Guidelines and targets: Coping with the information overload

The Greek philosopher Heraclitus is quoted as saying, "Change is the only constant in life". I confess I had to look this up, but there is no shame in that, if we are to concur with Einstein's advice to "never memorise something that you can look up".

These two sayings seem especially pertinent in relation to current diabetes management. With advances in technology, new drug therapies, licence changes and new indications for familiar agents, and a plethora of new and updated guidelines from various bodies, it is becoming increasingly difficult to stay abreast of it all. I'm relieved that for the past 18 months I've only had to focus on diabetes, after moving from my more generalist role.

More of what's new later, but first I wanted to share with you some of the work that is going on behind the scenes for the journal. Our technical team has been working hard to improve various aspects of our web pages, including the search function. It is hugely frustrating when you can't find an article you are looking for, so hopefully you will notice a difference. To make it easier, our tech team plan to create some tool tips for the website, to make navigation even better.

For some time now, our focus for the journal has been to provide comprehensive, yet concise, practical resources, including the *How To* guides, *At a Glance* factsheets and, most recently, the *Need to Know* series. We have covered a broad range of topics and each full series can be easily accessed by visiting the Resources menu and following the links. PDFs can be quickly downloaded, and we have added quick links for you to share articles on various social media platforms. So, if Twitter or Facebook are your thing, we'd be hugely grateful if you could share resources that you find useful with your colleagues (I am something of a dinosaur when it comes to this)!

In the previous issue, Yassir Javaid wrote a very comprehensive guide on identifying and managing atrial fibrillation (AF), reminding us that all people with diabetes and a CHA_2DS_2VASc score of 2 should be offered anticoagulation, with direct-acting oral anticoagulants (DOACs) being the preferred first-line option in non-valvular AF. Dosing isn't that straightforward (definitely a case here for looking it up, rather than trying to memorise it). In this issue, we've followed up with a guide summarising everything you need to know about dosing DOACs – a handy resource for quick reference.

Given that AF is a major risk factor for stroke, it seemed appropriate to follow with an article on stroke in the context of diabetes. Mike Kirby summarises important features of stroke in those with diabetes and shares key messages from the European Cardiology Society/European Association for the Study of Diabetes on its management (Cosentino et al, 2020). Interestingly, the recommended blood pressure (BP) targets for people with diabetes are:

- Systolic BP of 130 mmHg (<130 mmHg if tolerated, but not <120 mmHg). For older people (aged >65 years) the systolic BP goal is 130–139 mmHg.
- Diastolic BP to <80 mmHg, but not <70 mmHg.

More "relaxed" BP targets may also be found for older people with diabetes and chronic kidney disease (CKD) in a guideline published jointly last year by the Association of British Clinical Diabetologists (ABCD) and the Renal Association. Here the recommended targets are:

- A BP <140/90 mmHg in those with type 2 diabetes, CKD and a urine albumin:creatinine ratio (ACR) <3 mg/mmol.
- A slightly lower BP of <130/80 mmHg where ACR >3 mg/mmol.
- In those >75 years, no lower than 150/90 mmHg.

NICE guidance on hypertension was updated in 2019 (NG136), and this is the guideline we

Jane Diggle
Specialist Diabetes Nurse Practitioner, West Yorkshire

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are directed to for those with type 2 diabetes. Providing there is no CKD, the recommended targets are age-dependent:

- Age <80 years: BP <140/90 mmHg.
- Age ≥80 years: BP <150/90 mmHg.

NICE points out that there is insufficient evidence to support lower BP targets for people with diabetes, other than in those with coexisting CKD. In that situation we must refer to its guideline on CKD assessment and management (NG203), updated last year, which recommends BP targets according to the degree of albuminuria:

- ACR ≥30 but <70 mg/mmol: BP 120–139/<90 mmHg.
- ACR ≥70 mg/mmol: BP 120–129/<80 mmHg.

The guideline does, however, acknowledge the need to balance the risks and benefits when offering medicines to those with frailty, comorbidities or who are taking many other prescribed medicines.

Many of the people we see have comorbid conditions – stroke and CKD are common in those with diabetes, particularly in the elderly. In such people it isn't easy to know which guideline to follow and which target to aim for – for a summary, please go to my *Need to Know* guide, and I will leave you to decide which to follow!

