Practical recommendations for the management of diabetes in patients with COVID-19

Stefan R Bornstein, Francesco Rubino, Kamlesh Khunti, Geltrude Mingrone, David Hopkins, Andreas L Birkenfeld, Bernhard Boehm, Stephanie Amiel , Richard IG Holt, Jay S Skyler, J Hans DeVries, Eric Renard, Robert H Eckel, Paul Zimmet, Kurt George Alberti, Josep Vidal, Bruno Geloneze, Juliana C Chan, Linong Ji, Barbara Ludwig

Diabetes is one of the most important comorbidities linked to the severity of all three known human pathogenic coronavirus infections, including severe acute respiratory syndrome coronavirus 2. Patients with diabetes have an increased risk of severe complications including Adult Respiratory Distress Syndrome and multi-organ failure. Depending on the global region, 20–50% of patients in the coronavirus disease 2019 (COVID-19) pandemic had diabetes. Given the importance of the link between COVID-19 and diabetes, we have formed an international panel of experts in the field of diabetes and endocrinology to provide some guidance and practical recommendations for the management of diabetes during the pandemic. We aim to briefly provide insight into potential mechanistic links between the novel coronavirus infection and diabetes, present practical management recommendations, and elaborate on the differential needs of several patient groups.

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Department of Medicine III (Prof S R Bornstein MD, Prof A L Birkenfeld MD, Prof B Ludwig MD), **and Paul Langerhans Institute Dresden of the Helmholtz Center Munich** (Prof S R Bornstein, Prof B Ludwig), **University Hospital Carl Gustav Carus, Dresden, Germany; Department of Diabetes, School of Life Course Science and Medicine, King's College London, London, UK** (Prof S R Bornstein, Prof F Rubino MD, Prof G Mingrone MD, Prof A L Birkenfeld, Prof S Amiel MD, D Hopkins MD); **Department of Endocrinology and Diabetology, University Hospital Zurich, Zurich, Switzerland** (Prof S R Bornstein, Prof B Ludwig); **Faculty of Medicine** (Prof S R Bornstein, Prof B Ludwig), **and Deutsche Forschungsgemeinschaft-Center for Regenerative Therapies Dresden** (Prof B Ludwig), **Technische Universität Dresden, Dresden, Germany; German Center for Diabetes Research (DZD e.V.), Neuherberg, Germany** (Prof S R Bornstein, Prof B Ludwig, Prof A L Birkenfeld); **Bariatric and Metabolic Surgery, King´s College Hospital, London, UK** (Prof F Rubino); **Diabetes Research Centre, University of Leicester, Leicester, UK** (Prof K Khunti MD); **Fondazione Policlinico Universitario Agostino Gemelli Istituto Di Ricovero e Cura a Carattere Scientifico, Rome, Italy** (Prof G Mingrone); **Department of Internal Medicine, Università Cattolica del Sacro Cuore, Rome, Italy** (Prof G Mingrone); **Institute of Diabetes Endocrinology and Obesity, King's Health Partners, London, UK** (D Hopkins); **Department of**

Introduction

From January, 2020, we have been facing an unprecedented outbreak of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),which has now become a global catastrophe. Data from the early months of 2020 suggest that most people with COVID-19 have comorbidities, the most prevalent of which are diabetes, cardiovascular disease, and hypertension.[1] A significant association with worse outcomes is seen in people with these comorbidities.[1] Studies have also shown that COVID-19 is associated with hyperglycaemia particularly in the elderly with type 2 diabetes.[2] In view of many uncertainties with COVID-19, a faculty of representatives from primary and specialist care have developed a consensus document on the management of diabetes for people at risk of or with confirmed COVID-19 for use in both primary and specialist care. The brief practical recommendations authored by this group were convened virtually. The recommendations are based on queries that have been emphasised to be important by clinicians, questions that have been raised by colleagues and social media, and recommendations guided by using focused-literature review. Clinical decision making in the management of diabetes is already complex and in normal circumstances we recommend clinicians follow guidelines for management of people with diabetes. However, the recommendations authored by our group add to the existing guidelines by considering specific points for the management of patients with diabetes and COVID-19 disease or at risk for metabolic disease.

