BRIEF REPORT

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Therapeutic uncertainties in people with cardiometabolic diseases and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19)

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) has been declared a pandemic by the World Health Organization and sent all countries scrambling to review emergency healthcare provisions. There is global evidence of each nation struggling to effectively manage the number of people being diagnosed with the virus. These are testing times which have not been experienced in recent generations and there are a number of insecurities regarding the management of people with COVID-19 and cardiometabolic diseases. This review highlights the current concerns related to COVID-19 and provides advice in terms of the therapeutic uncertainty and potential adverse harms associated with therapy when managing people, particularly those with cardiometabolic diseases, who have contracted or are at increased risk of contracting COVID-19.

KEYWORDS
type 2 diabetes

Within the space of 3 months severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) has become a global household entity. The speed with which COVID-19 was declared a pandemic by the World Health Organization (WHO) sent each country scrambling to review emergency healthcare provisions. There is global evidence of each nation struggling to effectively manage the number of people being diagnosed with the virus. COVID-19 is a novel RNA virus that has previously not been identified in humans. It is a virus that mainly affects the respiratory tract, causing characteristic symptoms of a fever, dry cough and dyspnoea, with a significant risk of severe complications including requiring intensive care unit support, presenting with acute respiratory syndrome, and death in certain patients.[1] These are testing times which have not been experienced in recent generations and there are a number of insecurities regarding the management of people with COVID-19. The uncertainty in appropriate treatments that has ensued is adding to anxiety amongst healthcare professionals (HCPs). However, we need to rely on current systems and on HCPs to continue to provide advice in terms of the therapeutic uncertainty and potential adverse harms associated with therapy when managing people, particularly those

with cardiometabolic diseases, who have contracted or are at increased risk of contracting COVID-19. This will help in patient care and build trust within this setting. The objective of the present brief report was to summarize and guide clinicians on the interaction of the management of people with COVID 19 with the therapies used in cardiometabolic diseases.

A systematic review and meta-analysis of clinical imaging features and outcomes in confirmed COVID-19 cases in a whole population analysed 18 studies, with the mean age of the patients in the studies being 51.97 years and 55.9% being male. Of these, 36.8% had comorbidities, with the most significant being hypertension (18.6%), cardiovascular disease (CVD; 14.4%) and diabetes (11.9%).[1] Diabetes is associated with multimorbidity, with 90% of people with type 2 diabetes having at least one chronic condition and 25% having four or more chronic conditions.[2] Hypertension is the most common supplementary condition, affecting two-thirds of people with type 2 diabetes. As expected, as the number of chronic conditions increased, there was a significant increase in polypharmacy, with more than half the patients with type 2 diabetes being prescribed six or more medications. Regarding COVID-19, there have been concerns that there is increased mortality in patients with CVD, diabetes, hypertension and cerebrovascular disease. The study, based on 44 672 confirmed cases in China, showed that the case fatality rate was 2.3% (1023 deaths) in the general population, compared to 10.5% in those with CVD and 7.3% in those with diabetes.[3] A further study showed that the most common comorbidities in 140 hospitalized patients with COVID-19 were hypertension (30%) and diabetes (12.1%).[4] These patients therefore need advice from HCPs regarding treatment for their multi-morbidities, require strict isolation measures, and may even require special attention if infected with COVID-19.

The majority of patients with diabetes also have hypertension and there have been recent claims regarding the use of the antihypertensive agents known as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), along with other medications, such as corticosteroids and non-steroidal anti-inflammatory medications, and the associated risks of adverse effects in patients with COVID-19. NHS England and other health authorities have issued statements regarding the use of these medications. ACE inhibitors and ARBs have been implicated as factors to acknowledge in those patients with poorer outcomes attributable to SARS-CoV-2 binding to target cells through ACE2 receptors.[5] These medications have been shown to upregulate ACE2 in animal studies and therefore there are concerns that patients taking these medications are at an increased risk of developing more severe coronavirus infections.[6] Perico et al[7] have stated, however, that evidence suggests ACE2 receptors in the lungs may play a protective role in COVID-19. Furthermore, the European Society of Hypertension, the European Society of Cardiology and a joint statement from the American College of Cardiology, the American Heart Association and the Heart Failure Society of America have also advised treatment with ACE inhibitors and ARBs to continue as per usual guidelines in patients at risk for COVID-19 or in those already diagnosed with COVID-19.[8–10] Currently there are no reliable experimental or clinical data available to

suggest otherwise, and they warn about the risk of stopping these medications suddenly causing acute heart failure and worsening of blood pressure.[10] Furthermore, discontinuation of these drugs and the associated risk of exacerbating heart failure, thus causing symptoms such as breathlessness, will in turn raise anxieties and cause ambiguity as to whether symptoms are infection-related or attributable to the chronic health conditions.[11]

