 0.01$) (Vanoli et al.).

In conclusion, the Cardiohealth station provided a method for the measurement of CIMT and detection of carotid plaque. The ease of use of the system meant that the measurements could be made as part of a routine clinic visit and the information relayed to physician and patient immediately. This may aid risk factor modification. The carotid measurements correlated with risk category as defined in the European guidelines on CVD prevention. When risk assessment for carotid atherosclerosis was incorporated into risk assessment, 17% of those at moderate risk were reclassified.

Conflict of interest

This work has been supported by an unrestricted educational grant from Panasonic. The sponsors have not had any input into the design of the study, the decision to publish, the analyses, or the content of the manuscript.

Author contributions

Maeve Cooney recruited patients, consented patient, performed all measurements using Cardiohealth station, recorded data, reviewed, and revised manuscript.

Marie-Therese Cooney designed study protocol, wrote the first draft of manuscript, and performed statistical analysis.

Ian Graham designed the study protocol, reviewed the results, reviewed, and revised the manuscript.

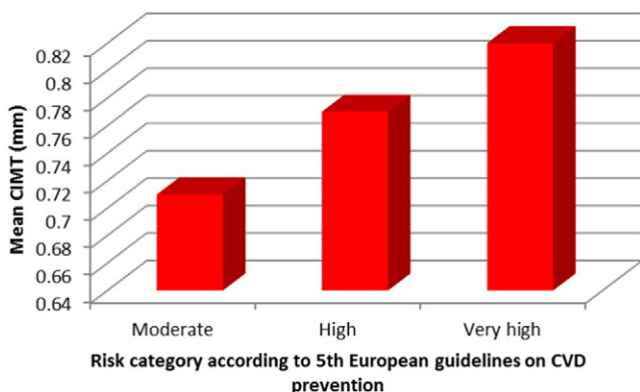


Fig. 2. Mean highest CIMT measurement in each risk category (mm).

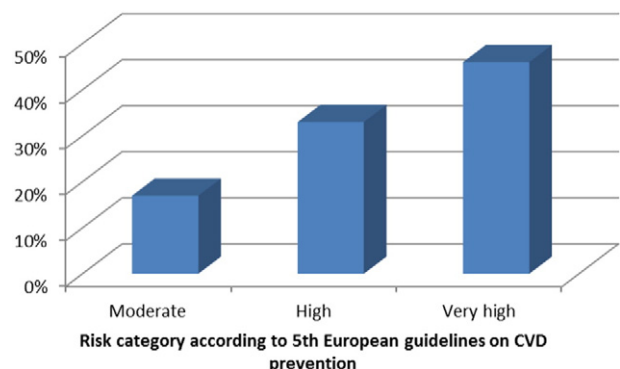


Fig. 3. Percentage of each risk category with elevated IMT.

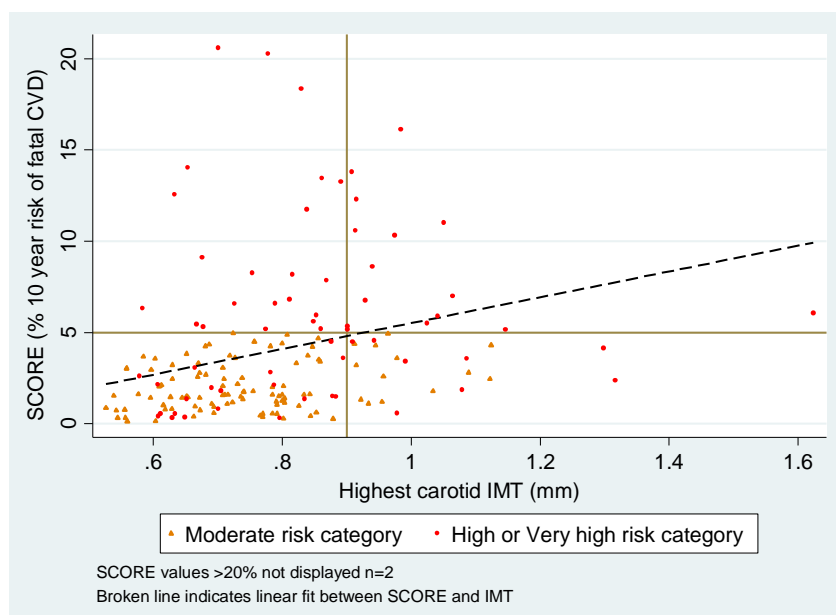


Fig. 4. Scatterplot of the estimated 10-year fatal CVD risk and highest measured carotid IMT.

Vincent Maher was involved in the design of the study, was responsible for the clinical care of patients attending clinic and provided medical interpretation of results, reviewed and revised the manuscript.

Barkat Khan collected clinical and laboratory results for patients and provided the medical interpretation of Cardiohealth station results for patients.

Tora Leong provided expertise on carotid intima-media thickness measurement, provided comments on, and revised the manuscript.

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