The potential links between diabetes and COVID-19 infection

Diabetes is a primary risk factor for the development of severe pneumonia and a septic course due to virus infections and occurs in around 20% of patients.[3,4] Diabetes was identified as a major contributor to disease severity and mortality in Middle East Respiratory Syndrome (MERS-CoV).[5] Evidence from epidemiological observations in regions heavily affected by SARS-CoV-2 and reports from the Centers for Disease Control and Prevention (CDC) and other national health centres and hospitals showed that the risk of a fatal outcome from COVID-19 is up to 50% higher in patients with diabetes than in those who do not have diabetes.[6] There are several hypotheses to explain the increased incidence and severity of COVID-19 infection in people with diabetes. In general, people with all forms of diabetes are at increased risk of infection because of defects in innate immunity affecting phagocytosis, neutrophil chemotaxis, and cell-mediated immunity; however, the high frequency of diabetes in serious cases of COVID-19 could potentially reflect the higher prevalence of type 2 diabetes in older people. Furthermore, diabetes in older age is associated with cardiovascular disease, which in itself could help to explain the association with fatal outcomes of COVID-19.

There are at least two specific mechanisms that might play a role in COVID-19 infection. First, to gain entry to its target cells, the SARS-CoV-2 virus hijacks an endocrine pathway that plays a crucial role in blood pressure regulation, metabolism, and inflammation.[7] Angiotensin-converting-enzyme 2 (ACE2) has been identified as the receptor for the coronavirus spike protein. ACE2 has protective effects primarily regarding inflammation. COVID-19 infection reduces ACE2 expression inducing cellular damage, hyperinflammation, and respiratory failure.[7] Acute hyperglycaemia has been shown to upregulate ACE2 expression on cells which might facilitate viral cell entry. However, chronic hyperglycaemia is known to downregulate ACE2 expression making the cells vulnerable to the inflammatory and damaging effect of the virus. Furthermore, the expression of ACE2 on pancreatic β cells can lead to a direct effect on β cell function.[8–10] Although these findings have not been

Diabetology, Endocrinology and Nephrology, University Hospital Tübingen, Tübingen, Germany (Prof A L Birkenfeld); **Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Centre Munich at the University of Tübingen, Tübingen, Germany** (Prof A L Birkenfeld); **Department of Endocrinology, Tan Tock Seng Hospital, Singapore, Singapore** (Prof B Boehm MD); **Lee Kong Chian School of Medicine, Nanyang Technological University Singapore, Singapore** (Prof B Boehm); **Human Development and Health, Faculty of Medicine, University of Southampton, UK** (Prof R I G Holt MD); **Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL, USA** (Prof J S Skyler MD); **Department of Endocrinology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands** (Prof J H DeVries MD); **Profil Institute for Metabolic Research, Neuss, Germany** (Prof J H DeVries); **Montpellier University Hospital and Institute of Functional Genomics, Centre national de la recherche scientifique, INSERM, University of Montpellier, Montpellier, France** (Prof E Renard MD); **Division of Endocrinology, Metabolism, and Diabetes, University of Colorado Anschutz Medical Campus, Aurora, CO, USA** (Prof R H Eckel MD); **Department of Diabetes, Central Clinical School, Monash University, Melbourne, VIC, Australia** (Prof P Zimmet MD); **Division of Diabetes, Endocrinology and Metabolism, Imperial College, London, UK** (Prof K G Alberti FRCP); **Centro de Investigación Biomédica en Red en Diabetes y Enfermedades Metabólicas Asociadas, Barcelona, Spain** (Prof J Vidal MD); **Obesity and Comorbities Research Center, Laboratory of Investigation in Metabolism and Diabetes/ Gastrocentro, Universidade de Campinas, Campinas, São Paulo, Brazil** (Prof B Geloneze MD); **Department of Medicine and Therapeutics, Hong Kong Institute of Diabetes and Obesity and Li Ka Shing Institute of Health Science, The Chinese University of Hong Kong, Prince of Wales Hospital,**

verified in humans, they suggest that diabetes might not only be a risk factor for a severe form of COVID-19 disease but also that infection could induce new onset diabetes.[8–10] Potential β cell damage caused by the virus leading to insulin deficiency is supported by the observation of Italian colleagues and co-authors of these recommendations who have reported frequent cases of severe diabetic ketoacidosis (DKA) at the time of hospital admission. Another important observation by the co-authors from various centres in different countries affected by COVID-19 is the tremendous insulin requirement in patients with a severe course of the infection. To what extent COVID-19 plays a direct role in this high insulin resistance is unclear. According to the personal experiences of co-authors of this Personal View, the extent of insulin resistance in patients with diabetes seems disproportionate compared with critical illness caused by other conditions.

