miRNAs in larger studies to confirm their role in CAD and to assess their predictive value to decide whether they have a role in clinical practice. But they also warn that large scale clinical implementation of microRNA biomarkers in clinical practice will still take several years.

So, how do they compare with current risk prediction models?

Current risk prediction models predict cardiovascular risk with AUC between 0.6 and 0.8. Thus, the microRNAs miR-132, miR-140-3p and miR-210, have predictive values that are comparable to the current risk prediction models.

‘These microRNAs for coronary artery disease risk prediction have not been validated in external populations yet and therefore their AUCs may be overestimated,’ said Dr Pinto-Sietsma. ‘On the other hand these microRNAs are presumed to be independent of age, since they were designed to identify the atherosclerotic process itself, which is a huge advantage compared to the current risk prediction models, which are mainly driven by age, making these prediction models inaccurate, especially for young individuals.’

She said circulating microRNAs do have the potential to advance cardiovascular diagnosis and treatment. ‘Because microRNAs have a completely different approach of identifying coronary artery disease compared to the current risk prediction models, microRNAs can improve the risk prediction when added to the current risk prediction models,’ she said.

‘Besides, not only can microRNAs add in the early identification of individuals at risk, they may also help distinguish subgroups of coronary artery disease patients at risk of, for instance, unstable angina and hereby prevent the adverse effects of a myocardial infarction. This could be a huge step forwards in personalized medicine.’

The journey to applying circulating microRNAs in a clinical setting may still be a long one, but the Amsterdam team believe it is worth pursuing, despite contradicting results from studies having tempered enthusiasm about circulating microRNA biomarkers.

But they stress that many good candidate microRNAs have been found that show potential to improve current risk prediction and that methods to measure and analyse microRNAs have been improved in recent years.

‘Therefore, now is the time to proceed with circulating microRNA research in the cardiovascular field’, said Dr Pinto-Sietsma. ‘Only by performing large studies with standardized measurement methods and using external validation cohorts, can we assess the added value to current risk prediction models and decide if they can be used in the clinic. Large scale funding and collaboration among different research groups is essential in this regard.’

doi:10.1093/eurheartj/ehx205

Plasma ceramides and cardiac risk

Mark Nicholls reports on a new blood test that may predict cardiovascular events in patients with or without coronary artery disease

A new type of blood test could be used to help physicians identify which patients with and without evidence of coronary blockages are at risk of a cardiovascular event.

Developed by researchers at Mayo Clinic in the USA, the test measures blood concentrations of plasma ceramides, a class of lipids that are highly linked to cardiovascular disease processes. It is believed to be sensitive enough that even individuals with normal levels of low-density lipoprotein (LDL) but still at risk may be identified.

Ceramides are lipids and, like cholesterol, are carried by LDL and become embedded in the arterial wall of atherosclerotic plaques. But as Dr Jeff Meeusen, co-director of Cardiovascular Laboratory Medicine at Mayo Clinic, explained: ‘Unlike cholesterol, which is mostly inert (both in the LDL and in the artery wall), ceramides are biologically active signal molecules that contribute to the pathophysiology of heart disease.’ Ceramides in the LDL increase the rate of lipoprotein infiltration across vascular endothelium, while ceramides in the vascular intima stimulate cytokines that draw inflammatory immune cells to the plaque site.

‘Ceramides in the plaque disrupt endothelial cell function preventing normal vasodilation/vasoconstriction’, he added, ‘while ceramides also activate platelets, increasing the likelihood of clots.’

The latest study, led by Dr Meeusen, showed that individuals with the highest levels of blood ceramides were found to have a 3–4 times greater risk of having a cardiovascular event compared with those...
with the lowest ceramide score, regardless of their LDL cholesterol level or the presence of a coronary artery stenosis.

The study covered 499 Mayo Clinic patients who were referred for coronary angiography to check for possible stenosis and were followed prospectively for 18 years, with researchers recording occurrences of myocardial infarction, stroke, revascularization, and death.

