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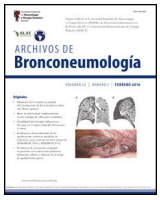

Editorial

Thromboprophylaxis in Patients With Cancer and COVID-19

Interest in thromboprophylaxis has increased since the onset of the SARS-CoV-2 pandemic. It quickly became clear that patients hospitalized for COVID-19 should receive pharmacological thromboprophylaxis with low-molecular-weight heparin (LMWH), unless contraindicated (in line with long-established clinical practice guidelines on antithrombotic prophylaxis in patients hospitalized for an acute medical process). However, early reports of a high rate of thrombotic events in some cohorts of patients hospitalized for COVID-19 despite the use of standard prophylactic doses of LMWH prompted various scientific societies and expert groups to propose the use of higher doses of LMWH in some patient subgroups.[1,2] At the time, the evidence supporting these recommendations was scant, and, as might be expected, more intense thromboprophylaxis was associated with an increase in hemorrhagic complications.[3]

Results from randomized clinical trials comparing various intensities of antithrombotic prophylaxis (standard, intermediate or therapeutic doses of LMWH) in hospitalized patients with COVID-19 have helped answer some, but not all, questions. In COVID-19 patients in intensive care units, the use of higher than standard LMWH prophylactic doses does not appear to provide clinical benefit,[4] but in patients admitted to conventional hospital wards the results are more heterogeneous. In a meta-analysis of aggregated data, therapeutic doses of LMWH compared with standard prophylactic doses were associated with a reduction in thromboembolic events, but also with an increase in major bleeding (although lower in absolute terms than the reduction in thrombosis) and no significant differences in mortality.[5] On the basis of these data, several guidelines were updated to propose the use of therapeutic doses of LMWH versus standard prophylaxis in selected COVID-19 patients in conventional hospital wards with no additional hemorrhagic risk factors.[6–8] Meta-analyses of individual patient data will soon be available, and these reports will probably help identify patient subgroups that benefit most from this strategy. Other pertinent topics addressed in the guidelines are the prolongation of prophylaxis after discharge (not generally recommended) and prophylaxis in non-hospitalized patients (not consistently recommended).

The latest version of the international clinical practice guidelines for the treatment and prevention of venous thromboembolism (VTE) in cancer patients, sponsored by the International Thrombosis and Cancer Initiative (ITAC),[9] includes for the first time a section on the treatment and prevention of VTE in patients with cancer and COVID-19. In these cases, the panelists recommend the same approach used in cancer patients without COVID-19. The argument for this recommendation is two-fold. Firstly, there is no evidence that the incidence of VTE in hospitalized patients with cancer and COVID-19 is higher than in non-cancer patients with COVID-19 (although it may have been more appropriate to compare the incidence of VTE in hospitalized cancer patients with and without COVID-19). Secondly, few specific data are available in the oncological population on the risk and benefit of different prophylactic strategies in patients with COVID-19. In fact, several of the clinical trials mentioned above excluded patients with active cancer and all of them excluded patients with primary or secondary central nervous system involvement.

Cancer patients are a special population with a high thrombotic and hemorrhagic risk due to multiple factors.[10] Hospitalization is a recognized risk factor for VTE in patients with active cancer.[11] For this reason, routine prophylaxis with LMWH is recommended in all hospitalized patients with cancer in the absence of any contraindication, except for patients admitted solely for the administration of cancer treatment and who are not bedridden. Nevertheless, 3–8% of patients develop an episode of VTE during hospitalization or within days after discharge, despite thromboprophylaxis.[12]

Whence the dilemma: should standard prophylactic doses be administered as suggested by the ITAC guidelines for cancer patients or therapeutic doses as suggested by the more general guidelines? (Table 1). The simple but less useful answer is that patients should be assessed on a case-by-case basis, taking into account the thrombotic/hemorrhagic risk balance in each case. However, although there are no published data, the changing characteristics of prevalent strains of the virus, widespread vaccination, and advances in disease management may mean that the thrombotic risk associated with COVID-19 is not now as crucial as it was in the initial waves of the pandemic. If this is indeed the case, the validity of the results of clinical trials that were mostly conducted at the beginning of the pandemic could be questioned, since in absolute terms, the use of therapeutic doses of LMWH would have a lower impact on the prevention of thrombotic events. Given this uncertainty and the increased hemorrhagic risk of cancer patients, it does not seem unreasonable to be prudent and suggest that, in general, patients with cancer and COVID-19 admitted to a conventional hospital ward should receive standard prophylaxis with LMWH.

Even less evidence is available for specific recommendations on thromboprophylaxis in cancer and COVID-19 in patients who do not require hospitalization. Many patients starting cancer

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Table 1
Summary of current recommendations/suggestions in different clinical practice guidelines on thromboprophylaxis in patients with COVID-19 (July 2022).

	CHEST guidelines	ASH guidelines	ISTH guidelines	ITAC (cancer) guidelines
Critical patients	Standard prophylaxis	Standard prophylaxis	Standard prophylaxis	na
Acute patients (conventional hospital ward)	LMWH therapeutic doses[a]	LMWH therapeutic doses[a]	LMWH therapeutic doses[a]	Standard prophylaxis
Prolongation of prophylaxis after discharge	Not recommended	Not recommended	Consider in selected patients	Not recommended
Non-hospitalized patients	na	na	Consider sulodexide[b]	According to individual risk[c]

[a] Selected patients with low hemorrhagic risk.
[b] Patients at high risk of disease progression, to reduce risk of hospitalization.
[c] Follow the same recommendations as in cancer patients without COVID-19.
na, not applicable.

treatment in routine practice do not undergo a thrombotic risk assessment, a situation that may lead to the underuse of outpatient thromboprophylaxis. In cancer patients with COVID-19, thromboembolic risk should be assessed, if it had not been done previously (there are several validated scales for this purpose).[13] Pharmacological thromboprophylaxis is probably indicated in a significant proportion of patients, irrespective of a COVID-19 diagnosis.

Emerging concepts such as personalized medicine and precision medicine are also applicable in the field of thromboembolic disease. Evidence-based guidelines are very useful, but they inevitably fail to address several circumstances commonly encountered in daily practice. Although these knowledge gaps are gradually closing thanks to scientific advances, there remains ample scope for practicing the art of medicine.

Conflicts of interest

The authors declare that they have no conflict of interests related with the contents of this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2022.08.006.

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