A second potential mechanism that might explain the link between COVID-19 and diabetes involves the dipeptidyl peptidase-4 (DPP-4) enzyme, which is commonly targeted pharmacologically in people with type 2 diabetes. In cell studies, DPP-4 was identified as a functional receptor for human coronavirus-Erasmus Medical Center (hCoV-EMC), the virus responsible for MERS.[11] Antibodies directed against DPP-4 inhibited hCoV-EMC infection of primary cells. DPP-4 enzyme is an ubiquitously expressed type II transmembrane glycoprotein. It plays a major role in glucose and insulin metabolism but also increases inflammation in type 2 diabetes.[12] Whether these mechanisms also apply to COVID-19 and whether diabetes treatment with DPP-4 inhibitors in clinical practice influences the course of the infection is currently unknown, but, if these mechanisms translate to SARS-CoV-2, the use of these agents could reduce DPP-4 concentrations and could provide therapeutic opportunities for treatment of COVID-19.[12]

Implications on diabetes management

The clinical relevance of the aforementioned mechanisms is currently uncertain, but health-care practitioners should be aware of their implications for patients with diabetes. We have compiled a simple flowchart for the metabolic screening and management of patients with COVID-19 and diabetes or at risk for metabolic disease. This includes recommendations regarding both the need for primary prevention of diabetes as well as the avoidance of severe sequelae of diabetes triggered by unidentified or poorly managed diabetes (figure). Furthermore, special considerations on anti-diabetes drugs commonly used in patients with type 2 diabetes in view of COVID-19 are presented in the panel.

Metabolic and glycaemic control

People with diabetes who have not yet been infected with the SARS-CoV-2 virus should intensify their metabolic control as needed as means of primary prevention of COVID-19 disease. This includes continuation and strict abidance with adequate control of blood pressure and lipids. Wherever possible, remote consultations using Connected Health models should be utilised to reduce exposure. They should also be encouraged to follow general advice from WHO, the CDC, and state and local governments about hand washing and physical distancing.

All patients without diabetes and particularly when at high risk for metabolic disease who have contracted the viral infection need to be monitored for new onset diabetes that might be triggered by the virus. All patients with COVID-19 disease and diabetes require continuous and reliable glycaemic control as suggested in the flowchart.

