Updates in the management of cardiovascular disease

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The sudden fall in temperature along with the surgery waiting room busy with people attending for flu and Covid vaccinations leaves me in no doubt that the Autumn/Winter season is here! Of course, this is always a time of year where pressures increase, but hopefully you still have time to read this packed issue.

The conference season is also in full flow, and we begin our issue with our usual digest of the key messages from the Annual Meeting of the European Association for the Study of Diabetes, held in Hamburg at the beginning of October. Once again, obesity dominated much of the conference and, as frustrating as it can be to hear about the effectiveness of diabetes drugs that have not yet been launched in the UK or are unavailable to us due to ongoing supply problems, it is good to see obesity finally being recognised as a priority for treatment.

Obesity is also the focus of our latest interactive case study, in which David Morris guides us through its assessment, implications and management. The GLP-1 receptor agonists do feature of course, but there are plenty of other options (including non-pharmacological) to help us support our patients, and David reminds us of these.

HbA_{1c} and its limitations

HbA_{1c} has long been used as a means of monitoring glycaemic control, not only providing a reliable measure of chronic hyperglycaemia but also correlating well with the risk of long-term diabetes complications. Indeed, we have come to regard HbA_{1c} as something of a gold standard test and have, since 2011, also relied on it for making the diagnosis of type 2 diabetes (see *How to correctly diagnose and classify diabetes*). From a practical perspective, there is much to commend this test – individuals do not have to fast, or to consume a 75 g glucose drink, sit quietly in a waiting room for 2 hours and then have a second venepuncture!

However, the test does have its limitations (Radin, 2014). Because HbA_{1c} reflects the average blood glucose levels over a 3-month period (the lifespan of the red blood cells [RBCs]), it should not be relied upon in circumstances where the glucose levels rise more rapidly. It should not, therefore, be used as a diagnostic tool when the symptoms suggest type 1 diabetes (e.g. in symptomatic children, young adults, where there is an acute onset of symptoms or in acutely unwell at-risk populations) or in those on medications that can rapidly increase glucose levels, such as steroids. Neither should the test be used to diagnose diabetes in pregnancy.

Other important limiting factors are any conditions that can affect the reliability of the HbA_{1c} test – in short, anything that can affect the lifespan of the RBCs. Conditions that prolong RBC life or are associated with decreased RBC turnover (e.g. anaemias associated with iron deficiency, or severe hypertriglyceridaemia) give a false high, whereas conditions that reduce RBC life or are associated with increased RBC turnover (e.g. anaemia from acute or chronic blood loss) give a false low.

Haemoglobinopathies, including sickle cell disease, can also affect the reliability of the HbA_{1c} test by altering the normal process of glycation, causing an abnormal peak on chromatography and making the RBCs more prone to haemolysis, thereby decreasing the time for glycation to occur and producing a falsely low HbA_{1c} result.

As a means of monitoring glycaemic control, HbA_{1c} will not give any insight into the peaks and troughs that can particularly occur with glucose-lowering therapies that can induce hypoglycaemia (e.g. sulfonylureas and insulin). In this situation, we need to know the typical daily glucose profile, and this is one reason why a review of a person's self-monitoring of blood glucose or, where appropriate, continuous glucose monitoring (CGM) is so important.

We spend a good deal of our time dealing with high HbA_{1c} levels (a topic we recently explored in *How to manage high HbA_{1c} in people with type 2 diabetes*), but less so with low levels.

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At a glance factsheet: Impaired hypoglycaemia awareness

Key details of impaired hypoglycaemia awareness and its implications, plus advice on diagnosing and managing it.

Diabetes & Primary Care **25**: [Early view publication]

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So, for something a little different this issue, David Morris and Probal Moulik take us through a case of an unexpectedly low HbA_{1c} and review the clinical situations in which the test is unreliable.

Assessing hypoglycaemia awareness

Of course, the avoidance of low blood glucose levels should always be a priority when prescribing glucose-lowering agents that are associated with hypoglycaemia, and this is a topic we have covered previously (see *How to prevent, identify and manage hypoglycaemia in adults with diabetes*). However, one aspect of this that I felt we could explore in more detail is impaired hypoglycaemia awareness. A reduced ability to recognise hypoglycaemia and take remedial action is a major risk factor for severe hypoglycaemia, and I was delighted when Vicki Alabraba agreed to address this in our latest *At a glance factsheet* – click here to read it.

In previous editorials, I have written about the eligibility criteria for using CGM in those people living with type 2 diabetes who are on multiple daily injections of insulin, and it is important to know that NICE NG28 now recommends that we offer CGM to those who have impaired hypoglycaemia awareness or recurrent severe hypoglycaemia (in Wales, eligibility is extended to all those with type 2 diabetes who are taking insulin). It isn't always easy to make an objective assessment of impaired hypoglycaemia awareness, so the two tools highlighted in the factsheet are really useful.

