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Title

Observational data during the covid-19 pandemic:
opportunity with uncertainty

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Authors

Sam Straw MBChB

Witte KK MD†

Affiliations

Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK

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† Corresponding author:

Dr Klaus K Witte

Head of Dept of Population and Clinical Science,

Leeds Institute of Cardiovascular and Metabolic Medicine

LIGHT building, University of Leeds

Clarendon Way, Leeds, UK, LS2 9JT

Phone: (+44) 113 3926108

E-mail: k.k.witte@leeds.ac.uk

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This editorial refers to “Risk of Severe COVID-19 Disease Associated with Angiotensin Converting Enzyme Inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB) in England: Population Cohort Study including 8.3 Million People”, by Hippisley et al. published in *Heart* (2020).

The exponential growth of the coronavirus disease 2019 (COVID-19) pandemic has led to an unprecedented hunger for information in the medical community, the media and the wider public. In response there has been an explosion of publications including more than 21,000 references on PubMed to 'COVID-19' since January 2020. Many of these are observational data of hospitalised patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), exploring demographics or proposed risk factors including pre-existent cardiovascular disease (including diabetes mellitus),[1] obesity,[2] and non-white ethnicity.[3] The low rate of testing in communities in many countries (including the UK) means that data are mostly limited to hospitalised patients such that a valid picture of risk and outcomes relevant to the wider population is difficult to establish. Specifically, there remains uncertainty about the role of medications inhibiting the renin-angiotensin-aldosterone system (RAAS), based on initial reports of their association with poor outcomes in COVID-19.[4] Possible explanations for this include underlying cardiovascular comorbidities in patients taking these medications, and that the entry of SARS-CoV-2 into cells is permitted by the angiotensin-converting enzyme 2 (ACE2) receptor.[5]

Can we trust observational data?

Observational data are challenging to work with, requiring care to avoid the pitfalls of observed and hidden interactions and biases whilst balancing the need to make the results accessible to non-statisticians. The reliability of conclusions drawn from observational data depend not only on its interpretation, but upon the data themselves. Uncertainty in only one aspect can lead to long term damage to public trust and confidence in science as highlighted by the consequences of the retraction of papers from two high-profile journals[6,7] leading to the halting of a critical clinical trial.

Aside from sufficient sample size, it is critical that datasets are from contemporary and relevant populations and use reliable sources. Initial reports from China provided crucial information on this emerging disease, however demographic differences including ethnicity, younger age and lower

prevalence of co-morbidities mean that the generalisability to developed European countries is limited.[8]

The COVID-19 pandemic highlights our tendency to value recently acquired information (availability bias) from anecdote, expert opinion and rapidly conducted observational studies which, especially in the question over RAAS inhibitors, contrasts with the evidence obtained over decades from multiple randomised controlled trials (RCT), including many thousands of patients, demonstrating the safety and efficacy of these medications for a variety of cardiovascular conditions. Nevertheless, in a rapidly changing environment, and when accepted rules are followed, observational data can help inform physicians and policymakers where a RCT is not possible or ethical, and, in the case of the COVID-19 pandemic, whilst effective therapies or vaccines remain a distant prospect.[9]

Assessing the risks with antagonists of the renin angiotensin system: start at the beginning

The UK is in a unique situation to provide robust and unbiased observational community-based data from all points in the patient pathway. The UK National Health Service is the single provider of free at the point of access medical care and a duopoly of Egton Medical Information Systems (EMIS) and SystmOne from The Phoenix Partnership cover more than 90% of primary care practices.[10] This uniformity of approach has previously delivered reliable information on cardiovascular risk prediction.[11] The results included in this issue of *Heart*, from a dataset consisting of more than 8 million patients registered on EMIS, provide the reassuring information that patients prescribed angiotensin-converting-enzymes inhibitors (ACEi) and angiotensin-receptor-blockers (ARB) are at lower risk of infection with COVID-19 despite higher rates of cardiovascular co-morbidity.[12] Although the hazard ratio was lowest for white patients, the pattern is mirrored in other ethnicities, except Caribbean and Black-African groups.

These data draw a line under early suggestions of increased risk associated with these agents,[13] showing that antagonists of the RAAS are not *per se*

associated with an increased community risk of COVID-19. This should reassure physicians and patients that these vital medications are not implicated in COVID-19 and should not be stopped.

What is severe disease?

On the other hand, although neither ACEi nor ARBs were associated with an increased risk of severe disease, defined as admission to the intensive care unit (ICU), we lack the mean age and co-morbidities of patients of different ethnicities to help us determine whether this is a valid conclusion. For example, white ethnicity and people older than 80 years had a lower rate of ICU admission, but it is unclear whether this is due to lower rates of severe disease or due to proactive decision making about the futility of mechanical ventilation for elderly, frail and multi-morbid patients. Paradoxically, without mortality data, a higher rate of ICU admission might be associated with *better* prognosis compared to those who deteriorated in whom escalation of care was considered inappropriate.

Data from Leeds Teaching Hospitals, which is the largest NHS trust in the UK, highlight this potential pitfall. During the COVID-19 pandemic, admitting physicians were encouraged to consult with patients regarding decisions about escalation of treatment and cardiopulmonary resuscitation in recognition of the potential for deterioration. These discussions were documented for 93% of hospitalised patients who tested positive for SARS-CoV-2. Of the 70% of patients in whom the decision was made that ICU care was inappropriate, 58% were 80 years or older and the majority (92%) were white. On the other hand, a positive decision to escalate treatment (should it be required) was 5.7 times more likely to be made for non-white patients, who were on average younger (58.0±15.4 vs 74±16.0 years). In an environment where advance directives are systematically assessed, ICU admission is therefore not a reliable indicator of disease progression or severe COVID-19.

Hence further analyses including mortality data are required to provide clarification on whether ACEi and ARBs offer survival benefit in patients with

severe COVID-19 and hypertension,[14] or diabetes mellitus[15] and the authors of the present manuscript are also well placed to help determine our approach to Caribbean and Black-African patients taking ACEi and ARBs. Each of these analyses must include the confounder of treatment-escalation decisions in multi-morbid patients presenting with severe COVID-19 although one challenge will be that few electronic healthcare records will include easily accessible and standardised information on ceiling-of-care decisions.

The big picture

The SARS-COV-2 pandemic is a test of society, of healthcare systems, of scientific integrity and of human nature. It is the most recent reminder that healthcare is only one aspect of health[16], that the cardiovascular system is not the same across ethnicities, that good supportive care in the absence of specific therapies is essential, and that the independent scientific process based upon precise peer review must be protected,[17] even when authors and editors are under immense pressure.

Moving forwards, fewer high-quality publications such as the data presented in this issue of *Heart* would serve us and our patients better.[18] To achieve this we need to progress to a worldwide approach that includes conformity of data provenance with the aim of high quality, unbiased, detailed datasets of appropriate sample size. When analysed robustly, with careful descriptions of uncertainty, observational data can provide important information to design and test the efficacy of complete pathways of health and social care beyond the expensive, cumbersome and artificial approach of RCTs. The UK is well positioned to lead this drive and although this will require a change of approach by policymakers, clinicians and the public, it has the potential to reap lasting benefit from the most challenging healthcare situation in generations and prepare ourselves for an uncertain future.

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