Vascular calcification in patients with Diabetes Mellitus

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Risk of cardiovascular disease

Cardiovascular disease;
- Stroke
- Coronary heart disease
- Peripheral vascular disease

Leading cause of death worldwide

Aging population will contribute to increasing rates of CVD

Changes in cardiovascular related mortality over time

We have witnessed a moderate reduction in mortality associated with CVD.

From:
- improved medical therapies
- improved interventions
- improved risk factor modification

However...

A diagnosis of diabetes mellitus confers at least a doubling in cardiovascular disease risk, independent of traditional risk factors.

<table>
<thead>
<tr>
<th>Adjusted for</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Coronary heart disease</td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>2.06 (1.82–2.34)</td>
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<tr>
<td>Plus smoking status</td>
<td>2.10 (1.85–2.39)</td>
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<tr>
<td>Plus BMI</td>
<td>2.00 (1.78–2.25)</td>
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<tr>
<td>Plus systolic blood pressure</td>
<td>1.91 (1.70–2.14)</td>
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<tr>
<td>Plus non-HDL cholesterol</td>
<td>1.93 (1.71–2.16)</td>
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<tr>
<td>Plus HDL cholesterol</td>
<td>1.87 (1.67–2.09)</td>
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<tr>
<td>Plus log-triglyceride</td>
<td>1.87 (1.67–2.09)</td>
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<table>
<thead>
<tr>
<th>Ischaemic stroke</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Adjusted for</td>
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<tr>
<td>Age and sex</td>
<td>2.56 (2.15–3.05)</td>
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<tr>
<td>Plus smoking status</td>
<td>2.59 (2.16–3.09)</td>
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<tr>
<td>Plus BMI</td>
<td>2.45 (2.08–2.88)</td>
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<tr>
<td>Plus systolic blood pressure</td>
<td>2.27 (1.94–2.65)</td>
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<tr>
<td>Plus non-HDL cholesterol</td>
<td>2.26 (1.94–2.64)</td>
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<tr>
<td>Plus HDL cholesterol</td>
<td>2.24 (1.94–2.60)</td>
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<tr>
<td>Plus log-triglyceride</td>
<td>2.24 (1.94–2.59)</td>
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So what to do?

Primary prevention of diabetes mellitus;
- difficult for health care professionals on an individual basis
- we are consistently reminding people about the importance of healthy lifestyle choices
- perhaps public health campaigns are likely to have the most benefit here

“It’s not a rash, it’s moss. You need to start being more active than a tree.”
Primary prevention of Cardiovascular diseases

Fortunately, a diagnosis of diabetes mellitus is NOT a diagnosis of cardiovascular disease.

We can prevent the onset of cardiovascular disease in the clinic.
Primary prevention of CVD

Preventing CVD can be difficult

Most cardiovascular risk factors have **NO** symptoms

For patients, it can be difficult to justify making drastic lifestyle changes for no immediate benefit or improvement in "symptoms".
Knowledge is power

Identifying those at risk of cardiovascular disease is paramount, particularly to encourage aggressive primary prevention interventions;
- patient education
- aggressive lifestyle modifications
- medical therapies
- frequent medical follow-up
Risk stratification - Framingham Risk score

The Framingham risk score has limitations.
- Developed from a single population (Framingham, US)
- Racial variation
- Doesn’t take into account other RFs that may be of relevance (BMI, FHx)
- Population based and not individualised

Over-estimates and under-estimates risk of CVD
Chinese populations

Figure 2. Ten-Year Prediction of CHD Events in CMCS Men and Women Using the Original Framingham Functions

Liu et al. Predictive value for the chinese population of the framingham CHD risk assessment tool compared with the Chinese Multi-provincial cohort study. JAMA. 2004;291:2591-2599
British Populations

Coronary calcium scoring

It reveals the amount of macrocalcified atherosclerotic plaque within the coronary arteries.

The more macrocalcified plaque, the more atherosclerosis and the greater the risk of suffering a CVD event.
Coronary calcium score and risk of CVD

The coronary calcium score is an independent predictor of CVD events and all cause mortality.

Detrano et al. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. NEJM. 2008; 358: 1336-1345.
Benefits of the CT coronary calcium score

- Cost is minimal (~100 - 200 dollars)
- Individualised
- Low radiation dose
- Strong predictive capabilities compared to traditional risk scoring tools
- It helps redistribute risk of intermediate risk patients (~40% of patients will be redistributed)

What does it mean?

**Interpretation of CAC**

CAC = 0.  
A zero score confers a very low risk of death, <1% at 10 years.

