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COMMENT

COVID-19 and hypertension: risks and management. A scientific statement on behalf of the British and Irish Hypertension Society

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Hypertension is the single largest global contributor to disability-adjusted life years lost [1]. The majority of the population aged over 60 years have hypertension [2], and it has been suggested that they may be at increased risk from the effects of COVID-19. Despite this, and perhaps due to its ubiquity in the older population, current UK Government guidance does not identify people with hypertension as 'at risk' [3], however, other bodies such as the British Heart Foundation and the Health Service Executive in Ireland do [4, 5]. This article seeks to summarise and interpret the current evidence for and against an increase in COVID-19 risk and severity for those with raised blood pressure, and discusses the implications for the choice of anti-hypertensive treatment.

Early small case series did not indicate an excess of hypertension in people admitted to hospital with COVID-19 [6]. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team published a large case series from China; they found an overall case fatality rate of 2.3% (1023 of 44,672 confirmed cases), which increased to 6.0% for people with hypertension [7]. These data were reported without adjustment for age. Both COVID-19 case fatality rates and hypertension prevalence increase with age, reaching 8.0% and over 50% respectively for the 70–79 year age group [2]. New emerging evidence from the largest epidemiological study to date, examining over 17 million health records in England suggests that hypertension or a recorded blood pressure ≥140/90 mmHg taken together are not associated with COVID-19 in-hospital mortality after full adjustment: Hazard Ratio (HR) 0.95, (95% confidence interval (CI) 0.89–1.01). In sensitivity analyses, diagnosed hypertension alone was associated with slightly increased risk (HR 1.07, 95% CI 1.00–1.15) which might reflect residual confounding due to the strong age-related association [8].

Several other small case series that examine hypertension prevalence with and without severe COVID-19 have appeared in the literature [9]. In March 2020, a study-level meta-analysis of 2552 confirmed COVID-19 patients reported a pooled odds ratio (OR) of 2.49 (CI: 1.98–3.12; 11 studies) for severe disease in the presence of hypertension, with low heterogeneity between studies ($I^2 = 24\%$). The OR for death was similar and weak evidence from meta-regression suggested that hypertension might be a clinical predictor of COVID-19 severity in people aged over 60 [10]. Likewise, a retrospective cohort analysis of 191 patients treated in hospital in China (not included in the meta-analysis) confirmed apparent high mortality in patients presenting with hypertension: 48% versus 23% of survivors [11].

Similar findings were reported with previous coronavirus infections, such as severe acute respiratory syndrome and Middle East Respiratory Syndrome [12, 13]. The mechanism by which hypertension leads to increased risk from COVID-19 is undoubtedly complex and may well relate to underlying co-morbidity. The prognosis for people with hypertension is markedly worse when COVID-19 infection is complicated by myocardial injury and in the presence of cardiovascular disease [8, 14]. End organ damage and cardiovascular events are associated with poorer control of high blood pressure, and mean blood pressure rises with age [15, 16]. It seems plausible, therefore, that older age, poorer blood pressure control and cardiovascular disease can

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explain the observed associations between age, hypertension and severity of COVID-19 infection.

Are anti-hypertensive medications a risk for severity of COVID-19?

The viral structural spike (S) protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry to cells; this has led to suggestions that use of ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) may be implicated in poorer outcomes with COVID-19 [17, 18]. Whilst gaining much publicity, with attendant worry for patients and clinicians, this theory has been debated and ACE inhibitor and ARB treatment has also been associated with improved outcomes in some reports [19, 20]. Polymorphism in expression of the ACE2 receptor gene in association with hypertension and excess cardiovascular risk in ethnic minority groups has also been suggested as a partial explanation for observed excess mortality from COVID-19 in these populations [21, 22]. The National Institute for Health and Care Excellence are currently undertaking a rapid review of this topic [23]. Recent observational studies of confirmed COVID-19 patients have increased confidence that these drugs are not harmful: a case-control study of 6272 COVID-19 patients in Lombardy, Italy, matched to 30,759 controls, confirmed higher use of ACE inhibitors and ARBs in patients than controls, but after adjustment for greater prevalence of underlying cardiovascular disease, there was no evidence that ACE inhibitors (OR 0.96; 95% CI 0.87–1.07) or ARBs (OR 0.95; 95% CI 0.86–1.05) were associated with different risks of COVID-19 [24]. Two large retrospective cohort studies have also been published; one found no association between ACE inhibitor or ARB use and a positive coronavirus test in 18,472 people from Ohio and Florida (weighted OR 0.97; 95% CI 0.81–1.15), whist another study of 12,594 electronic health records from New York, found no association between *any* anti-hypertensive medication (ACE inhibitors, ARBs, beta-blockers, calcium-channel blockers, or thiazide diuretics) and increased likelihood of either a positive coronavirus test or an increased risk of severe COVID-19 illness [25, 26].

