ORAL ANTICOAGULATION: NEW WAYS AND OLD JOBS

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The time after the ESC congress is always full of information about updates to the guidelines and many discussions around new trials and their results, which are sometimes very challenging ones.

PREVENTION OF ATHEROTHROMBOTIC EVENTS

Before the congress, the European Medicines Agency approved the new regimen of rivaroxaban 2.5 mg twice daily in combination with low-dose acetylsalicylic acid 75 to 100 mg once daily for the prevention of atherothrombotic events in adults with coronary artery disease or symptomatic peripheral artery disease at high risk for ischemic events.[1] Within this context, it was very interesting to hear the results from other rivaroxaban trials.

COMPASS trial secondary analysis

First, in the late-breaking science session, the secondary analysis of the COMPASS trial was presented; the primary results became a scientific background for the new indication of rivaroxaban.[1] In the COMPASS trial, successful treatment with low-dose rivaroxaban and acetylsalicylic acid was associated with an increased risk of bleeding events, mainly gastrointestinal. Thus, a secondary analysis was conducted to test whether gastrointestinal or genitourinary bleeding was associated with increased rates of gastrointestinal and genitourinary cancer diagnosis in patients with vascular diseases (coronary artery disease or peripheral artery disease) on long-term antithrombotic therapy. A total of 27 395 patients with stable coronary artery disease or peripheral artery disease were randomized to rivaroxaban 2.5 mg twice daily plus acetylsalicylic acid, rivaroxaban 5 mg twice daily, or acetylsalicylic acid once daily only. Bleeding was defined using modified ISTH criteria.

A very strong association was revealed between gastrointestinal or genitourinary bleeding and gastrointestinal or genitourinary cancers; 1082 patients were

diagnosed with cancer during the COMPASS trial. About 1 new cancer diagnosis in 5 was predicted by a prior bleeding event. A Cox proportional study of association between gastrointestinal bleeding and gastrointestinal cancer demonstrated a 12-fold increase in the risk of diagnosed gastrointestinal cancer after bleeding (HR, 12.9; 95% CI, 9.77-17.0; *P*<0.0001). In addition, a Cox proportional study of association between genitourinary bleeding and genitourinary cancer demonstrated an 80-fold increase in the risk of diagnosed genitourinary cancer after bleeding (HR, 83.4; 95% CI, 58.6-118.6; *P*<0.0001). John Eikelboom (CA) concluded that any gastrointestinal or genitourinary bleeding should be investigated urgently to determine the underlying cause regardless of antithrombotic treatment, which could provide earlier and more effective treatment for gastrointestinal and genitourinary cancers. Of course, this data should be confirmed further in an extended follow-up of the COMPASS trial participants.[1]

THROMBOPROPHYLAXIS

In the Hotline sessions, two studies, which investigated thromboprophylaxis in patients with sinus rhythm, were presented: COMMANDER-HF[2] and MARINER.[3] These two studies were conducted due to knowledge available on disease progression by inducing inflammation, endothelial dysfunction, and arterial and venous thrombosis with the activation of thrombin-related pathways, especially in medically ill patients in MARINER and only patients with heart failure in COMMANDER-HF.[4]

COMMANDER-HF trial

Faiez Zannad (FR) presented the results from COMMANDER-HF, which investigated whether low-dose rivaroxaban reduces the morbidity and mortality associated with vascular and hemostatic dysfunction in patients with heart failure.[2] COMMANDER-HF was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial that tested the hypothesis that rivaroxaban, at a dose of 2.5 mg twice daily, added to background antiplatelet therapy, would be associated with lower rates of death and cardiovascular events than placebo among patients with recent worsening of chronic heart failure, reduced ejection fraction, coronary artery disease, and no atrial fibrillation. A total of 5 022 patients from 628 cities in 32 countries were randomly assigned to receive low-dose rivaroxaban or matching placebo. The primary efficacy end point was a composite of all-cause mortality, myocardial infarction, or stroke. The primary safety outcome was a composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. The results did not show a beneficial effect of low-dose rivaroxaban in patients with heart failure compared with placebo. Thus, the primary efficacy outcome occurred in 25% of patients in the rivaroxaban group and 26.2% in the placebo group (HR, 0.94; 95% CI, 0.84-1.05; *P*=0.27). A similar nonsuperiority effect of rivaroxaban was observed for the principal safety

outcome, which occurred in 0.7% patients in the rivaroxaban group and 0.9% in the placebo group (HR, 0.80; 95% CI, 0.43-1.49; *P*=0.48). The investigators suggested that the most likely reason for these results is that heart failure, rather than death, mediated by atherothrombotic events contributed to a substantial proportion of all deaths.

MARINER trial

The aim of another thromboprophylaxis trial, MARINER, was to investigate whether rivaroxaban would reduce the risk of symptomatic or fatal events when initiated at discharge for 45 days to medically ill patients who were at risk for a venous thromboembolism.[3] The primary safety outcome was major bleeding. Apparently, these results were eagerly awaited due to current guidelines that do not recommended the routine use of prophylaxis, with an exception of an acute hospital stay. MARINER included more than 12 000 medically ill patients who were ≥40 years old and who had been hospitalized for at least 3 to 10 days with additional risk factors for a venous thromboembolism, as indicated by an IMPROVE risk score of 4 or higher or a risk score of 2 or 3 plus a D-dimer level of more than twice the upper limit of the normal range. The patients were randomized to either placebo or rivaroxaban 10 mg/day or 7.5 mg/day depending on creatinine clearance for 45 days. The primary efficacy outcome in the rivaroxaban group occurred in 50 (0.83%) patients vs 66 (1.10%) in the placebo group (HR, 0.76; 95% CI, 0.52-1.09; *P*=0.14). The same tendency was observed in the principal safety outcome: major bleeding occurred in 17 (0.28%) patients in the rivaroxaban group and 9 (0.15%) in the placebo group (HR, 1.88; 95% CI, 0.84-4.23). Certainly, this study did not show significant benefit with rivaroxaban vs placebo. The investigators suggest that this result is possibly due to the study's limitations, including difficulty in defining venous thromboembolism–related death and the possible underdosing of patients with moderate renal impairment.

CONCLUSIONS

Thus, it remains unclear whether we should coagulate or not... Two trials investigated oral anticoagulants in patients with sinus rhythm in medically ill patients. Despite the nonbeneficial results, it does not reduce the significance of the studied hypothesis. The statement made by Marple in 1950 that "patients with congestive heart failure are prone to develop thromboembolic complications which increase the morbidity and mortality of the disease" reflects the rationale for the first attempts to introduce oral anticoagulants into the treatment of patients with heart failure.[5,6] Moreover, there is limited evidence on thromboembolic risk in patients with HFPEF based on post hoc analyses of large clinical trials focused on HFPEF. Although oral anticoagulants might have been a reasonable therapeutic option in individual patients with heart failure, the routine use

of anticoagulation therapy in patients with heart failure in sinus rhythm is not supported by the currently available data. ■

Declaration of interest: The authors have nothing to declare.

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