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Mitral stenosis in not a rare disease. Rheumatic fever is the principal cause of mitral stenosis. Anulus calcification and congenital heart disease are recognized as other causes of mitral stenosis.[1] In developed countries, the prevalence is about 0.6 in 1000 in USA but it is much higher in developing nations: 21 cases per 1000 in Asia, 15 cases in 1000 in Africa and 17 cases in 1000 in South America.[2] Atrial fibrillation occurs in about 32% of symptomatic patients, thus decreasing cardiac output and exercise capacity, and greatly increasing the risk of thromboembolism.[3] Oral anticoagulation is therefore mandatory in these patients. Although Direct Oral Anticoagulants (DOACs) have been found to be non-inferior or superior versus vitamin K antagonists (VKAs; e.g., warfarin) in preventing cardioembolism in patients with atrial fibrillation,[4] patients with atrial fibrillation and rheumatic heart disease were not enrolled in earlier trials, thus excluding this pathological condition from approved indications.[5] Since ensuring adequate anticoagulation with laboratory monitoring whilst using VKAs may be difficult in developing countries, DOACs have the potential to improve the extension of oral anticoagulation without the need of any laboratory control. The commitment to plan a superiority trial (DOAC vs VKA) came in 2016 from the Cardiology community, which aimed to design a superiority trial involving a single dose DOAC (no laboratory monitoring) versus VKA (with laboratory monitoring), and since the latter showed a poor Time in the Therapeutic Range in countries of Asia, Africa and Latin America.[6] Thus, a multicentric, randomized, noninferiority trial to evaluate the efficacy and safety of the factor Xa inhibitor, rivaroxaban, in comparison with VKA was planned and recently completed (INVICTUS trial). The trial involved patients with rheumatic

heart disease in Africa, Asia and Latin America,[7] enrolling patients with atrial fibrillation and echocardiographically documented rheumatic heart disease. 85% of trial participants had mitral-valve stenosis, which was moderate-to-severe in 82%. These participants had a CHA_2DS_2VASc score of at least 2, a mitral-valve area of no more than 2 cm^2, left atrial spontaneous echo contrast, or left atrial thrombus. Patients were randomly assigned to receive standard doses of rivaroxaban (20 mg/day) or dose-adjusted VKA (INR 2.0-3.0). The mean ± standard deviation (SD) duration of follow-up was 3.1±1.2 years. The primary efficacy outcome was a composite of stroke, systemic embolism, myocardial infarction, or death from vascular (cardiac or noncardiac) or unknown causes. The primary safety outcome was major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH).[8] A total of 4531 participants were included in the final analysis. Mean age of the patients (72.3% women) was 50.5 years.

In the intention-to-treat analysis, 560 patients in the rivaroxaban group and 446 in the VKA group had a primary-outcome event (Hazard Ratio [HR]: 1.25, 95% CI, 1.10–1.41). Stroke was more frequent in the rivaroxaban group (HR: 1.54, 95% CI 1.10 to 2.16) as well as death (HR: 1.23, 95% CI 1.08 to 1.40) and death from vascular cause (HR: 1.26. 95% CI 1.08 to 1.47). The restricted mean survival time was 1599 days in the rivaroxaban group and 1675 days in the VKA group (difference, −76 days; 95% CI −121 to −31; P<0.001). A higher incidence of death occurred in the rivaroxaban group than in the VKA group (restricted mean survival time, 1608 days vs. 1680 days; difference, −72 days, 95% CI −117 to −28). No significant between-group difference in the rate of major bleeding was noted. However, fatal bleeding was lower in the rivaroxaban group (4 vs 15 patients; HR: 0.29, 96% CI 0.10 to 0.88). The Authors stated that the results of this trial were unexpected, perhaps because of the reduced power for the outcome of stroke, whose rates in the two groups were lower than expected. In addition, the difference in the rate of stroke was modest, which suggests that the difference could be due to chance. We do not agree with this observation since, globally, stroke was more frequent in the rivaroxaban group by 50% in comparison with that of VKA. However, the Authors recognize that the higher rates of death in the rivaroxaban group were certainly not due to chance. In this regard, they recognised that patients in the VKA group had a monthly regular relationship with the physicians in comparison with those in the rivaroxaban group. A better general care is an important outcome of any medical intervention. This approach is known to be important in the management of VKA, as for example as demonstrated in the long experience of anticoagulation clinics in Italy.[9,10] Another possible reason to explain the trial results comes from the consideration, as the Authors underline, that adherence to rivaroxaban therapy was worse than that of VKA because of the lack of regular follow up, since laboratory monitoring was no longer necessary. We recently demonstrated that adherence and persistence to either VKA or DOAC is good, provided that careful periodical monitoring is instigated.[11] Interestingly, the Authors noted that the lower rate of the composite outcome in favour of VKA became considerable after three years, probably due to a progressive better management of VKA in the long course of the trial. Gregory Lip, in an accompanying Editorial,[12] acutely expressed the need for a "*holistic treatment*

of patients with rheumatic heart disease–associated atrial fibrillation, beyond the anticoagulation per se".
In other words, the concept of a periodical follow-up of patients treated with DOAC appears to be important to offer a complete approach in terms of personalized care, especially in consideration of other comorbidities, which are, in general, frequent in anticoagulated patients. The lack of this organization for rivaroxaban participants could explain why deaths were less common in the VKA group.

