

# WORLD CONGRESS ON RHEUMATIC HEART DISEASE

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**Title:** ORAL ANTICOAGULATION FOR ATRIAL FIBRILLATION IN RHEUMATIC HEART DISEASE

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**Background & Aims:** The risk of stroke in patients with atrial fibrillation (AF) increases significantly when combined with mitral stenosis (MS). Patients with moderate-to-severe MS were excluded from the historic vitamin K antagonist (VKA) trials and, latterly, from most of the contemporary non-VKA oral anticoagulant (NOAC) trials. Today, VKAs remain the only oral anticoagulant (OAC) approved for patients with AF associated with moderate-to-severe MS.

The INVICTUS trial was the first to compare VKAs with rivaroxaban in AF patients with haemodynamically significant rheumatic valve lesions (mainly MS) in order to address the poor adherence and performance of VKAs in RHD endemic areas.

**Methods:** INVICTUS was a randomized, open-label, non-inferiority study which recruited patients with echocardiographically documented RHD, AF, and an elevated stroke risk (at least one of: mitral valve area [MVA]  $\leq 2$  cm<sup>2</sup>, CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , spontaneous echo contrast, or thrombus in the left atrium on echo) and were randomly allocated to rivaroxaban 20 mg daily (15 mg daily if creatinine clearance was  $< 50$  mL/min) or a dose-adjusted VKA (target INR 2-3 with at least monthly monitoring).

We analyzed the methodology and significance of the results of INVICTUS, with particular emphasis on how relevant the results and conclusions were to real-world patients with RHD-AF.

**Results:** INVICTUS provided surprising results: of those receiving rivaroxaban, 8.21% (560 out of 2275 patients) had a primary efficacy outcome event (stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes) compared to 6.49% (446 out of 2256 patients) of those receiving a VKA (HR 1.25, 95% CI 1.10-1.41). The rate of death in the rivaroxaban arm was significantly higher than in those taking a VKA - 552 vs 442 patients (HR 1.23, 95% CI 1.09-1.40). There was no significant difference in stroke or systemic embolism (HR 1.24, 95% CI 0.92-1.68) or hemorrhagic stroke between both groups. Based on these results, the INVICTUS investigators concluded that VKAs should remain as the OAC of choice in all patients with RHD-AF.

We believe there are a number of important caveats to consider when interpreting this trial, including: 1) most patients (~82%) had significant MS (therefore results cannot be extrapolated to all RHD patients, most of whom have latent/mild disease); 2) those in the VKA arm had algorithmic adjustment of their INR, resulting in significant improvements in time in therapeutic range from 33.2% at enrollment to 64.1% at 4 years (algorithms are not typically used in real-world practice so these INR results are likely unrealistic); and 3) those in the VKA arm underwent monthly monitoring for INR control (this could have resulted in improved medical care and optimization of guideline-directed medical therapy compared to the NOAC arm).

**Conclusions:** It is clear from INVICTUS that, for now, NOACs should remain contraindicated in all patients with RHD-AF who have haemodynamically significant MS (i.e., MVA  $\leq 2$  cm<sup>2</sup>). However, given the lack of evidence to suggest otherwise, we believe it is appropriate to retain NOACs as a potential option for stroke prophylaxis alongside VKAs for RHD-AF patients without haemodynamically significant MS. This may still represent the only opportunity to provide safe anticoagulation for high-risk RHD patients from endemic areas with limited or no access to intensive INR control.