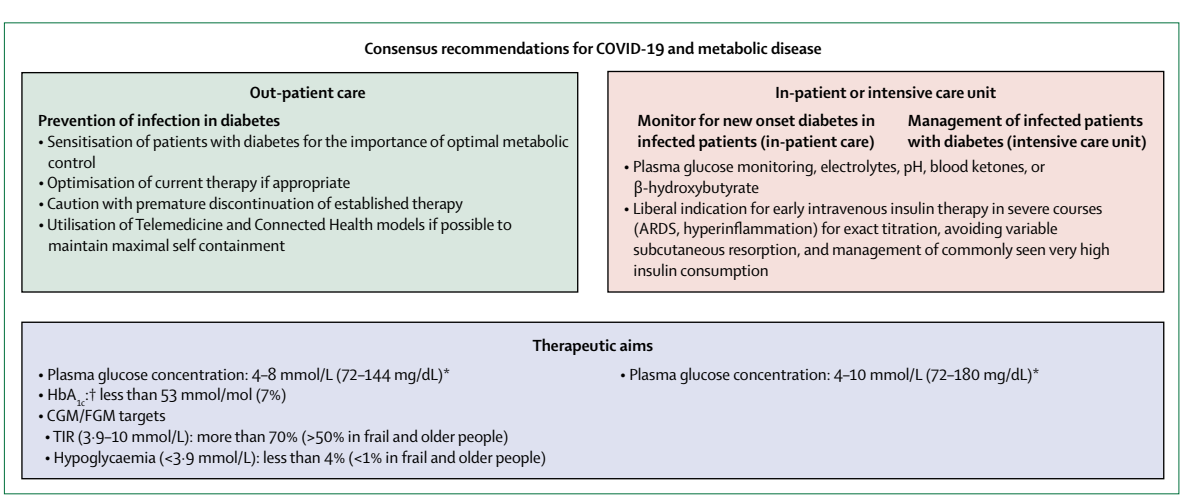

Figure: **Flowchart for metabolic screening and type 1 and 2 diabetes management of patients with COVID-19**
Older patients refers to those aged 70 and above. ARDS=Acute Respiratory Distress Syndrom. CGM=Continous Glucose Measurement. FGM=Flash Glucose Measurement. HbA_{1c}=haemoglobin A_{1c}. TIR=time in range. *Target concentrations for lower plasma glucose can be adjusted to 5 mmol/l (90 mg/dl) in frail patients. †HbA_{1c} testing might not be possible at the time, but previous measurements if available allow for differentiation of chronic and acute decompensation.

Management of hyperglycaemia and associated metabolic conditions

Most patients with type 2 diabetes have other components of the metabolic syndrome including hypertension and dyslipidaemia. Therefore, continuation with an appropriate antihypertensive and lipid-lowering regimen in all these patients is of crucial importance.

Treatment with ACE inhibitors and angiotensin 2 receptor blockers could increase the expression of ACE2, which could accelerate the entry of the virus into the cells.[13] However, as SARS-CoV-2 might impair the protective ACE2/Mas receptor pathway and increase deleterious angiotensin-2 activity, the use of ACE inhibitors and angiotensin 2 receptor blockers could protect against severe lung injury following infection. On the basis of currently available evidence, we recommend that patients should continue with their antihypertensive regimens including ACE inhibitors and angiotensin 2 receptors. This view is endorsed by a recent position statement from the European Society of Cardiology and the Heart Failure Society of America, American College of Cardiology, American Heart Association, who strongly recommended continuation of treatment with ACE inhibitors and angiotensin 2 receptor blockers.[14]

Statins have been shown to restore the reduction of ACE2 induced by high lipids such as low density lipoprotein or lipoprotein(a).[15] The pleiotropic anti-inflammatory effects of statins have been attributed to the upregulation of ACE2. However, although we believe that modulation of ACE2 expression is associated with both infection and mortality rates in COVID-19, statins should not be discontinued because of the long-term benefits and the potential for tipping the balance towards a cytokine storm by rebound rises in interleukin(IL)-6 and IL-1ß if they were to be discontinued. Given the close links between diabetes and cardiovascular disease, we recommend control of lipid concentrations in all patients with COVID-19.

There are certain subgroups of people with diabetes who might require specific consideration. Elevated hemoglobin A_{1c} in people with type 1 diabetes compromises immune function rendering them more susceptible to any infectious disease. These individuals will need more intense monitoring and supportive therapy to reduce the risk of metabolic decompensation including DKA, in particular for those taking sodium glucose co-transporter 2 inhibitors (SGLT2). According to the expertise from the co-authors, an increase in the prevalence of severe DKA in COVID-19 positive patients with established type 1 diabetes has been observed, but this might in part be because of delayed hospital admission. Thus, making patients with type 1 diabetes aware of this complication and re-educating them about typical symptoms, home-measurement of urine or blood ketones, acute behaviour guidelines, and liberal and early inquiry of professional medical advice and sick day rules is crucial. Patients who have undergone transplantation of islets, pancreas or kidney, or those on immunosuppressive therapy will be at particularly increased risk; additionally, the potential effect of coronavirus infection on pancreatic function in this group is unknown and monitoring for a recurrence of insulin requirement in those who are insulin independent after their transplant is important.

The increasing number of patients with type 2 diabetes and concomitant fatty liver disease will probably have an increased risk for a more pronounced inflammatory response including the so-called cytokine storm, and these patients should be considered at increased risk of severe COVID-19 disease. Therefore, screening for hyperinflammation using laboratory trends (eg, increasing ferritin, decreasing platelet counts, high-sensitivity C-reactive protein, or erythrocyte sedimentation rate) are of crucial importance and might also help to identify subgroups of patients for whom immunosuppression (steroids, immunoglobulins, selective cytokine blockade) could improve the outcome.