Patients were similar in age and with regard to blood pressure, smoking status and high-density lipoprotein (HDL), while those excluded were those who had diabetes or a previous myocardial infarction, stroke or procedure to open stenosed coronary arteries. Researchers measured four different types of ceramides in the blood at baseline—three linked with cardiovascular disease and a fourth that is abundant in all cells and not specifically associated with disease, but useful to normalize for intra-individual variability.

From this the Mayo team utilized a Ceramide Risk Score, which was previously developed by their Finnish collaborators and published in the European Heart Journal as a FASTTRACK CLINICAL RESEARCH article in 2016. Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol. This score is a 12-point scale with interpretive categories as follows: 0–2 (lower risk), 3–6 (moderate risk), 7–9 (intermediate risk) and 10–12 (higher risk).

### Ceramide risk score

Elevated plasma ceramides are associated with increased risk of myocardial infarction, acute coronary syndromes, and mortality within 1–5 years. Score is based on trial data including >4000 subjects.

<table>
<thead>
<tr>
<th>Ceramide score</th>
<th>Risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>Lower</td>
</tr>
<tr>
<td>3–6</td>
<td>Moderate</td>
</tr>
<tr>
<td>7–9</td>
<td>Increased</td>
</tr>
<tr>
<td>10–12</td>
<td>Higher</td>
</tr>
</tbody>
</table>

Among those patients, 46% had mild or no stenosis and were considered the ‘without coronary artery disease’ group. ‘As expected, these patients had a lower incidence of events: 3.1% vs. 5.8% per person year compared to those with >50% stenosis in at least one artery’, said Dr Meeusen.

Categorizing these sub-groups according to ceramide value found that patients without coronary artery disease (CAD) and with the lowest ceramides had an incidence of 2.2% per person year, he added. Patients without CAD and at the highest ceramide levels had an incidence rate nearly four times higher (7.8%), which was equivalent to the rate of patients with CAD and intermediate or high ceramide levels.

Overall, 5.1% of patients had a major cardiovascular event each year but the risk of having an event became higher as ceramide levels increased: for each one point increase in the ceramide risk score, the risk rose by 9%. The rate of events was double among people with the highest ceramide score compared with those with the lowest (8.1% vs. 4.1%, respectively).

Clinical chemist Dr Meeusen said: ‘Our research suggests that evaluating ceramide levels in patients who are not at immediate risk for coronary artery disease events may help cardiologists decide who could benefit from proactive and preventive treatment, such as statins, or lifestyle changes to prevent a serious cardiac event down the road.’

The patients in the ‘without CAD’ group will be a population that sees real benefit.

A negative or equivocal angiography finding (mild or no stenosis) is good in that it confers a lower risk of subsequent events but it also casts some uncertainty on the treatment options. ‘These patients were referred to angiography for a reason (e.g. abnormal ECG, angina, exertional dyspnoea). Measuring ceramides in this group can help identify which patients would get the most benefit from more frequent monitoring or a more aggressive therapeutic strategy.’

The trial was funded by Mayo Clinic with the new test now available through Mayo Medical Laboratories, which collaborated with some of the original researchers who established the role of ceramides in CVD and Finnish diagnostics discovery company Zora Biosciences Oy.

Dr Meeusen added that the study also found that ceramides could identify high-risk patients among those with LDL-C <2.6 mmol/L (100 mg/dL). ‘Our study found that the incidence of events among patients with low LDL-C and high ceramides was 16.4% per person year compared to only 3.7% per person year for patients with low LDL-C and low ceramides.’

‘If patients’ symptoms are subtle and they know their LDL-C is in the desirable range, they may be less motivated to take meds regularly or follow a diet or exercise plan. With a ceramide score in-hand, clinicians can engage their patients as active participants for shared treatment decision making, knowing that their risk is not as low as the LDL-C might suggest.’

Conflict of Interest: none declared.

References

References are available as supplementary material at European Heart Journal online.