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Guidelines for type 2 diabetes: keeping a finger on the pulse

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Cardiovascular (CV) disease remains the biggest cause of morbidity and mortality in patients with type 2 diabetes (T2D).[1] Individual drugs from two classes of glucose-lowering agents, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is), have demonstrated improved CV outcomes in high CV-risk subjects with T2D. This is reflected in recently updated guidelines from several professional associations – but not in the National Institute for Health and Care Excellence (NICE) guidelines in the UK.[2] We believe that NICE and other national/international health authorities need the ability to respond rapidly to new data, particularly when there is potential to improve outcomes and save lives.

Eight CV outcome trials (CVOTs) have already reported[1] and more are due to report as soon as this year, including CANVAS with canagliflozin, an SGLT2i (clinicaltrials.gov). Flexibility in the Food and Drug Administration (FDA) 2008 guidelines[3] on how to design, perform and analyse these CVOTs (resulting in different trial designs, patient populations and definitions of high-risk patients) has made these trials difficult to compare. Despite these discrepancies, so far all published trials have demonstrated CV safety in high-risk individuals, and three (EMPA-REG OUTCOME with an SGLT2i, empagliflozin [2015] and LEADER and SUSTAIN-6 with GLP-1RAs, liraglutide and semaglutide, respectively [both 2016]) have also demonstrated CV protection (although superiority was not pre-specified in SUSTAIN-6).[1,4]

In early 2017, the American Diabetes Association (ADA) published updated Standards of Medical Care in Diabetes, recommending empagliflozin and liraglutide in patients with CV disease, to reduce the mortality risk in these patients.[5] Several national guidelines, including those from Switzerland and Canada, have also responded quickly to these new data. However, NICE in the UK has not yet responded to this evidence, despite EMPA-REG OUTCOME being published three months before the most recent NICE guidance in 2015 (NG28). Concerning liraglutide use, NG28 requires urgent revisiting, given the evidence from LEADER in 2016 that liraglutide has shown CV benefit, including reduced mortality.[1]

NG28 in 2015 stated that areas 'that have not been reviewed may be addressed in 2 years' and NICE would consider a standing update committee for diabetes, which would enable a more rapid update as and when new and relevant evidence is published.[2] These aspirations appear to have emerged; a committee has met, and the update will be published in December 2017. However, previously, NICE has been reluctant to consider unlicensed indications, data published after their review process has started and, critically, to make any changes based on single studies; to satisfy the improved timescale for change, NICE may need to consider breaking these self-imposed rules.

To conclude, when trials demonstrate the potential for therapies to significantly improve clinical practice and patient outcomes, health advisory bodies have a duty of care, not only to be thorough and astute, but to fast-track their processes for consideration of the clinical implications of potentially important new data on managing patients at considerable risk of death or severe disability. Health authorities need to be able to review such data rapidly to consider whether such patients might benefit from the CV protection that these potentially major medical breakthroughs might offer.

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Declaration of interests

Anthony Barnett declares honoraria for lectures and advisory work from Novo Nordisk, Lilly Industries, Sanofi Aventis, MSD, Novartis, AstraZeneca, Janssen, and Boehringer Ingelheim. Julian Halcox declares fees related to advisory board and speaker bureau from Novo Nordisk, and grant from AstraZeneca. Paul O'Hare declares grant and personal fees from Novo Nordisk, personal fees from Sanofi, and non-financial support plus personal fees from MSD.

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~~Commentary~~ Correspondence article to *Lancet Diabetes and Endocrinology*

Guidelines for type 2 diabetes: keeping a finger on the pulse

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~~The risk of c~~Cardiovascular (CV) disease remains the biggest cause of morbidity and mortality ~~higher~~ in patients with type 2 diabetes (T2D) ~~than in those without the disease.~~[1] ~~Cardiovascular disease (CVD) remains the leading cause of mortality in patients with type 2 diabetes (T2D) in the UK and elsewhere. Data from the Health Survey for England and Scottish Health Survey cohorts indicate that nearly half of subjects with T2D die from CVD.~~[1] ~~–~~Individual d~~D~~rugs from ~~T~~ two ~~relatively new~~ classes of glucose-lowering agents, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is), have demonstrated improved ~~cardiovascular (~~CV~~)~~ outcomes in high CV-risk subjects with T2D. This is reflected in recently updated guidelines from several professional associations – but not in the National Institute for Health and Care Excellence (NICE) guidelines in the UK.[2~~1~~2] ~~This commentary discusses why w~~We believe that NICE and other national~~/ and~~ international health authorities need the ability to respond rapidly to new data, particularly when there is ~~the~~ potential to improve outcomes and save lives.

