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Review Article

Fallacies in medical practice: Renin-angiotensin-aldosterone system inhibition and COVID-19 as a Paradigm



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ABSTRACT

In emergency situations, such as during the coronavirus disease 2019 (COVID-19) pandemic, medical community looks for quick answers and guidance. Under these circumstances, experts instead of admitting ignorance, feel obliged to give an answer, often pressurized by political or other authorities, even when such an answer is unavailable. Under these circumstances, publications based on fallacious reasoning are virtually unavoidable. In the present review, we summarize examples underlying fallacious reasoning recommendations regarding treatment with Renin-Angiotensin-Aldosterone inhibitors (RAASi) in the COVID-19 context. Most scientific societies emphasize that RAASi use is safe and that these agents should not be discontinued, based mainly on the results of observational studies (OSs) and occasionally preprints, as relevant randomized controlled trials (RCTs) are currently lacking. However, over the past 4 decades, results from successful RCTs have repeatedly proved that practices based on OSs were wrong. Lack of RCTs results in uncertainty. In this setting, the physician's wisdom and knowledge related to pathophysiologic mechanisms and effect of pharmacologic agents become even more important as they may limit fallacies. Based on these principles, in diseases (e.g., mild, or moderate arterial hypertension, etc.) where equally effective alternative therapies to RAASi are available, these therapies should be applied, whereas in diseases (e.g., heart failure, diabetic kidney disease, etc.), where equally effective alternative therapy compared to RAASi is not available, RAASi should be used. Admittedly this strategy, like all the other recommendations, is not based on solid evidence but is intended to be individualized and follows the Hippocratic "Primum non nocere".

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"Medicine is the science of uncertainty and the art of probability" Sir William Osler

1. Introduction

Physicians when practicing medicine strive to achieve perfection and avoid errors. Error, however, is human and unavoidable. Thus, physicians being human make mistakes, and when an error

occurs the patient may suffer. While errors from one physician may affect one or a few patients, publications based on false assumptions may result in medical errors that affect hundreds of thousands of patients; these errors occur in patients in whom the authors were not directly involved in their care. Each author, and especially authorities issuing guidelines and position statements, should keep this fact in mind and should not hesitate to admit ignorance when solid information is not available.¹ There are several examples of such errors in medical history, but unfortunately, instead of learning from previous mistakes, we have learned only one thing, that is, how to repeat these mistakes. Such errors may be seen more often in emergency situations²⁻⁴, such as during the coronavirus disease 2019 (COVID-19) pandemic, where the medical community looks for quick answers and guidance. In this case, experts participating in committees, instead of being honest and admit ignorance (as Socrates stated "I know one thing that I know nothing"), feel obligated and in certain instances may be

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pressurized by political or other authorities to provide an answer, even when such an answer is not available.

Under these circumstances, publications based on fallacious reasoning are virtually unavoidable. Though fallacies can be found in all areas of clinical practice and under several circumstances, this brief review will focus on the fallacies related to the use of Renin-Angiotensin-Aldosterone inhibitors (RAASi) during the COVID-19 pandemic.

2. COVID-19 and RAASi

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) that causes COVID-19 enters human cells by binding its viral spike protein to the membrane-bound form of the angiotensin-converting enzyme (ACE) 2.⁵ This has raised concerns that RAASi, such as ACE inhibitors (ACEi), angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA), which increase membrane-bound ACE2 may be harmful in the presence of COVID-19.^{6,7} However, professional scientific societies and experts discouraged discontinuation of RAASi during the COVID-19 pandemic.^{8–10} These recommendations were frequently based on fallacies.

Fallacies are common errors in reasoning. Although it is difficult to classify, in modern studies, fallacies can be distinguished as formal and informal.¹¹ Formal (or deductive) fallacies occur when the conclusion does not follow a previous statement from which another is inferred or follows as a conclusion (premise). Though the reasoning in formal fallacies appears logical, it is always wrong. A reasoning process from which to reach a “logical” conclusion often follows the pattern: (1) RAASi are beneficial in arterial hypertension; (2) COVID-19-positive elderly subjects often suffer from arterial hypertension; and therefore (3) RAASi are beneficial in COVID-19-positive elderly subjects with arterial hypertension. In this case, the conclusion is wrong (formal fallacy) as it is possible that RAASi may be dangerous to COVID-19 positive elderly subjects with arterial hypertension as they increase tissue ACE2, which is the SARS-CoV-2 entrance receptor.