Updates in managing cardiovascular disease

For a long time, the glucose-lowering options for people with type 2 diabetes were limited to metformin, sulfonylureas and insulin – this seems hard to imagine now, with the ever-increasing number of choices that are available. It occurred to me that we are now also seeing a similar explosion of lipid-lowering therapies. For the past 20 years, the options beyond statin therapy were fairly limited, but suddenly we are being bombarded with unfamiliar names and new classes of lipid-lowering drugs. The NICE CG181 guideline on *Cardiovascular disease: risk assessment and reduction, including lipid modification* was updated in May 2023, and there has been a raft of Technology Appraisals relating to these newer therapies:

- TA385 – Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia.
- TA694 – Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia.
- TA733 – Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia.
- TA805 – Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides.
- TA393 – Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia.
- TA394 – Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

One could be forgiven for feeling a bit confused! However, in our second *At a glance factsheet* of this issue, Claire Davies provides a quick reference guide to the newer lipid-lowering therapies available, their modes of action and their position in the treatment pathway. I also strongly recommend NHS England's *Summary of national guidance for lipid management for primary and secondary prevention of cardiovascular disease* as a practical source of reference.

At the end of August 2023, the European Society of Cardiology published its updated Guidelines for the management of cardiovascular disease in patients with diabetes. It is a really comprehensive document that covers lifestyle, glycaemic targets, blood pressure and lipid management, cardiovascular disease (CVD) screening, risk stratification, heart failure, chronic kidney disease (CKD), arrythmias, peripheral arterial disease and much more. It is well worth looking at but, at just shy of 100 pages long, it is not going to be a quick read, so I am truly grateful to Pam Brown for providing a welcome summary of the key messages and important changes. Of relevance is the new evidence that has emerged from the cardiovascular and cardiorenal outcome studies that have been published since the guideline's last iteration in 2019.

On a similar topic, we are well aware of the significance of albuminuria as an independent marker of cardiovascular risk, as well as being an early sign of CKD and a risk factor for CKD

progression. Fortunately, treatments have evolved that can slow CKD progression and reduce cardiovascular risk, particularly in those with albuminuria, making its early identification all the more important. Unfortunately, it is notoriously difficult to obtain samples of urine from our patients to send to the lab, and it is probably the care process we struggle to achieve more than any other.

Albumin-to-creatinine ratio (ACR) testing is recommended for adults at risk of CKD; this includes people with diabetes, hypertension and other risk factors, including acute kidney injury, CVD, structural renal tract disease, recurrent renal calculi or prostatic hypertrophy, multisystem diseases with potential kidney involvement, family history of end-stage kidney disease and opportunistically detected haematuria, as well as those who are prescribed drugs that have an effect on kidney function. ACR testing should be done in people with diabetes and in those without diabetes who have an eGFR of less than 60 mL/min/1.73 m^2.

The current standard of care for urine ACR testing involves asking the patient to collect a urine sample at home, which they bring back to the healthcare provider to be sent to the lab for analysis. A confirmed ACR reading of 3 mg/mmol or above should be seen as clinically important. Reagent strips are not recommended unless they can specifically measure albumin at low concentrations and express the results as an ACR. A smartphone-based diagnostic test that can be used at home and allows semi-quantitative ACR measurement has also been developed. Despite some evidence that this approach may be cost-saving and a review by NICE in 2020, to my knowledge there has not been widespread uptake of this sort of technology.

Interestingly, the THOMAS study, based in the Netherlands, compared different ways of testing for albuminuria and the outcomes achieved. Pam provides a summary of the findings and reminds us that we probably do need to look for innovative ways to improve the uptake of ACR testing.

Early-onset type 2 diabetes

Communicating the number of years of life lost for those with diabetes is never going to be an easy conversation, but the stark reality is that the condition is associated with a shortened life expectancy, particularly in those with established CVD. Developing type 2 diabetes at a younger age has a significantly worse prognosis, as our previous factsheet demonstrates. A study recently published in the *Lancet Diabetes & Endocrinology* (Emerging Risk Factors Collaboration, 2023), and summarised in *Diabetes Distilled*, really highlights how important it is for us to consider a person's age at diagnosis as part of our review and, where this is less than 40 years, to adopt a more aggressive approach to cardiovascular risk reduction and glycaemic management.

I hope you enjoy the issue. As always, if there are any topics you'd like to see covered in future issues, please do contact us at dpc@omniamed.com, as we are always open to suggestions! ■

Emerging Risk Factors Collaboration (2023) Life expectancy associated with different ages at diagnosis of type 2 diabetes in high-income countries: 23 million person-years of observation. *Lancet Diabetes Endocrinol* **11**: 731–42

Radin MS (2014) Pitfalls in hemoglobin A1c measurement: When results may be misleading. *J Gen Intern Med* **29**: 388–94

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At a glance factsheet: Newer lipid-lowering therapies in type 2 diabetes

A quick guide to the newer lipid-lowering therapies, their different modes of action and their place in treatment.

Diabetes & Primary Care **25**: [Early view publication]

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