In people with diabetes, it has been advised that HCPs be aware that these patients are at an increased risk of metabolic decompensation, and that if patients are managed at home, HCPs need to ensure they have an increased supply of monitoring equipment for glucose and ketones, adequate medication supplies, and information regarding following stringent social distancing measures.[12] Furthermore, metabolic acidosis has been shown to be a risk in patients with severe COVID-19 infection.[13] This is a particular risk in patients with diabetes on metformin, as metformin can exacerbate lactic acidosis. It has previously been suggested that patients at an increased risk of lactic acidosis should suspend their metformin during their in-hospital stay, and provided with adequate insulin treatment.[14] Similarly, patients on sodium-glucose co-transporter-2 inhibitors who are infected by COVID-19 are at an increased risk of diabetic ketoacidosis (DKA), and it has therefore been recommended that the medication is temporarily stopped if unwell. HCPs should inform patients of signs and symptoms of DKA, and should also emphasize strict adherence to sick day rules.[15]

Poor glycaemic control in patients with or without COVID-19 is associated with an increased risk of infections, especially in the elderly because of the increased risk of complications. Infections associated with diabetes include respiratory tract infections such as pneumonia and tuberculosis. Despite the current lack of evidence of the association of high glycated haemoglobin and increased risk of COVID-19 infections of or complications, this may put people with diabetes at increased risk of COVID-19, and therefore good glycaemic control and medication adherence is vital.[16] People with diabetes and hypertension have multi-morbidities which is associated with poor medication adherence. One meta-analysis of eight studies regarding the association between poor medication adherence and excess mortality in chronic disease showed a mean rate of poor adherence of 37.8%.[17] The study also showed that good adherence was associated with a reduction in hospital admissions and mortality in patients with type 2 diabetes.[17] HCPs therefore need to address this issue, especially during these times, when patients are anxious, which is associated with poor adherence. A meta-analysis of 31 studies concerning depression and medication adherence in the treatment of chronic diseases showed that there was a 1.76 times increased risk of a depressed patient non-adhering to treatment.[18] Patients with diabetes and mental illness may therefore experience a decompensation of their mental illness due to COVID-19, and this may result in decreased medication adherence. These patients need to be re-assured and encouraged by HCPs to take their medications, even with remote consultations or using mobile phone technologies, to improve adherence. Advice needs to be given regarding how stopping these treatments will lead to further morbidity and mortality. Additionally, there

have also been reports of patients with life-threatening conditions such as myocardial infarction, delaying medical attention due to the COVID-19 outbreak.[19] It is paramount to address these issues and ensure appropriate management of patients with chronic conditions, especially those associated with high mortality.

For corticosteroid use, in previous outbreaks of severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV), corticosteroids were used extensively.[20] Nonetheless, the WHO has given guidance against the use of corticosteroids in COVID-19 because of the possibility of further harm, unless these medications are needed for other health conditions.[21] Therefore, those with adrenal insufficiency, such as Addison's disease or secondary adrenal failure, should continue to take medication, and to follow sick-day rules if they become unwell, without delay.[22] More importantly, they should also follow social distancing measures indefinitely.

We are still in the early phases of clinical trials, and future research into the use of the medications above, along with others, will hopefully be undertaken quickly, to assist in these distressing times. The National Institute for Health and Care Excellence (NICE) has recently published the first rapid COVID-19 guidelines to help maximize safety for patients and staff. There is also some positive evidence on the use of certain medications in the treatment of COVID-19, including chloroquine and hydroxychloroquine. A systematic review concluded that chloroquine appears to be effective in preventing SARS-CoV-2 replication and that, based on its known safety, clinical research on chloroquine in patients with COVID-19 is justified.[23] One small study showed that hydroxychloroquine treatment was significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect was reinforced by azithromycin.[24] We must however proceed with caution with the use of hydroxychloroquine until further data become available as patients with SARS-CoV-2 complications can present with hypotension, tachycardia, bradycardia, arrhythmia or even sudden cardiac death.[25] These may also be associated with hydroxychloroquine since it can prolong QTc interval, particularly in patients with heart failure and previous myocardial infarction. It would therefore be advisable to periodically monitor ECG during this treatment.[26]

COPCOV is a randomized controlled trial that will be assessing chloroquine/hydroxychloroquine prevention of coronavirus disease in the healthcare setting (Clinicaltrials.gov: NCT04303507). This will hopefully provide more data to reassure clinicians about the benefits and safety of this agent. Patients with diabetes will also need to be carefully monitored as there is recent evidence from a systematic review that hydroxychloroquine has potential antidiabetic properties with the potential risk of hypoglycaemia. This, in turn, is associated with increased risk of cardiac arrhythmia, which is associated with increased cardiovascular events and mortality.[27]

Whilst these treatments are still in exploration, it is most important at this time that patients on cardiometabolic and endocrine medications are supported and encouraged to adhere to treatment regimes, obtain support to reduce mental health issues, and are advised to adhere to lifestyle recommendations to reduce the risk of other detrimental health effects and further unnecessary admissions to the already overstretched healthcare system.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Idea proposal by K.K., S.K. and N.K. composed the initial draft, S.S. reviewed and corrected the draft.

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