CAC = 1-100.  
Low risk, <10%

CAC = 101-400.  
Intermediate risk, 10-20%

CAC = 101-400 & >75th centile.  
Moderately high risk, 15-20%

CAC > 400.  
High risk, >20%

What do we do with this information?

Medical therapy

• Statin therapy
• Aspirin therapy may be of benefit
• Further investigation may be of benefit in those with CAC >1000.

Education and Lifestyle intervention

• Patients tend to benefit from knowledge of their CAC
• Quantifying disease present in a patient's arteries is valuable knowledge
The EISNER trial

Performing a CAC and providing patients with results;
- Improves LDL cholesterol
- Waist circumference and abdominal girth
- Systolic blood pressure
Compared to those who do not have a CAC

In addition, there is a dose response improvement in risk factors

There is improved CVD risk factor control in this group.

CAC in high risk patients?

We don’t have enough data to support performing CAC scoring in high risk individuals (eg. Older diabetic individuals)

Medical therapy is unlikely to change

However, we know that providing CAC scores to individuals at any risk improves their compliance and CVD RFs – perhaps the same is true for high risk individuals?
CAC scoring in diabetics

Owing to the increased risk of CVD events in people with diabetes mellitus, most people >60 with diabetes are treated as high risk. Despite this, in people with diabetes, the CAC score is still predictive, independent of baseline RFs and glycaemic control.

Take a closer look!
Vascular calcification

An important component of atherosclerosis and vascular disease

Occurs in two forms; **intimal** and **medial**

Patients with diabetes mellitus

More severe atherosclerosis (intimal)  More severe medial calcifications
Medial artery calcifications and diabetes

Medial arterial calcifications and risk of;
- Amputation
- Coronary heart disease
- Stroke

Medial artery calcifications are associated with increased risk of cardiovascular diseases in people with Diabetes Mellitus.

There is no doubt that the severity of vascular calcifications is strongly associated with CVD events in people with Diabetes Mellitus.
Consecutive coronary calcium scoring

We saw the predictive capabilities of a single coronary calcium score.

Performing consecutive coronary calcium scores, at least 2 years apart, further identifies those at “High” and “Low” risk of CVD events.
HbA1c and CVD events and CAC

HbA1c and CHD risk

In white American individuals, The rate of CHD events is, compared to HbA1c 6.0;

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>7.0 – 7.9%</td>
<td>1.15</td>
</tr>
<tr>
<td>8.0 – 8.9%</td>
<td>1.29</td>
</tr>
<tr>
<td>9.0 – 9.9%</td>
<td>1.41</td>
</tr>
<tr>
<td>10.0 – 10.9%</td>
<td>1.34</td>
</tr>
<tr>
<td>&gt;/= 11.0%</td>
<td>1.44</td>
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HbA1c and CAC progression

CAC and progression

1. The more calcium someone has - the more at risk they are from CVD
2. If someone has a high calcium score, but no progression over two years, their risk may not be so high.
3. If we stop calcium progression, can we reduce risk?
Inflammation and calcification

Inflammatory cascades are now well established in the development of atherosclerosis and cardiovascular disease.

Recently, we found the reducing atherosclerotic inflammation, we can reduce the risk of CVD events - without changing cholesterol

Colchicine, a similar agent?

Colchicine is a unique anti-inflammatory agent, often prescribed for Gout.

Inflammatory pathways in gout are thought to be similar to the inflammatory pathways in atherosclerosis.

The LoDoCo trial

Inhibitors of Vascular calcification – Vit K

Vascular calcification is a slow process

18F – Sodium Fluoride
Positron Emission Tomography

The ViKCoVaC trial

Vascular Smooth Muscle Cell

- Apoptotic bodies
- Matrix vesicles

Calcification Stress
- e.g. mineral imbalance

Mineralization
- Impaired Matrix Vesicle

NO CALCIFICATION

- Inhibitors upregulated
- Matrix-GLA protein
- (Activation by Vitamin-K)

CALCIFICATION

- Loss of inhibitors
- Accelerated by Inflammation

Vitamin K

Colchicine
Summary

- Cardiovascular disease is the leading cause of death worldwide
- Diabetes confers a doubling in the risk of CVD
- Identifying those at risk of CVD can help target interventions
- Coronary calcium scoring may help identify those at risk of CVD
- Coronary calcium scoring may help improve CVD risk factor control
- Progression of coronary calcium may be a stronger predictor of CVD
Thank you

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Questions?