The majority of patients with type 2 diabetes are living with conditions of overweight or obesity. Body mass index

Hong Kong Special Administrative Region, China (Prof J C Chan MD)**; and Department of Endocrinology and Metabolism, Peking University People's Hospital, Peking University Diabetes Center, Beijing, China** (Prof L Ji MD)

Correspondence to:
Prof S R Bornstein, Department of Medicine III, University Hospital Carl Gustav Carus, 01307 Dresden, Germany
Stefan.Bornstein@uniklinikum-dresden.de

For more information on **CDC COVID-19 guidelines** please see https://www.cdc.gov/mmwr/Novel_Coronavirus_Reports.html

For more information on **COVID-19 in Italy** please see https://www.iss.it/en/coronavirus

Panel: Consideration of potential metabolically interfering effects of drugs in suspected or COVID-19 positive patients with type 2 diabetes

Metformin

- Dehydration and lactic acidosis will probably occur if patients are dehydrated, so patients should stop taking the drug and follow sick day rules
- During illness, renal function should be carefully monitored because of the high risk of chronic kidney disease or acute kidney injury

Sodium-glucose-co-transporter 2 inhibitors

- These include canagliflozin, dapagliflozin, and empagliflozin
- Risk of dehydration and diabetic ketoacidosis during illness, so patients should stop taking the drugs and follow sick day rules
- Patients should avoid initiating therapy during respiratory illness
- Renal function should be carefully monitored for acute kidney injury

Glucagon-like peptide-1 receptor agonists

- These include albiglutide, dulaglutide, exenatide-extended release, liraglutide, lixisenatide, and semaglutide
- Dehydration is likely to lead to a serious illness so patients should be closely monitored
- Adequate fluid intake and regular meals should be encouraged

Dipeptidyl peptidase-4 inhibitors

- These include alogliptin, linagliptin, saxagliptin, and sitagliptin
- These drugs are generally well tolerated and can be continued

Insulin

- Insulin therapy should not be stopped
- Regular self-monitoring of blood-glucose every 2–4 hours should be encouraged, or continuous glucose monitoring
- Carefully adjust regular therapy if appropriate to reach therapeutic goals according to diabetes type, comorbidities, and health status

Connected Health models and Telemedicine should be used to continue regular reviews and self-management education programmes virtually and ensure patients are adherent to therapy.

is an important determinant of lung volume, respiratory mechanics, and oxygenation during mechanical ventilation, especially in the supine position. Therefore, patients with obesity and diabetes could be at specific risk of ventilatory failure and complications during mechanical ventilation. Clinical experience with young patients with obesity and COVID-19 supports this notion. Furthermore, individuals with obesity or with diabetes have an altered innate and adaptive immune response, characterised by a state of chronic and low-grade inflammation with higher concentrations of the pro-inflammatory leptin and lower anti-inflammatory adiponectin.[16] Additionally, obesity is often associated with physical inactivity leading to aggravated insulin resistance. This condition per se impairs immune response against microbial agents including macrophage activation and inhibition of pro-inflammatory cytokines and leads to a dysregulation of the immune response contributing to complications associated with obesity.[17]

Furthermore, SARS-CoV-2 can induce long-term metabolic alterations in patients who have been infected with the virus, as has been reported previously with the SARS virus.[18] Therefore, a careful cardiometabolic monitoring of patients who have survived severe COVID-19 disease might be necessary.

Importantly, we should also bring attention to the subgroup of people with diabetes who work as health-care professionals. Given that COVID-19 might be more prevalent among the sick than is currently being diagnosed, health-care professionals with diabetes should be deployed away from front line clinical duties where possible. For cases in which this is not possible or desirable, high-grade protection or increased protection should be used.

