The Potential Role of Carotid Ultrasound Screening for the prevention of Cardiovascular Disease: A cost-effective addition

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- Cardiovascular disease is a leading cause of mortality and morbidity globally
- Millions of deaths and billions of Euros could be avoided if more focus was put on prevention
- Carotid ultrasound can add information beyond assessment of traditional risk factors that may help clinicians make decisions about the necessity of medical treatment for primary prevention
- The additional information provided by carotid ultrasound could change treatment decisions and by doing so, avoid CVD events in the future in a cost-effective manner.
Introduction

Cardiovascular disease (CVD) is recognised as a leading cause of mortality and morbidity globally. The World Health Organisation (WHO) estimated that 17 million people die of CVD events, particularly heart attacks and stroke, every year. Looking specifically at Europe, it was estimated that CVD causes 4 million deaths, representing 47% of all deaths in Europe. It is the leading cause of death in women in all countries of Europe and the main cause of death in men in all but 6 countries.

CVD accounts for 10% of all disability adjusted life years (DALYs) in low and middle-income countries and 18% in high income countries. The DALY is a combination of potential life lost due to premature death with years of productive life lost due to disability.

The burden of CVD is also reflected in the global financial cost of CVD which is estimated at US $863 billion a year and expected to rise to US$1,044 billion a year by 2030 – an increase of 22%. It is estimated that currently about US$ 474 billion (55%) is due to direct healthcare costs and the remaining 45% to productivity loss from disability, illness or premature death. The burden to the EU economy of CVD is estimated at €196 billion a year, with 54% due to health care costs, 24% due to productivity losses and 22% to informal care of people with CVD.

There has been recognition from agencies such as the WHO and United Nations that millions of deaths could be averted and economic losses reduced by billions of dollars if added focus is put on prevention. Primary prevention works – 50% of the reductions seen in coronary heart disease (CHD) mortality relate to changes in risk factors, and 40% to improved treatments. Nevertheless, millions of people with risk factors and CVD conditions remain undiagnosed. The UK Department of Health (DoH) Cardiovascular Disease Outcomes Strategy noted that while 7.6 million people are diagnosed with hypertension in the UK they believe there are a further 6.8 million undiagnosed, that is, 47% of those with hypertension remain undiagnosed. The implications of under-diagnoses are significant. Peripheral arterial disease is widely recognised as being under-diagnosed, with many people therefore not being offered appropriate treatment. This leads to an increased risk of claudication, skin ulcerations and need for limb amputations, as well as a higher risk of developing other cardiovascular conditions with their consequent morbidity and risk of death.

While mortality from CVD has decreased dramatically over the past few decades, it is recognised that many more deaths could be prevented through healthier lifestyles and better risk factor detection and management. The European Society of Cardiology (ESC) guidelines recommend risk factor screening in adult men over 40 years old and in women over 50 years old or post-menopausal. The most recognised measure of risk in Europe is SCORE (Systematic Coronary Risk Evaluation) which considers the combined effect of multiple risk factors. A person with a SCORE

5 DoH Cardiovascular Disease Outcomes Strategy: improving outcomes for people with or at risk of cardiovascular disease 2013. www.dh.gov.uk/publications
value >5% is considered high risk, and requires lifestyle advice and may also benefit from drug treatment.

However, algorithms such as SCORE have their limitations. One study noted that more than half of the coronary events over a 5 year period occurred in people who did not classify as high-risk according to algorithms used to calculate their cardiovascular risk, including SCORE. Another study noted that approximately 30% of people who are at a major risk of cardiovascular event would only have been classified as having an intermediate risk according to the usual criteria of algorithms based on traditional risk factors.

This introduces the discussion on the potential added value of new imaging techniques for improvement in risk stratification and therapeutic decision-making. The focus of this paper is the potential added value of carotid ultrasound in detecting subclinical disease from both a clinical and economic perspective.

Carotid Ultrasound

It has been noted that carotid intima-media thickness (CIMT) is related to cardiovascular risk, and its measurement by means of ultrasound makes it possible to detect thickening in the initial phases of atherosclerosis. The results of a meta-analysis involving over 37,000 subjects followed for an average of 5.5 years, showed that given an absolute CIMT difference of 0.1mm, the risk of future myocardial infarction increased by 10% - 15%, and the stroke risk increased by 13% - 18%. CIMT is considered a surrogate marker of cardiovascular disease, an independent risk factor, and a tool for early detection of atherosclerosis. More recent work has also confirmed carotid plaque as an additional measurement that can improve accuracy. A meta-analysis including over 54,000 patients with a follow-up of 8 years concluded that ultrasound assessment of carotid plaque had higher diagnostic accuracies for the prediction of future myocardial infarction. They recommended that CIMT assessment should always be supplemented by a thorough scan of the extracranial carotid arteries for carotid plaque to increase diagnostic performance of carotid ultrasound.