It is important to recognise that, to date, no randomised trial evidence exists to demonstrate either benefits or risks of continuing ACE inhibitors or ARBs on the incidence or outcomes of COVID-19. It must also be acknowledged that these observational data carry risks of residual confounding [27]. One retrospective cohort study found a positive association between ACE inhibitor or ARB use and admission to hospital (OR 1.93; 95% CI 1.38–2.71) or intensive care (OR 1.64; 95% CI 1.07–2.51) in small subgroup analyses ($N = 421$ and 161, respectively) [26]. These secondary outcomes are rightly viewed with caution due to the potential for residual confounding by co-morbidity and also imprecision (as evidenced by wide confidence intervals) due to small sample sizes [28]. Nevertheless, these studies taken together convey a consistent message of absence of harm associated with anti-hypertensive medications during infection with coronavirus, and clinical equipoise should therefore apply. Whilst these drugs appear increasingly unlikely to worsen COVID-19 severity, the consequences of poor blood pressure control, under normal circumstances, are well documented [16]. Consequently, the British and Irish Hypertension Society (BIHS), and our European and International partner societies, have issued clear position statements advising against cessation of anti-hypertensive therapy on the grounds of concern over risks with COVID-19 (available at: https://bihsoc.org/bihs-statement-on-acei-arb-and-covid19/) [29]. Current evidence does not support published opinions that doctors may consider stopping treatment with ACE inhibitors and ARBs in well-controlled patients with mild (Stage 1) hypertension and coronavirus infection [30]. The unintended consequences of discontinuing effective treatments for hypertension, without a suitable replacement titrated against appropriate blood pressure measurements and under direct medical supervision, could put patients at increased cardiovascular risk. In addition, managing such titration at a time when primary care is prioritising acute illness over routine contacts (including surgery blood pressure checks), makes the proposed strategy impractical and risks further diluting access to care.

So, what can we say to hypertensive patients who may be anxious about taking anti-hypertensive medication and about their risks from infection during the COVID-19 pandemic?

The evidence base remains incomplete, so strong recommendations are difficult. However, people with complications of hypertension, such as ischaemic heart disease, are already regarded as being at high risk from COVID-19. It seems reasonable to advise those with poorly controlled hypertension (i.e. blood pressure above guideline targets), particularly if prolonged, to also consider themselves to be at elevated risk, and, therefore, to follow appropriate social distancing advice [3]. For younger individuals with hypertension, there is an association of obesity with COVID-19 severity among Western populations [2, 8, 31, 32]. Generally, for people with good control of blood pressure, risks of undiagnosed cardiovascular disease are low, and they could therefore be reassured. All hypertensive patients

should be strongly reassured that continuing their current medications is both safe and desirable.

We should support all our hypertensive patients in continuing to strive for, and maintain, good blood pressure control by continuing to take their medications as prescribed, and by endeavouring to follow and maintain sensible lifestyle choices, including regular exercise [3].

Large numbers of people are being affected by COVID-19 with potentially profound consequences, however, their continued surveillance will also provide further data that will help us to understand the true risk from elevated blood pressure, its treatment and co-morbidities, on outcomes of the disease. Careful and continuous research is vital for an understanding of the mechanisms underlying any additional risk from hypertension with COVID-19, and to determine the best and safest ways to treat those with severe manifestations of disease. Our patients are best served when their treatment is based on available evidence rather than speculation, and the growing body of evidence suggests that continuation of ACE inhibitors and ARBs during the current COVID-19 pandemic is safe.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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