Informal (or inductive) fallacies are endless. In the informal fallacies, the statement or claim is not supported with adequate reasons for acceptance. A strong inductive argument follows this pattern: (1) There is lack of evidence that RAASi increase risk in COVID-19, and therefore (2) RAASi are safe in COVID-19.

3. RAASi and formal fallacies

Several examples of formal fallacies related to COVID-19 and RAASi are presented.

A typical example of formal fallacy is found in the paper of Kuster et al.,⁹ where the authors state: “Clearly, much more research is needed to clarify the multifaceted role of the RAAS (renin-angiotensin-aldosterone system) in connection with SARS-CoV-2 infection. Although there is data from animal studies suggesting potentially deleterious effects of the RAAS, prove-of-concept in humans is still lacking. Similarly, a few animal and human studies suggest upregulation of ACE (angiotensin-converting enzyme) 2 in response to RAAS inhibition through a yet to be identified mechanism, but whether this increases viral load in a critical way and how viral load per se relates to disease severity remain unknown”. Despite admitting the lack of knowledge, the authors confidently conclude that “based on currently available data and in view of the overwhelming evidence of mortality reduction in cardiovascular disease, ACEi and ARB therapy should be maintained or initiated in patients with heart failure, hypertension, or myocardial infarction according to current guidelines as tolerated, irrespective of SARS-CoV-2. Withdrawal of RAAS inhibition or preemptive switch to

alternate drugs at this point seems not advisable since it might even increase cardiovascular mortality in critically ill COVID-19 patients”.

Another example of a formal fallacy can also be found in the position statement by Vaduganathan et al., in which the authors state,⁸ “Given the common use of ACE inhibitors and ARBs worldwide, guidance on the use of these drugs in patients with Covid-19 is urgently needed. Here, we highlight that the data in humans are too limited to support or refute these hypotheses and concerns. Specifically, we discuss the uncertain effects of RAAS blockers on ACE2 levels and activity in humans, and we propose an alternative hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury. We also explicitly raise the concern that withdrawal of RAAS inhibitors may be harmful in certain high-risk patients with known or suspected Covid-19”. After this introductory statements the authors concluded, “On the basis of the available evidence, we think that, despite the theoretical concerns and uncertainty regarding the effect of RAAS inhibitors on ACE2 and the way in which these drugs might affect the propensity for or severity of Covid-19, RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, are being evaluated for, or have Covid-19 (see text box), a position now supported by multiple specialty societies”.

Another example of a formal fallacy can be found in a recent statement by the European Medicines Agency (EMA)¹² (10 June 2020 EMA/284513/2020) that states, “Recent observational studies of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs, also called sartans) have not shown an effect of these medicines on the risk of becoming infected with severe acute respiratory syndrome coronavirus 2 (the virus causing COVID-19) and do not indicate a negative impact on the outcome for patients with COVID-19 disease. EMA therefore reiterates its previous advice that patients should continue to use ACE inhibitors or ARBs as advised by their doctors”. The references on which the EMA base their statement include: (1) retrospective and observational studies (OSs); (2) studies with a low sample size or preprints; (3) studies not supporting the safety of RAASi; and (4) studies supporting the safety of RAASi but emphasizing that caution is required in the interpretation of findings. Thus, the EMA recommendation is not supported by the premises and is a typical example of a formal fallacy.

4. RAASi and informal fallacies

Examples of informal fallacies related to COVID-19 and RAASi are outlined below.

4.1. Red herring fallacy

This fallacy is diverting attention from the real issue by focusing on an issue having relevance only on the surface. A typical example of a “red herring fallacy” is found in a recent paper by Sama et al.,¹³ in which the authors concluded, “In patients with heart failure, plasma concentrations of ACE2 were higher in men than in women, but use of neither an ACE inhibitor nor an ARB was associated with higher plasma ACE2 concentrations. These data might explain the higher incidence and fatality rate of COVID-19 in men, but do not support previous reports suggesting that ACE inhibitors or ARBs increase the vulnerability for COVID-19 through increased plasma ACE2 concentrations”.¹³ This conclusion is incompatible with existing knowledge regarding ACE2 and SARS-CoV-2 vulnerability. Functionally, there are two forms of ACE2. The full-length ACE2 contains a structural transmembrane domain, which anchors its extracellular domain to the plasma membrane.¹⁴ The extracellular domain has been demonstrated as a receptor for the spike (S) protein of SARS-CoV, and recently, for SARS-CoV-2. The soluble