~~Concerns regarding adverse CV outcomes in a meta-analysis of rosiglitazone trials,[3] as well as increased mortality in the 'Action to Control Cardiovascular Risk in Diabetes' (ACCORD) trial, led the Food and Drug Administration (FDA) in the US to issue a 'Guidance for Industry' in 2008 for evaluating CV safety for new anti-diabetes therapies.[4,5] Since this guidance was released, e~~Eight CV outcome trials (CVOTs) ~~of glucose-lowering agents~~ have already reported ~~(three for dipeptidyl peptidase-4 inhibitors [DPP-4is], three for GLP-1RAs, one with an SGLT2i, and one with a long-acting insulin analogue).[5~~[21] and~~–~~ ~~Many~~ more ~~CVOTs~~ are due to report as soon as this year, including CANVAS with canagliflozin, an~~other~~ SGLT2i (clinicaltrials.gov).

~~The f~~Flexibility in the Food and Drug Administration (FDA) 2008 guidelines[3~~4~~] on how to design, perform and analyse these CVOTs (resulting~~ed~~ in different trial designs, patient populations and definitions of high-risk patients)~~,~~ has~~ve~~ made~~making~~ these trials difficult to compare. ~~However, d~~Despite these discrepancies, so far all published trials ~~for DPP-4is, GLP-1RAs and an SGLT2i~~ have demonstrated CV safety ~~(non-inferiority)~~ in high-risk individuals, and three (EMPA-REG OUTCOME with an SGLT2i, empagliflozin [2015] and LEADER and SUSTAIN-6 with GLP-1RAs, liraglutide and semaglutide, respectively [both 2016]) have also demonstrated CV protection (although superiority was not pre-specified in SUSTAIN-6).[2~~1~~,4~~5~~]

~~At the beginning of~~In early 2017, the American Diabetes Association (ADA) published updated Standards of Medical Care in Diabetes, recommending empagliflozin and liraglutide in patients with ~~CVD~~CV disease, to reduce the mortality risk in these patients.[6~~5~~] Several national guidelines~~, , including those from Switzerland~~[7] ~~and Canada,~~[8] ~~including~~ those from Switzerland and Canada, have also ~~been quick to~~ respond~~ed quickly~~ to these new data~~., making firm recommendations to prioritise liraglutide and empagliflozin in~~

~~patients with CVD.~~ However, NICE in the UK has not yet responded to this evidence, despite EMPA-REG OUTCOME being published three months before the most recent NICE guidance in 2015 (NG28). Concerning liraglutide use, ~~current NICE guidelines~~NG28 requires urgent revisiting ~~particularly with regard to the 1.8mg dose~~, given the evidence from LEADER in 2016 that liraglutide has shown CV benefit, including reduced mortality.[~~5~~21] ~~Additionally, the 'continuation' rules for GLP-1RAs appear paradoxical, requiring both a minimum drop in glycated haemoglobin (HbA_{1c}) and weight loss, without evidence that the benefits are restricted to these circumstances.[9] The guidelines also currently adopt a 'waiting for failure' approach after the first intensification step, only recommending intensification when HbA_{1c} is 7·5% or higher. This is not an appropriate target for many patients, particularly those that are younger and more recently diagnosed with T2D.~~

~~When NICE published~~ NG28 in 2015~~, it~~ stated that areas 'that have not been reviewed may be addressed in 2 years' and ~~i~~NICE~~t~~ would consider a standing update committee for diabetes, which would enable a more rapid update~~,~~ as and when new and relevant evidence i~~was~~~~is~~ published.[~~2~~12] These aspirations appear to have emerged; a committee has met, and the update will be published in December 2017. ~~However, this will be over two years after EMPA-REG OUTCOME was published, and 11 months after empagliflozin's EU licence update. Additionally, to satisfy this timescale for change, NICE will need to break self-imposed rules.~~ However, p~~P~~reviously, NICE has been reluctant to consider unlicensed indications, data published after their review process has started and, critically, to ~~make any~~make any changes based on single studies; to satisfy the improved~~is~~ timescale for change, NICE ~~will~~ may need to consider breaking these self-imposed rules.~~.~~

~~Since these CVOTs are all single studies, this could mean that all of these compelling data are ignored. Additionally, CANVAS will only be published after the NICE reviewing process has started, liraglutide awaits a licence update following LEADER and semaglutide is currently unlicensed. The CV outcome differences between GLP-1RAs would require NICE (and other national and international guidelines, many of which may be awaiting the decisions of NICE) to recommend individual drugs, rather than making recommendations on drug class.~~

To conclude, when trials demonstrate the potential for therapies to significantly improve clinical practice and patient outcomes~~, (such as reductions in major adverse CV events, including mortality beyond 30%),~~ health ~~authorities~~ advisory bodies have a duty of care, not only to be thorough and astute, but to fast-track their processes for consideration of the clinical implications of potentially important new data on ~~management of~~managing patients at considerable risk of death or severe disability.~~–~~ Health authorities need to be able to review such data rapidly to consider whether such patients might benefit from the CV protection that these potentially major medical breakthroughs might offer.

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