To put your thoughts into practice, why not work through the most recent resources from David Morris's popular interactive learning series? Building on last issue's basics of managing hypertension, this time he provides more complex scenarios that you might encounter.

Of course, targets are one thing, but so too is the accuracy of the measurement! I do sometimes wonder if I am the only person using a manual sphygmomanometer and stethoscope, with such widespread use of the digital BP machine. The latter certainly seems to be the default for the students passing through our surgery for work experience. Automated devices may not measure BP accurately if there is pulse irregularity (e.g. owing to AF) and not flag up possible irregularity, so the advice from the British and Irish Hypertension Society is that we should palpate the radial or brachial pulse before measuring the BP.

I recently observed a nursing student undertaking a supervised "episode of care" that involved re-checking a person's BP following a raised measurement at a pre-op assessment. She used an automated device (his pulse is regular, incidentally) but it recorded a fairly high reading. I suggested she might like to use my "old-fashioned method" and, sure enough, this generated a significantly lower reading. Now, of course, the 5-minute wait may have been a contributing factor and perhaps the patient had "relaxed into the consultation" – who knows? But I'm sticking with my stethoscope and sphyg!

It isn't uncommon, though, for people to record high BP readings at hospital pre-op assessments. Optimising risk factors prior to surgery is really important, so Ketan Dhatariya and Pam Brown have updated How to prepare people with diabetes for surgery, which now encourages us to actively review glycaemic control and BP when referring people with suspected cancer and other conditions that might require urgent surgery. Of course, in those situations poor control must not delay the referral, but we can make use of the time between referral and surgery for active "prehabilitation", which should ensure surgery proceeds without delay. I was surprised to learn that 15% of all operations in the UK are in people with diabetes. Of course, there have been far fewer elective operations over the past 18 months owing to the pandemic, but that is set to change as we enter the recovery phase. I can't help wondering, how many people will be faced with ongoing delays to their surgery as a result of worsening glycaemic control? It is difficult to know if glycaemic levels have worsened as a result of COVID-19 – the evidence is quite mixed. However, I have noticed significantly higher HbA_{1c} levels in many of my patients over the past year – certainly higher than the 69 mmol/mol pre-op goal that is recommended.

On a more positive note, I do recall seeing a gentleman shortly after lockdown who felt completely dispirited by his deteriorating HbA_{1c} and resulting cancellation for a knee replacement. It turns out it was just the incentive he needed and, with support from our health and wellbeing coach, he has managed to reduce

his HbA_{1c} from 72 to 44 mmol/mol and his weight from 120 to 91 kg. He tells me he has never felt better!

Much of my October 2021 editorial was taken up with my thoughts on the draft of the update to the NICE guideline on the management of type 2 diabetes in adults. The long-awaited NG28 update was published on 15 February 2022 – just one day after Valentine's Day. Did NICE imagine we would all still be of a loving disposition?

I haven't had time to scrutinise and fully digest it but, so far, I can't see much has changed from the draft. The greatest impact to practice is likely to be the positioning of sodium–glucose cotransporter 2 (SGLT2) inhibitors earlier in the treatment pathway for certain groups, including those with chronic heart failure or established atherosclerotic cardiovascular disease (CVD) or a cardiovascular (CV) risk of 10% or more. We are advised to offer an SGLT2 inhibitor to those with CKD and an ACR >30 mg/mmol, and consider one where ACR is between 3 and 30 mg/mmol. We are reminded to use an SGLT2 inhibitor with proven CV benefit and to ensure that all the criteria are met according to that product's marketing authorisation (licence).

So, what does this mean in practice? The prescriber will need to be clear about which SGLT2 inhibitors have proven CV benefit.

ABCD and Diabetes UK published a joint position statement with recommendations for non-diabetes specialists on the use of SGLT2 inhibitors in people with type 2 diabetes in January 2021 (Dashora et al, 2021). Within this document, I discovered a useful table summarising the evidence from clinical trials of the cardiorenal benefits of available agents. However, it is important to remember that these trials differed in terms of design and population, and direct comparisons should not be made.