(plasma) form of ACE2 lacks the membrane anchor and circulates in small amounts in the blood. It has been proposed that this soluble form may act as a competitive interceptor of SARS-CoV and other coronaviruses by preventing binding of the viral particle to the surface-bound full-length ACE2.^{14,15}

4.2. Argument from ignorance (*Argumentum ad Ignorantiam*)

One commonly employed type of fallacy is the argument from ignorance. There is no evidence that therapy with RAASi increases the risk of coronavirus disease; thus, the assumption that such therapy increases the risk should not be true.

A typical example of argument from ignorance is found in the statement by the European Society of Cardiology Council on Hypertension that states, “The Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence (i.e., lack of evidence) to suggest that treatment with ACEi or ARB should be discontinued because of the COVID-19 infection”.¹⁶ When this statement was made (13 Mar 2020), even the results of OSs were not available.

4.3. Extrapolation from One Condition to Another (*False dilemma/false dichotomy*)

This type of fallacy fails by limiting the options to two when in fact there are several more options. For example, “RAASi increases the risk in hypertensive patients in the context of COVID-19, or it does not.” This is a true dilemma, since there are really only two options in this case. It would be fallacious, however, to state, “RAASi increases the risk in hypertensive patients and patients with heart failure (HF) in the context of COVID-19, or it does not.” RAASi may, for example, increase risk in hypertensive patients and decrease risk in patients with HF in the context of COVID-19, as these two patient groups significantly differ in several aspects. For example, compared with HF, outcomes are significantly better in patients with hypertension, and there are alternative therapies for the treatment of arterial hypertension other than RAASi, whereas therapeutic options for HF are limited.^{17,18} A typical example of false dilemma is found in the paper by Danser et al., which states,¹⁹ “We therefore strongly recommend that patients who are taking ACE inhibitors or ARBs for high blood pressure, heart failure, or other medical indications should not withdraw their current treatment regimens unless they are specifically advised to do so by their physician or healthcare provider.”

4.4. Hasty generalization

A hasty generalization usually occurs when there is a rush to reach to a conclusion and make recommendations without having sufficient evidence. Scientists are often obligated to make recommendations about complex problems in a rush and often without evidence originating from appropriate clinical trials.

A typical example is found in a recent editorial by Jarcho et al.,²⁰ that states, “Taken together, these three studies (one of the studies was subsequently retracted) do not provide evidence to support the hypothesis that ACE inhibitor or ARB use is associated with the risk of SARS-CoV-2 infection, the risk of severe COVID-19 among those infected, or the risk of in-hospital death among those with a positive test. Each of these studies has weaknesses inherent in observational data, but we find it reassuring that three studies in different populations and with different designs arrive at the consistent message that the continued use of ACE inhibitors and ARBs is unlikely to be harmful in patients with COVID-19”.²⁰

4.5. Appeal to Authority (*argumentum ad verecundiam*)

This fallacy seeks to secure acceptance of the conclusion on the grounds of its endorsement by persons whose views are held in general respect and happens when authority is misused. Like many of the other fallacies in this list, the *argumentum ad verecundiam* is difficult to define. The opinion of the authorities should be respected, but authorities also have an obligation to make statements carefully, and most importantly when evidence is not available to publicly admit it. When everyone “takes their word for it” without supporting evidence, then this can be a problem. Statements of authorities in situations of uncertainty can have negative consequences for decision-making, quality of care, and outcomes on hundreds of thousands of patients. We believe that this informal fallacy played an important role in the acceptance by prestigious medical journals of two recently retracted studies that suffered from easily recognizable flaws.^{21,22}

5. Shortcomings of OSs and strengths of RCTs

Although randomized controlled trials (RCTs) are not infallible, they remain the gold standard to define whether a therapy is better than placebo. In contrast, there are problems related to OSs, the majority of which are related to selection bias due to the lack of randomization.²³ To overcome these problems, complex statistical analyses are used, such as propensity matching. However, all these corrections and adjustments cannot replace randomization.²⁴