Nevertheless, can we find other possible reasons to explain the results of this trial? If we go back to the pathophysiology of the disease, we know that a very low shear rate develops concomitantly to the worsening of the stenosis. The reduced flow rates through the stenosis induce turbulence,[13] which can cause red blood cell (RBC) aggregation, is a phenomenon recognized to be a risk factor for cardioembolism.[14] RBC aggregates are known to be visible as spontaneous echo contrasts (SEC) in mitral stenosis [15] but also, in atrial fibrillation [16] (Figure 1). In patients with mitral stenosis and sinus rhythm, if SEC is present, von Willebrand factor is increased, thus also indicating an endothelial dysfunction. [17] Rastegar et al demonstrated that SEC are mediated by the fibrinogen levels (i.e., as Fibrinogen concentration increased, the SEC became denser).[18] On the other hand, RBC aggregates can also release microparticles,[19] which in turn are able to activate blood coagulation via the contact activation[20-21] (Figure 2). In particular, Factor IX can be activated directly by an elastase-like enzyme on the RBC membrane.[22] Exposure of phosphatidylserine by RBC is another crucial step for activation of blood coagulation, providing an optimal substrate for clotting factors which are ready to be involved in blood clot formation. [23]

Is there a link between SEC and inflammation in mitral stenosis? Recently, a report by Kelesoglu et al demonstrated an independent association between SEC and Systemic Immune Inflammation Index (SII) in patients with mitral stenosis. Moreover, SII levels correlated with the degree of SEC.[24] SII is an accepted index of inflammation. [25] SII is defined as platelet x neutrophil–lymphocyte ratio. In other words, it appears that a chronic inflammatory state is present in the course of mitral stenosis as already shown by Guilherme et al [26] and by Sharma et al, who found elevated levels of IL-6, CRP and sCD-40L in patients with mitral stenosis and atrial fibrillation.[27] It has been shown that the in vivo expression of tissue factor is dependent on IL-6.[28] The tissue factor–factor VIIa complex activates factor IX, forming a tenase complex with activated factor IX and factor X, generating additional factor Xa, so inducing a positive-feedback, greatly facilitated by the presence of platelets, which can be activated by proinflammatory mediators or by thrombin. [29] Taken together, all these considerations indicate how blood coagulation can be activated in the course of mitral stenosis. Both the tissue factor and the contact activation seem to be involved in the creation of a thrombotic burden. Although VKA are able to reduce thrombin via the inhibition of several clotting factors, strategically placed, thus profoundly interfering with the intrinsic (factor IX), extrinsic (factor VII) and common (factor X) pathways of blood coagulation, rivaroxaban may work less well in blunting such a potent procoagulant force by inhibiting only factor Xa. An example of such phenomenon also comes from the experience afforded by the comparison of dabigatran versus warfarin in prosthetic mechanical heart

valves. [30] In that trial dabigatran was not able to counteract the contact activation of blood coagulation at the usual dosages as later demonstrated by Jaffer et al.[31]

Finally, was the rivaroxaban dosage appropriate in the INVICTUS trial? Perhaps an administration twice a day employing 15 mg every 12 hours might have been more appropriate for counterbalancing the thrombotic milieu of patients with mitral stenosis and atrial fibrillation, since the half-life of Rivaroxaban is around 12 hours.[32] Another condition in which Rivaroxaban resulted inferior to warfarin is the anti-phospholipid syndrome (APS), [33] probably because of similar pathophysiological reasons: an important prothrombotic burden driven by both cellular and complement activation [34] on one hand *vs* the single dosage of rivaroxaban on the other, as stated above. A new potential strategy may be provision of dual DOACs (anti-Xa anti-IIa), because of synergy between lower dosages of each, as has been recently demonstrated *in vitro*.[35] The authors hypothesized that this strategy may also work *in vivo*. Alternatively, anti-XII and antiXI anticoagulants, [36] along with a low dose of a DOAC might reflect another approach in the management of severe mitral stenosis. In conclusion, the potential explanation for the failure of rivaroxaban versus warfarin in the INVICTUS trial seems to be: the lack of a clinical follow-up during the course of the treatment, as otherwise facilitated by the anticoagulation clinics for VKA, and the multiple points for blood coagulation activation secondary to the chronic inflammation state of mitral stenosis.

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Figure 1. Spontaneous Echo Contrast and subsequent fibrin deposition.

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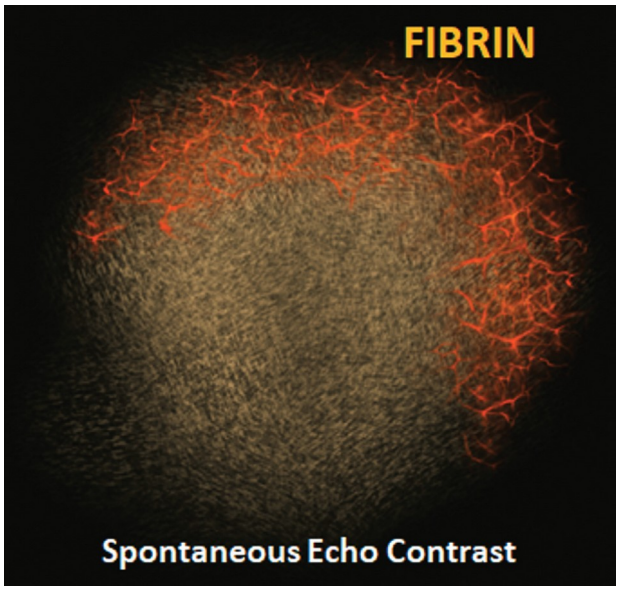

Figure 2. Red Blood Cells aggregates and derived microparticles.

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