The advantages of carotid ultrasound are that it is non-invasive, relatively inexpensive and does not irradiate; hence this measure can be repeatedly performed with no adverse effects on the participant. The technology is also widely available and so may represent a very practical solution for many healthcare systems.

Within the ESC guidelines it is noted that carotid ultrasound scanning can add information beyond traditional risk factors that may help clinicians make decisions about the necessity of medical treatment for primary prevention. The 2010 ACCF/AHA Guidelines also note that CIMT is...
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a reasonable measure of CV risk in asymptomatic adults, with benefits which exceed the potential risk\(^1\).

Nevertheless, the added value of carotid ultrasound screening and whether or not it is a cost-effective use of resources is still debated. To further these discussions, an interactive model was developed to estimate the potential added value of introducing single carotid ultrasound screening to existing risk-assessment methods such as SCORE. The potential number of CVD events avoided over a 10 year period and the cost per CVD event avoided were estimated.

**Model Hypothesis:** Subsequent to primary screening with traditional risk factors, introducing carotid artery ultrasound screening in asymptomatic individuals defined as low-intermediate risk (SCORE ≥1% and <5%) may improve the accuracy of risk stratification. This may ultimately result in more appropriate interventional treatment and a reduction in cardiovascular events. Carotid artery ultrasound screening is assumed to consist of both CIMT measurement and carotid plaque detection.

**Methodology:** An Excel model was developed to assess the potential impact of introducing carotid artery ultrasound scanning in asymptomatic people defined as low-intermediate risk. The model assesses both the clinical impact (in terms of fatal and non-fatal events avoided) and the economic impact over a time horizon of 10 years. The model was developed in conjunction with Abacus International.

![Figure 1: Model Flow](image)

Input data was taken from peer-reviewed literature whenever possible; however, the model was designed to allow the user to tailor certain parameters to their own locality and resource availability. The model has been initially developed for Spain. While Spain has low rates of CHD compared to other Western countries, there is a paradoxically high prevalence of traditional CV

risk factors\textsuperscript{14} which has led to substantial interest in prevention strategies. As noted in a recent report from the Spanish Society of Cardiology\textsuperscript{4}, cardiovascular risk should be determined in all asymptomatic adults with no evidence of CVD.

**Worked example and assumptions:**
- Starting population of 5000 people aged between 55 and 75 years of age considered using TRFs.
- Low to intermediate risk = 74.5\%\textsuperscript{15} of starting population, therefore 3724 carotid scans required.
- Two ultrasound scanners currently available to support carotid artery scanning; no additional requirements for capital investment in new equipment.
- The reimbursement rate of a carotid ultrasound scan is assumed to be €150.
- The proportion of low-intermediate risk people with carotid atherosclerosis = 27.4\%\textsuperscript{16}.
- People reclassified from low to intermediate risk to high risk are all assumed to receive pharmacological treatment including a generic statin (estimated annual cost €57.40). The risk reduction associated with this treatment was assumed to be 25\%\textsuperscript{17} and applied in a constant manner throughout the 10 year time horizon of the model.
- All people are assumed to receive lifestyle advice regardless of risk, however no risk reduction specific to this is assumed in the model.
- Compliance with pharmacological treatment is assumed to be 100\% for simplicity (this is considered further in sensitivity analysis).
- Adverse events with statins were not included in the model. A recent systematic review noted that while there were previous concerns about low cholesterol increasing the risk of mortality from non-CHD causes, pre-existing disease such as early cancer, respiratory disease etc. are more likely to cause low cholesterol and raised mortality than the statin treatment itself. Among those with and without pre-existing CVD, the evidence now suggests that any possible hazards of statin treatments are far outweighed by the benefits\textsuperscript{17}.
- Sensitivity of ultrasound for carotid artery scanning was assumed to be 90\% and specificity assumed to be 94\%\textsuperscript{18}.
- False positive patients are anticipated to benefit from treatment to the same degree as true positive patients based on recent findings from the Cholesterol Treatment Trialists study that indicated benefits are similar in people at lower (<1\% per year) risk of a major cardiovascular event\textsuperscript{17}.
- The default 10-year risk of a fatal CVD event in low to intermediate patients was assumed to be 2.5\%, mid-point between 0 and 5\%.
- For the estimation of risk in the high-risk group, the model uses a relative risk increase of 62\% based on the ARIC study\textsuperscript{19}.
- Total event rates are calculated by multiplying the fatal event rates by 3 (the FINRISK multiplier)\textsuperscript{6}.

