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COMMANDER-HF: is there anything more to reveal?

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Background:
Despite the improvements in therapies for patients with a diagnosis of heart failure with reduced ejection fraction (HFrEF), the prognosis remains poor both in terms of mortality and morbidity (1, 2). The role of anticoagulation in HFrEF patients with atrial fibrillation (AF) and a CHADSVASc score of 2 or more is well established (1). However a number of studies have failed to demonstrate any benefit of anticoagulation with warfarin in patients with HFrEF and sinus rhythm (3-6). Interest in a strategy of anticoagulation with DOACS in this population was, however, reignited by a signal seen in sub-group analyses of the ATLAS ACS 2-TIMI 51 and COMPASS trials. These demonstrated that in patients with heart failure and recent acute coronary syndrome or stable coronary artery disease respectively, low dose rivaroxaban (a direct factor Xa inhibitor) reduced morbidity and mortality (7, 8).

Take Home Messages

- The role of anticoagulation in patients with HFrEF, AF and a CHADSVASc of two or more is well established
- COMMANDER-HF demonstrates that there is no place for routine anticoagulation in patients with heart failure with reduced ejection fraction and sinus rhythm
- The observation that stroke risk was reduced in this population could suggest that we are missing AF in these patients
- Should we now perform prolonged monitoring in these patients to detect AF?

The trial:
The COMMANDER-HF trial was a multicentre, randomised, double-blind, placebo-controlled, event-driven trial that enrolled 5022 patients (9). Inclusion criteria selected patients with at least a three month history of heart failure, ejection fraction less than 40%, coronary artery disease and an episode of worsening heart failure within 21 days requiring treatment. Important exclusion criteria were atrial fibrillation, an indication for long term anticoagulation or a high risk of bleeding. Patients were randomised to low dose rivaroxaban (2.5mg twice-daily) or placebo in addition to standard medical care and were followed up for a median of 21.1 months.
There was no difference in the primary endpoint (a composite of death from any cause, myocardial infarction or stroke) between groups. Furthermore there was no significant difference in the individual components of this composite endpoint

except for the risk of stroke. Treatment with rivaroxaban reduced the risk of stroke by a third (hazard ratio 0.66 (95% CI 0.47-0.95). Additionally, there were no significant differences between any of the secondary endpoints (including heart failure hospitalisations).

In terms of safety, patients taking rivaroxaban had a significantly higher rate of major bleeding (3.3% versus 2.0%), however no differences in fatal or critical-space bleeding rates were seen. The authors concluded that in patients with worsening HFrEF in sinus rhythm with underlying coronary artery disease, the addition of low dose rivaroxaban did not reduce the primary composite endpoint or rehospitalisation rates for heart failure.

Discussion:
COMMANDER-HF was a well conducted trial and its findings suggest that in patients with a recent decompensation of heart failure the majority of future events are not related to thrombotic complications (10). This is consistent with previous data from trials of warfarin in similar populations. These findings arise despite the fact that the study was performed in a group of patients with coronary disease who could have been expected to be more likely to benefit from the addition of low dose rivaroxaban than the general heart failure population (7, 8). Whilst this study emphatically answers the question as to whether all heart failure patients in sinus rhythm benefit from the addition of low dose rivaroxaban, the observed reduction in stroke risk by a third should precipitate further inquiry. Given the data demonstrating the effect of rivaroxaban on stroke risk reduction in patients with AF (albeit at a higher dose), it is plausible that the benefit in COMMANDER-HF is a result of this effect (11).
The study protocol however excluded patients with a history of AF, but does not document how this was adjudicated. This is particularly important because asymptomatic AF is common and hence some of the COMMANDER-HF population may not have been investigated due to a lack of symptoms (12). Only a small number of patients (13%) in COMMANDER-HF had a cardiac device capable of detecting AF. Furthermore the protocol also allowed the enrolment of patients with isolated, transient AF at the discretion of the physician. It is unclear what steps were taken to ensure that this was isolated and transient. It is therefore possible that some of the COMMANDER-HF patients could have had AF that was either undocumented or felt to be transient.

Even if all the patients included in the COMMANDER-HF trial had never had AF previously, there is a possibility that these patients could have developed AF during the trial. The biochemical and cardiac structural changes associated with HFrEF put patients at a higher risk of developing AF (12, 13). This was clearly demonstrated in the study by Shanmugam et al, who reported an incidence of high atrial rates at 1 year of 33% in a cohort of HFrEF patients with a CRT who were in sinus rhythm (14). Whilst this group is not directly comparable to the

COMMANDER-HF group due to the lower ejection fractions and the fact that all patients had an indication for CRT it does demonstrate the high incidence of AF in an HFrEF population. Furthermore two large device studies performed in less select populations including patients with pacemakers and ICDs for all indications, found similar results with AF episodes identified in around a third of patients (15).

The first clinical presentation of AF can be a stroke (16). Three studies have clearly demonstrated the increased diagnostic yield of AF with prolonged monitoring in patients presenting with unexplained stroke (16-18). It is therefore highly likely that AF would be found as the cause for some of the strokes in COMMANDER-HF who had a baseline CHADSVASc score of 4.3.

Comparison between COMMANDER-HF and ROCKET-AF is difficult due to both the lower total daily dose in COMMANDER-HF and the differences between the control groups (placebo in COMMANDER-HF and warfarin in ROCKET-AF). The dose of rivaroxaban used in COMMANDER-HF is the same as in the COMPASS trial, and both trials demonstrated a reduction in the stroke risk (19). It is therefore uncertain as to the mechanism behind the risk reduction provided by rivaroxaban in the COMMANDER-HF group, is it providing vascular event protection as in COMPASS or is it offering some degree of anti-thrombotic protection in a group of patients at high risk of AF?

Conclusions

COMMANDER-HF has demonstrated that low dose rivaroxaban has no place in the management of patients with HFrEF and sinus rhythm. The risk of stroke was however lower in patients treated with low dose rivaroxaban. Is it possible that this risk reduction resulted from the prevention of thromboembolism due to clinically silent episodes of AF or is it a reflection of the protection that rivaroxaban offers in stable atherosclerotic disease or a combination of the two mechanisms? Given these data is it now time to search more extensively for atrial fibrillation in patients with heart failure to guide the appropriateness of anticoagulation? Further studies are now required to answer these questions.

Disclosures

JH has received educational support from Bayer

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