Search strategy and selection criteria

We identified the references for this publication through searches of PubMed for articles published between Apr 29, 2009, and Apr 5, 2020, using combinations of the terms "coronavirus", "COVID-19", "SARS-CoV-2", "nCoV", "diabetes", "risk factors", "severe acute respiratory syndrome", "acute respiratory distress syndrome", and "co-morbidities". We reviewed guidelines for the management of COVID-19 published by WHO, American Diabetes Assiciation, and the US Centers for Disease Control and Prevention. We added articles through searches of the authors' personal files. We also reviewed relevant references cited in retrieved articles. Articles published in English, Italian, and Chinese were included. The final reference list was generated on the basis of relevance to the topics covered in this publication, with the aim of emphasising the multiple challenges the health-care professionals from practitioners to intensive care staff might face in the management of patients with diabetes and at risk of or with COVID-19, and providing practical recommendations for the care of this vulnerable subgroup.

Surgical treatment of type 2 diabetes—metabolic surgery

Provision of elective surgical procedures—including metabolic surgery—is being postponed in many hospitals around the world to increase capacity for in-patient beds and acute care. However, postponing elective metabolic surgery during the outbreak of COVID-19 is advisable regardless of issues of hospital capacity. Patients with type 2 diabetes and obesity are at increased risk of complications of COVID-19,[17] compounding the potential negative influence of surgical stress in the recovery period. Furthermore, although specific data are not available, there are plausible concerns that pneumoperitoneum and the use of haemostatic instruments during laparoscopy (by far the most common approach used in metabolic surgery because of its ability to reduce morbidity and mortality) might lead to viral aerosolisation, thus increasing the risk of transmission of the virus to both patients and staff.

Whether patients with type 2 diabetes who have had metabolic surgery will be protected from adverse outcomes of COVID-19 relative to their peers who have not undergone surgical treatment simply because of better glycaemic control remains unclear.[19] However, metabolic surgery could induce nutritional deficiencies, including reduced absorption of vitamins and micronutrients, which play important roles in the regulation of the immune and stress response.[20] Although there are no data yet to suggest that patients who had metabolic surgery are at greater risk of infection or complications from COVID-19, these patients should receive particular attention and close monitoring.

Special considerations on use of diabetes drugs

Although optimising glycaemic control to reduce the risk of severe COVID-19 disease is important, specific considerations around treatment modality should be made (panel). Lactic acidosis associated with metformin, or euglycaemic or moderate hyperglycaemic diabetic ketoacidosis associated with SGLT-2 inhibitors are rare events; however, we recommend these drugs should be discontinued for patients with severe symptoms of COVID-19 to reduce the risk of acute metabolic decompensation.[21] Importantly, discontinuing these drugs is not recommended prophylactically for out-patients with diabetes without any symptoms of infection or in the absence of evidence for a serious course of COVID-19. Furthermore, at present, no convincing evidence exists to suggest that DPP-4 inhibitors should be discontinued. Further analyses on affected patients with various diabetes treatments and COVID-19 could allow elucidation of the effects of DPP-4 inhibitors.[12] Importantly, if drugs are discontinued, the alternative treatment of choice—in cases for which this option is feasible—is insulin.[21]

Given the multiple stresses associated with COVID-19 including but not limited to respiratory failure, the defects in insulin secretion and the frequent occurrence of diarrhoea and sepsis, most patients will require

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insulin and especially since many cases are reported with very high insulin consumption, this will need to be managed by intravenous infusion.[22] Considerable care is required in fluid balance as there is a risk that excess fluid can exacerbate pulmonary oedema in the severely inflamed lung. Furthermore, potassium balance needs to be considered carefully in the context of insulin treatment as hypokalaemia is a common feature in COVID-19 (possibly associated with hyperaldosteronism induced by high concentrations of angiotensin 2) and could be exacerbated following initiation of insulin.[22]

We do realise that all our recommendations and reflections are based on our expert opinion, awaiting the outcome of randomised clinical trials. Executing clinical trials under challenging circumstances has been proven feasible during the COVID-19 pandemic, and trial networks to provide evidence-based therapies are arising.[23] Investigating subgroups with diabetes and how these relate to COVID-19 outcomes will be important, in particular investigating if some of the various management approaches would be particularly effective in managing diabetes in a COVID-19 context.[24]

Contributors

All authors did the literature search and drafted sections of the manuscript. SRB and BL combined and edited the drafts and supervised the manuscript. BL prepared the panel and figure of the manuscript. All authors subsequently revised the final manuscript.

Declaration of interests

SA reports that she serves on Advisory Boards for Novo Nordisk, Abbott, and Medtronic. All other authors declare no competing interests.

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