Over the past 4 decades, results from successful RCTs have repeatedly proved that practices based on OSs were wrong.²⁴ Two examples are outlined. One example is hormone replacement therapy in post-menopausal women and the other example is beta-adrenergic blockade therapy in patients with HF and preserved ejection fraction (HFpEF). In the Women’s Health Initiative (WHI; n = 151,870), the outcome of hormone replacement therapy was different in OSs compared to RCTs. OSs suggested that hormone replacement therapy in post-menopausal women had beneficial effect on reducing cardiovascular events after adjusting for confounding factors and stratifying on factors that were hypothesized to modulate the effects of hormone therapy. In contrast, an RCT indicated that hormone replacement therapy was harmful.²⁵ Likewise, beta-adrenergic blockade therapy in patients with HFpEF in 15 OSs (n = 26,211) was shown to reduce mortality, but in two RCTs (n = 888), it was not found to decrease mortality.²⁶ As a result, the guidelines do not recommend beta-adrenergic blockers for the treatment of HFpEF.

In conclusion, the vast majority of current studies regarding the safety of RAASi in the COVID-19 era have to be viewed in the context of a retrospective observational design. Though investigators used standard techniques in an attempt to reduce bias, it should be mentioned that OSs cannot replace RCTs (Table 1).

Clinical implications

“Where is the wisdom we have lost in knowledge?

Where is the knowledge we have lost in information?” -T.S. Eliot

Prior to the development of clinical practice guidelines in 1984, medical practice was based mostly on knowledge related to pathophysiologic mechanisms, effect of pharmacological agents on the human body, and the physician’s “wisdom” (i.e., clinical experience, medical ethics, and common sense). Wisdom of the physician is developed and maintained over time by solving clinical problems and facing clinical situations on a daily basis over a long period of

Table 1
Summary with the main conclusions

Physicians when practicing medicine should strive to achieve perfection and avoid errors. However, error is human and unavoidable.
Fallacies are common errors in reasoning and can be distinguished as formal and informal. They frequently occur when researchers work under pressure to give answers.
Clinical research in the era of the lethal COVID-19 pandemic is predominantly based on observational studies
Randomized controlled trials remain the gold standard to define whether a therapy is better than placebo.
The results from successful well-done randomized clinical trials have repeatedly proved that practices based on observational studies are wrong.
The majority of studies examining the safety of the Renin-Angiotensin-Aldosterone inhibitors use in the COVID-19 era are observational.

time; there is no substitute for this.²⁷ As Montaigne stated, “We can be knowledgeable with other’s men knowledge, but we can’t be wise with other men’s wisdom”. Common sense, which could be inherited and/or can be acquired with continuous training, means paying attention to the obvious, accepting responsibility, recognizing your own mistakes, avoid repeating the same mistake, recognizing your limitations, and following the continuous evolutions of Medicine.

The same rules should be applied in the use of RAASi in the context of COVID-19 as written suggestions on this issue are based only on observation and not on RCTs (**Graphical abstract**). In this setting the physician’s wisdom and knowledge related to patho-physiologic mechanisms and effect of pharmacologic agents become even more important. On the basis of these principles, the following suggestions can be made. In disorders and diseases (e.g., mild, or moderate arterial hypertension, other) where equally effective alternative therapies to RAASi are available, then these therapies should be applied, since the interactions between ACE2 receptors and COVID-19 are not yet precisely defined. On the other hand, in disorders and diseases (e.g., heart failure, diabetic kidney disease, other), where equally effective alternative therapy compared to RAASi are not available, then RAASi should be used.²⁸ *Admittedly this strategy, like all the other recommendations on this issue, is not based on solid evidence, but is intended to be individualized, and in this regard, differs from the “one size fits all” approach. Moreover, it follows the Hippocratic “Primum non nocere” that today’s physicians have come to understand subconsciously in its appropriate context.*

Clinical directions

On the basis of the discussions related to fallacies, it is proposed that the same approach as outline in the section “Clinical Implications”, should be applied to all diseases/disorders by physicians in clinical practice when solid information is not available.

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Competing Interests

The authors declare no competing interests related to the content of the manuscript.

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