According to the NG28 committee, there are varying levels of certainty in the clinical trials and the network meta-analyses about:

- Which individual SGLT2 inhibitors were effective at improving CV outcomes.
- Whether there were real differences in CV benefits between the different SGLT2 inhibitors.

The guideline also emphasises that: "The committee agreed that there was more certainty of cardiovascular benefits in adults with type 2 diabetes and chronic heart failure or established atherosclerotic cardiovascular disease because they were participants in all the included trials, while people at high risk of developing cardiovascular disease were included in fewer trials. So, they recommended dual therapy with an SGLT2 inhibitor with proven cardiovascular benefit in addition to metformin for both groups, but only as an option to consider for people without established cardiovascular disease, to reflect the lower certainty."

In this population, metformin monotherapy remains the recommended first-line treatment option. So, what else do prescribers of SGLT2 inhibitors have to consider? Well, they will also need to refer to the agents' Summary of Product Characteristics (SmPCs; available at www.medicines.org.uk/emc). The indications and corresponding eGFR thresholds for initiation and ongoing use have been subject to change over recent months.

In my opinion, we first have to consider why are we prescribing an SGLT2 inhibitor (i.e. what is the indication?). Is it for blood glucose lowering? Most of the SmPCs refer to this as "insufficiently controlled diabetes". This is the case for canagliflozin, dapagliflozin and empagliflozin, though for ertugliflozin the term is "glycaemic control". I'm not sure if this is a case of semantics or if it makes a material difference? In any event, we should probably bear in mind that, while many of the agents can be initiated at an eGFR <45 mL/min/1.73 m^2, their blood glucose-lowering efficacy is likely to be reduced and absent in those with severe renal impairment.

Ertugliflozin is indicated for glycaemic control alone, should only be initiated where eGFR ≥60 mL/min/1.73 m^2 and stopped if it falls and remains persistently <45 mL/min/1.73 m^2.

Dapagliflozin is indicated for the treatment of symptomatic chronic heart failure with reduced ejection fraction (HFrEF). If you're looking for more information on heart failure, and how you define a reduced ejection fraction, take a look at our guide. Dapagliflozin is also licensed for CKD/diabetic kidney disease. Across all these

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indications, it may be initiated providing eGFR is ≥15 mL/min/1.73 m^2.

Empagliflozin is, however, now licensed for initiation to eGFR ≥30 mL/min/1.73 m^2 in those with established CVD. It is also indicated for the treatment of symptomatic chronic HFrEF, providing eGFR is ≥20 mL/min/1.73 m^2, though this is soon likely to change to include heart failure with preserved ejection fraction in the light of evidence from EMPEROR-Preserved study (Anker et al, 2021).

Where canagliflozin is prescribed for insufficiently controlled diabetes, the 100-mg dose may be initiated (providing eGFR >60 mL/min/1.73 m^2) and increased to 300 mg (providing the eGFR remains ≥60 mL/min/1.73 m^2). Canagliflozin may also be used for the treatment of diabetic kidney disease and a dose of 100 mg initiated, providing the eGFR is ≥30 mL/min/1.73 m^2, but should be stopped if eGFR is persistently <30 mL/min/1.73 m^2 and ACR <30 mg/mmol, though where there is more significant albuminuria (ACR ≥30 mg/mmol) it may be continued up until dialysis or transplantation.

My intention here is not to confuse you, but more to highlight the complexities. Yet another example of needing to look it up! These eGFR thresholds have been subject to change, so it is with huge gratitude to my Joint Editor-in-Chief, Pam Brown, that I can direct you to her invaluable *Need to Know* guide that provides SGLT2 inhibitor indications, doses and licences in two clear tables. This has already been updated since it was first published, and further changes to licences are anticipated fairly soon. We will continue to update it accordingly, so remember to check the latest copy. I can assure you, it will be considerably quicker than searching the SmPCs!

Embrace change and don't forget, you don't need to memorise things you can look up. Until next time… ■

Anker SD, Butler J, Filippatos G; EMPEROR-Preserved Trial Investigators (2021) Empagliflozin in heart failure with preserved ejection fraction. *N Engl J Med* **385**: 1451–61

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