TYPE 2 DIABETES, LIPIDS AND CARDIOVASCULAR RISK

Introduction
Recent clinical trials of new glucose-lowering medications have shown macrovascular benefit in type 2 diabetes, reducing both cardiovascular morbidity and mortality in patients. This is clinically very important and will influence our clinical management as the epidemic of ‘diabesity’ continues to unfold across the world.

Diabetes, both type 1 and type 2, is associated with premature death and a significant loss of life years. At 40, 50 and 60 years of age, men with diabetes and without a prior history of vascular disease, incur a loss of about 6.3, 5.8 and 4.5 years of life, respectively.

“Pre-menopausal women with diabetes lose estrogen protection from cardiovascular disease and are as vulnerable as their male counterparts with diabetes,” Dr Kok noted. Their rate of early mortality is even worse than that of men.

The major cause of premature death in type 2 diabetes is vascular events, particularly of cardiovascular origin.

KEY MESSAGES
• Newer glucose-lowering medications reduce both cardiovascular morbidity and mortality
• Metformin reduces cardiovascular risk in overweight type 2 diabetic patients and has recently been shown to improve the cardiovascular risk profile of patients after acute myocardial infarction (STEMI)
• Multifactorial intervention targeting hypertension, lipid-lowering and hypercoagulability is still key to cardiovascular risk reduction in diabetes
• Early treatment with appropriate agents should aim to reach target HbA1c levels safely in order to maximise cardiovascular protection.

Targeting vascular disease in diabetes
As early as 1960, clinical trials such as the University Group Diabetes Programme (UGDP) aimed at investigating which, if any, treatments for type 2 diabetes were effective in reducing morbidity and mortality.¹ The UGDP study became mired in controversy because early sulphonylureas, such as tolbutamide, showed cardiotoxicity. The cardiotoxicity of first-generation sulphonylureas was thought to be related to the blocking of ischaemic preconditioning, an essentially protective mechanism.

The first clinical trial to show cardiovascular benefit from glucose-lowering was the UKPDS study of newly diagnosed type 2 diabetic patients.² “It took 20 years of follow-up to show macrovascular benefit, but this was achieved, in spite of the use of older sulphonylureas and non-modern insulins,” Dr Kok noted.

Contrasting earlier trials such as the UGDP with the UKPDS and other modern trials of cardiovascular outcomes such as the VADT³ and ADVANCE trials,⁴ benefits emerge, if intensive treatment is initiated early in the development of the disease. The ACCORD trial⁵ added to the evidence for how intensification should not be achieved, as the intensive arm of this trial showed excess all-cause mortality as a result of efforts.
to rapidly reach a low HbA\textsubscript{1c} target of less than 6\% in high-risk type 2 diabetic patients.

“To achieve cardioprotection in our patients today, it is essential to treat early with appropriate agents and aim to reach target HbA\textsubscript{1c} levels safely,” Dr Kok pointed out.

A personalised approach to glycaemic targets in the context of reducing cardiovascular risk is summarised in Table 1 and is derived from the American Diabetes Association and European Association for the Study of Diabetes 2015 Guidelines.\textsuperscript{6}

<table>
<thead>
<tr>
<th>Table 1. A personalised approach to glycaemic targets in the context of cardiovascular risk</th>
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<tr>
<td>• Glycaemic control should always be approached in the context of a comprehensive cardiovascular risk factor reduction programme</td>
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<td>− Blood pressure control, lipids management, antiplatelet therapy</td>
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<td>• Reducing hypoglycaemic has a clear microvascular benefit; benefit is less clear for macrovascular events, disease</td>
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<td>− May be harder to measure and/or take longer to manifest</td>
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<td>• Results from large trials suggest that overly aggressive glycaemic control in older patients with more advanced disease may have an unfavourable risk/benefit profile</td>
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<td>• Personalised therapy is indicated, taking into account potential risks and benefits, adverse effects of glucose-lowering medications, and patient’s age and health status</td>
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**Multifactorial approach to reducing cardiovascular risk**

The long-term follow-up of the STENO-2 trial,\textsuperscript{7} a multifactorial intervention trial, showed that this approach achieved the best results for both microvascular and macrovascular protection and is an important reminder of the need to address overweight, hypertension, lipid-lowering and glucose control. In this 21-year follow-up of the initial 7.8 year study, the original 160 patients were followed up on an observational basis, while still being treated as for the original intense-therapy group. There was a median of eight years of life gained in the intensive-therapy group of patients in this extended study.

