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EDITORIAL COMMENT

Direct oral anticoagulants in chronic thromboembolic pulmonary hypertension: More high-quality and multinational trials are needed!

Anticoagulantes orais diretos na hipertensão pulmonar tromboembólica crónica: são necessários mais ensaios clínicos aleatorizados multinacionais de elevada qualidade!

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease which, although rare, is associated with significant morbidity and mortality when left untreated. It is characterized by the obstruction of the pulmonary arterial vasculature by organized thrombotic material, with consequent fibrotic reaction, intimal thickening, vascular remodeling, and plexiform lesions, leading to increased resistance and pressure in pulmonary circulation, right heart overload, right ventricular failure, and death.[1] Pulmonary arterial endarterectomy (PEA) surgery is the first-line therapy which, when performed in experienced centers, has hospital mortality of less than 5% and provides hemodynamic and functional improvement with good long-term survival.[2] Balloon pulmonary angioplasty (BPA) is an alternative approach in inoperable or residual/recurrent CTEPH patients after PEA, with favorable results in terms of functional clinical improvement, exercise capacity, haemodynamics and survival.[3,4]

There is consensus that the development of CTEPH is a complication of acute thromboembolic disease (which can occasionally be silent), with a very variable incidence described in the literature, between 0.1 and 9.1% in the first two years after an episode of pulmonary embolism (PE).[5] For that reason, and despite the absence of data from randomized controlled trials, lifelong therapeutic anticoagulation in CTEPH patients is strongly recommended by international guidelines, even after PEA,[6] and there are

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some observational studies supporting it.[7] The rationale for anticoagulation in this field is the prevention of recurrent venous thromboembolism.

Historically, vitamin K antagonists (VKAs) have been the anticoagulant of choice in these patients. More recently, extrapolating the direct oral anticoagulants (DOACs) results from PE trials, several clinicians have chosen to anticoagulate their CTEPH patients with DOACs.[8] There are several well-known reasons that motivate them to make this decision, similarly to what happened previously in other contexts such as in the treatment of atrial fibrillation or PE. The management of vitamin K antagonists is challenging and thromboembolic or bleeding events are frequent when the intensity of anticoagulation is not adequate. Anticoagulation with DOACs allowed a simpler regimen, without the need for monitoring and with a more predictable therapeutic effect. A possible disadvantage of DOACs is the difficult assessment of treatment adherence.[9]

Although anticoagulant treatment with DOACs in a CTEPH population is attractive, there are few clinical data to support it. In fact, because CTEPH is an infrequent disease, strong evidence might be difficult to obtain. Barati et al.[10] provided the data from a randomized controlled trial comparing the efficacy and safety of a DOAC (rivaroxaban) versus warfarin in CTEPH patients after PEA. In total, 96 patients were randomized 2:1 after surgery: 61 patients received warfarin and 35 were anticoagulated with rivaroxaban. In this randomized study, there were no significant differences in the occurrence of venous thromboembolic events in the first, third and 6 months after surgery between groups. The rate of bleeding events, re-admission and mortality was also similar between groups.

There are previous studies that are contradictory to the current one, which raises questions of safety and efficacy of DOACs in CTEPH operated patients: in the retrospective multicenter study by Bunclarck et al.[11] with 794 operated CTEPH patients treated with warfarin and 206 patients treated with DOACs, the recurrence of venous thromboembolic events was significantly higher in the DOAC group (4.6%/person-year) compared to the warfarin-anticoagulated group (0.76%/person-year), although the bleeding risk was low and similar in both groups (0.67% versus 0.68%). In a study by Jeong et al.,[12] acute and subacute thrombus detection at time of PEA was significantly more prevalent in 166 patients treated with DOACs (13.3%) compared with 239 patients VKAs (6.7%). The retrospective nature of these studies may provide selection bias. But both had included a larger sample of patients from different centers involved in multinational registries.

On the other hand, the study by Barati et al.[10] overcame one of the main limitations of the previous studies by providing the randomized allocation of interventions, which addresses the potential biases from known and unknown confounders. Nevertheless, important limitations should be mentioned, some of which have already been pointed out by the authors:

First, it is a single-center study, and the presence of blinding methods and an independent data and safety monitoring board were not described. We understand that randomized controlled trials (RCTs) are limited by several barriers that increase its complexity and costs. Evidence for the effectiveness of interventions should rely on well-conducted RCTs, that requires funds, resources, and infrastructures, hardly accessible to independent academic researchers.[13] To improve the quality of academic RCTs, a multinational collaboration is essential. We need multicentric RCTs and multicentric high-quality registries. And this is even more important if we are studying less prevalent diseases.

Second, the short follow-up prevented us from drawing longer-term conclusions and the excess mortality in the first months after surgery also reduces the power of the study. Also, regarding the outcomes, thrombosis location and symptoms were not described, therefore using DVT and PE trials as examples, this should be acknowledged.

Third, the authors did not exclude high-risk patients with thrombotic antiphospholipid syndrome (APS). APS was present in approximately 13–14% of the patients in this trial. In a multicenter randomized trial of Pengo et al.,[14] rivaroxaban was tested in patients with an history of thrombosis and triple positivity in all three laboratory tests exploring the presence of anti-phospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-B2-glicoprotein I antibodies). This trial showed an increased rate of arterial thromboembolic events with rivaroxaban compared to warfarin in patients with antiphospholipid syndrome and was stopped prematurely. The composite primary outcome of thromboembolic events, major bleeding and vascular death occurred significantly more frequently in the rivaroxaban group compared to warfarin (19% versus 3%). A systematic review with meta-analysis with seven studies (including Pengo et al.) showed that DOACs, rivaroxaban in particular, had an increased risk of thromboembolic events.[15] Considering these results, high-risk APS patients should have been excluded from a trial evaluating the efficacy and safety of DOAC, nevertheless the results presented by Barati et al. do not point toward this direction. Therefore, in the presence of a non-high-risk thrombophilic disorder we may choose to anticoagulate with a DOAC on an individualized basis and careful way. On the other hand, the authors were careful to exclude situations that could increase the risk of DOAC bioaccumulation, as liver and renal failure and co-administration with potent CYP3A4 and P-glycoprotein inducers or inhibitors.[9] After PEA, only few patients will need vasodilator therapy (approximately 20% in the Bunclarck et al. study)[11] and, for that reason, the risk of potential interaction between DOACs and phosphodiesterase inhibitors, bosentan or riociguat, for example, is lower. The safety of DOACs in patients with nonoperable CTEPH treated with balloon pulmonary angioplasty and pulmonary vasodilator therapy remains of concern and high-quality multicentric randomized trials in this group are needed. Future investigations may help to understand which combinations of DOACs/targeted vasodilator therapy have the lowest risk of drug-to-drug interaction and to define the need to adjust DOACs doses. Similar to the trial with atrial fibrillation and pulmonary embolism, we need to raise the awareness of the clinical and scientific community for this field in order to carry out robust comparative studies between the different DOACs and VKAs in the CTEPH population. This would be an adequate way to further support the widespread use of DOACs in this population. Simultaneously, it is necessary to encourage and

create infrastructures that help academics (with or without the support of pharmaceutical industry) to overcome the barriers to multicentric and multinational randomized trials.

Conflicts of interest

RC has no conflicts of interest to declare.

DC has participated in educational meetings and/or attended conferences or symposia (including travel, accommodation, and/or hospitality) with Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, Ferrer, Pfizer, Novartis, and Roche.

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