RAASI, NSAIDs, antidiabetics, and anticoagulants: More data needed to be labeled as harmful or neutral in SARS-CoV-2 infection

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We read with great interest the data analysis by Cippà et al. (1) on the associations between in-hospital mortality and drugs taken by the patients with COVID-19 disease for various comorbidities. The method chosen by the authors to examine the effects of drugs led data mainly on renin–angiotensin–aldosterone system inhibitors (RAASI), yet they also discuss other molecules used for several comorbidities, and the resulting messages become clinically very important.

The strong evidence of the utility of RAASI emerging from the study reinforces the physiological and biological hypothesis suggesting certainly no harm and possibly a protective action (2) of these drugs in COVID-19 patients.

The data on the protective action of anticoagulants also represent a strong message, given the angiopathic nature of COVID diseases. Although randomized trials should lead to clearer algorithms (3), and given the recognized efficacy of heparin, a recent study on a very large national database (>100,000 patients) showed no protection against mortality in COVID-19 patients who were taking direct oral anticoagulants (DOAC) vs. those not on DOAC (4). This appears crucial and of utmost importance because several papers and pathology demonstrated that lung (and internal organ) damage is mainly due to a microangiopathic thrombosis in which NETosis is very likely implicated (5, 6), and given that DOAC do not disrupt NETs-thrombi (5, 7) and NETosis has been considered a trigger of the thromboinflammation (6), we believe that anti-NETosis therapy (i.e., heparin, Bruton's tyrosine kinase inhibitors, and others) (8) should be deeply considered. The authors should then fully report on the type of anticoagulants and, possibly, on their indication (if already taken for non-COVID reasons, e.g., venous thrombosis, atrial fibrillation, valvular heart disease, pulmonary embolism, etc., or started at hospitalization for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection), to understand whether the benefits for severe SARS-CoV-2 patients were derived by preventing or stabilizing the worsening of the basal morbidity. This would be beneficial for some patients.

The most surprising message, however, is the negative consequence of taking nonsteroidal antiinflammatory drugs (NSAIDs) or oral antidiabetics. Why were these patients on NSAIDs, since none of the comorbidities listed in table 1 of ref. 1 needed NSAIDs, also relatively contraindicated by the mild-to-moderate renal failure present in more than 60% of the patients? In general, though the World Health Organization does not advise against NSAIDs, in agreement with FitzGerald (9) we think NSAIDs (except acetylsalicylic acid) should be avoided, yet why were NSAIDs part of the therapeutics?

The second point concerns antidiabetics. Diabetes is a proven risk in COVID-19–infected patients. However, it has been recently reported that dipeptidyl peptidase 4 inhibitors do not protect cardiovascular or kidney function in DM2 (type 2 diabetes), yet glucagon-like peptide 1 analogs demonstrated reduced death from cardiovascular causes and stroke and sodium-glucose cotransporter 2 (SGLT2) inhibitors (10) reduced cardiovascular death or hospitalization for heart failure. Therefore, the paper should be clear on whether all diabetics were on these drugs.

In conclusion, the clear message is on RAASI, yet an in-depth clarification of drugs that should be clearly given because they are safe, of those that could be maintained because they lead to no harm, and of those that should be strictly avoided because they are dangerous represents an urgent need during the pandemic.

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