\textsuperscript{14} Casasnovas, J. et al. (2012) Aragon workers’ health study – design and cohort description. BMC Cardiovascular Disorders 12: 45
\textsuperscript{15} Spanish epidemiology data source:
\textsuperscript{19} Nambi et al. 2010 Carotid intima-media and presence or absence of Plaque Improves prediction of Coronary Heart Disease Risk. The ARIC (atherosclerosis Risk in Communities) Study. JACC, Vol. 55 (15): 1600 – 1607.
Results:
Potential Outcomes
Preliminary TRF screening of our 5000 sample population identified 3724 low to intermediate risk people. After carotid ultrasound scanning on these people, 1080 were reclassified as high risk - 162 of these reclassified people are false positive (they are reclassified as high risk when in fact they are low to intermediate risk). This is due to the less than 100% specificity. In addition, 102 high risk patients remain in the low-intermediate classification, due to the less than 100% sensitivity rate. Newly identified high risk patients receive pharmacological treatment and the model estimates that 31 CVD events could be avoided (10 fatal events and 21 non-fatal events) over the following 10 years. Looking at this in a different way, the numbers needed to screen (NNS) are 120 people to avoid one CVD event or 361 people to avoid one fatal CVD event.

Typically acceptable NNS estimates for currently used screening programs are in the 100 to 1000 range20.

![Figure 2: Potential outcome](image)

Cost-effectiveness
To determine whether the introduction of carotid ultrasound screening in this population might be cost-effective, the model calculates the comparative costs of the 2 strategies including both direct healthcare costs and the indirect societal costs associated with lost productivity in the selected population.

The additional cost of screening plus the additional cost of treatment for the newly identified high risk patients is partially offset by the reduction in CVD events (see Figure 3) such that the cost per CVD event avoided is €18,865.

The current example suggests that the introduction of carotid artery ultrasound scanning is potentially cost-effective from a policy/payer perspective at 10 years depending on the willingness to pay threshold adopted. The results of this model will vary depending on the various parameters the user inputs to the model.

Sensitivity Analysis:

As with all models, there are simplifying assumptions that need to be taken into consideration and the key parameters that we identified as influencing the results of the model were:

- Risk reduction associated with pharmacological treatment:
  - An improved treatment relative risk reduction to reflect the possibility of combination pharmacological treatment such as a statin plus non-steroidal anti-inflammatory and anti-hypertensive (risk reduction 38%; estimated generic annual cost €92)
  - A diminished relative risk reduction to reflect less than perfect compliance and continuation rates. For example, UK NICE Guidelines note a compliance rate of over 95% in one primary prevention study and rates of continuation with statin therapy of 87% after 3 years of treatment in primary prevention trials.
- Cost of pharmacological treatment given to reclassified high risk patients (default assumes a low priced generic; sensitivity analysis assumes a higher priced but still generic statin)
- Age of the starting population – which affects the proportion of patients who would be defined as high risk using traditional risk factors (age is recognised as a significant risk factor)

Changing these parameters in a simple one-way sensitivity analysis has an impact on both outcomes and cost-effectiveness.

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22 NICE Clinical Guidelines (TA94) Statins for the Prevention of Cardiovascular Events
<table>
<thead>
<tr>
<th></th>
<th>Default</th>
<th>Sensitivity Analysis</th>
<th>NNS to avoid CVD event</th>
<th>Cost/CVD event avoided</th>
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<tr>
<td><strong>Age of starting popn. (36% risk of atherosclerosis)</strong></td>
<td>55 – 75 (27.4% risk)</td>
<td>50 – 56 (36% risk)</td>
<td>95</td>
<td>€13,921***</td>
</tr>
</tbody>
</table>

*The cost of treatment is also increased to reflect statin, non-steroidal anti-inflammatory and anti-hypertensive (€92)

**Within a subgroup of participants aged 50 – 56 carotid plaque was noted in 35.7 (194 participants in Spain)\(^\text{14}\)

**As the sample is younger savings from reduced loss in productivity are higher as more people are expected to be in employment.

### Current Model Limitations:

Quality of Life – while this model includes a cost-effectiveness analysis, it has been limited to an estimation of the cost per CVD event avoided. In looking to develop the model further, it would be pertinent to consider how patient quality of life (QoL) is affected by treatment and CVD events. Some non-fatal CVD events are known to have a devastating impact on patient QoL.

### Conclusions:

The developed model suggests that in certain scenarios the addition of a carotid ultrasound scan to traditional risk factor screening in low to intermediate risk people could avoid future CVD events in a cost-effective manner. As with many models, there are a number of simplification assumptions that have been noted above. However, basic one-way sensitivity analysis suggests that the positive impact may be maintained. The key benefit of this model is that it is an interactive tool that allows stakeholders to input local data relevant to them and consider the implications of carotid ultrasound screening for their considered population. Acceptability will vary between stakeholders and will depend on their future cardiovascular strategy.
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