“Modest weight loss can drastically reduce abdominal visceral fat,” Dr Kok pointed out.

The Look AHEAD study\textsuperscript{8} showed that intensive lifestyle intervention aimed at body weight reduction, combined with less intensive diabetes support and education in type 2 diabetes, was not able to achieve significant cardiovascular risk reduction after almost 10 years. “This was because the use of antihypertensive medication, statins and glucose-lowering medication was lower in the intensive group than in the control group,” Dr Kok commented.

It is important to note that metformin showed cardiovascular risk reduction in overweight type 2 diabetic patients in the UKPDS study, and this benefit was retained over 10 years.\textsuperscript{9}

A more recent trial of metformin and its effects on cardiovascular risk profile in patients without diabetes presenting with acute myocardial infarction (STEMI), showed that four months of therapy resulted in a modest improvement in the cardiovascular risk profile, compared with placebo.\textsuperscript{10}

Comprehensive cardiovascular risk factor reduction programmes in type 2 diabetes should also include antiplatelet therapy to address the hypercoagulability state of type 2 diabetes. “Dual antiplatelet therapy is the gold standard of care for type 2 diabetic patients after an acute coronary syndrome or elective percutaneous coronary intervention,” Dr Kok noted.
TyPe 2 diabeTes, liPids and cardiovascular risk

Recent clinical trials have shown the need to differentiate between the various DPP-4 inhibitors, with the TECOS trial of sitagliptin\textsuperscript{11} not showing an adverse effect on heart failure hospitalisation, and achieving a reduction in insulin dosage needs. “This places sitagliptin in a more favourable position with regard to cardiovascular outcomes than the other DPP-4 inhibitors,” Dr Kok noted.

But it is the SGLT-2 inhibitors that are showing the most benefit with regard to cardiovascular events.

The LEADER\textsuperscript{12} study of liraglutide, a GLP-1 agonist, also showed cardiovascular benefit with a 22\% relative risk reduction in cardiovascular death. “This benefit was achieved in addition to effective glucose control,” Dr Kok noted.

Lipid control in type 2 diabetes

“It is difficult to reach target cholesterol levels in diabetic patients, particularly as we try to get to LDL-cholesterol levels below 1.8mmol/l.” Powerful statins, such as atorvastatin and rosuvastatin, are required, although the IMPROVE-IT trial has shown that ezetimibe added to simvastatin can drive LDL-cholesterol levels to target and below 1.3mmol/l. This combination also showed cardiovascular benefit in all pre-specified subgroups over the treatment period of 2.5 years.

Micronised fenofibrate reduces tri-glyceride levels, which are still a target for lipid control in type 2 diabetes.

Of interest is the fact that elderly diabetic patients benefit from statin therapy, even after 80 years of age.

In conclusion, newer glucose-lowering agents, the SGLT-2 inhibitors and the GLP-1 agonists, offer cardiovascular benefit in type 2 diabetes. Combined with a multifactorial approach, the clinician can now offer patients a management regimen that confers real benefits in respect of future atherosclerotic disease.

**Cardiovascular benefits of newer glucose-lowering agents**

**Lipid control in type 2 diabetes**

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Effect of metformin on cardiovascular risk factors: The GIPS-III trial}
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References


DISCLOSURE

ADVISORY BOARDS: AstraZeneca, Abbott, BMS, Pfizer, Novartis, Janssen Pharmaceuticals, Boehringer-Ingelheim, Novo Nordisk, Sanofi, Merck, MSD, Lilly, Mundipharma, Adcock Ingram.

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