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### Re: 'Prothrombin G20210 Mutation and Lower Extremity Peripheral Arterial Disease: A Systematic Review and Meta-analysis'

Vasquez et al.<sup>1</sup> showed that prothrombin G20210 mutation is significantly elevated in patients with peripheral occlusive arterial disease (POAD) suffering from critical limb ischemia (CLI) but not in the others. Interestingly, this mutation has been reported to be more prevalent in patients with Buerger's disease.<sup>2,3</sup> Avcu et al.<sup>2</sup> found an increased frequency of the G20210 mutation in Buerger's disease (OR 7.98, 2.45–25.13). Buerger's disease is characterized by diffuse arterial thrombosis and a severe clinical picture, most often at the CLI stage. In a recently published case control study among patients with premature POAD the author's team found that G20210 mutation was significantly more frequent in Buerger's disease (4.2% vs. 1.7 in controls).<sup>3</sup> This difference was not found for atherosclerosis related POAD (2.6%). When compared with the 64 POAD patients, the 49 with Buerger's disease had CLI in 88% versus 28% in atherosclerosis related POAD. As suggested by Vasquez et al.,<sup>1</sup> G20210 mutation might be one among several factors favouring thrombosis and leading to CLI in POAD, and prospective cohort studies would be useful to evaluate the role of this mutation to predict progression in POAD.

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### Response to 'Re: Prothrombin G20210A Mutation and Lower Extremity Peripheral Arterial Disease. A Systematic Review and Meta-analysis'

We read with interest the letter by Boulon et al.<sup>1</sup> The proposed association between prothrombin G20210A and thromboangiitis obliterans is very interesting. Prior studies have suggested that prothrombin G20210A interacts with other cardiovascular risk factors (especially smoking) to increase the risk of vascular events,<sup>2</sup> and this interaction could further explain the association of prothrombin G20210A and thromboangiitis obliterans seen by Bérard et al. and Avcu et al.<sup>3,4</sup> The literature search conducted in our systematic review did not identify the study by Bérard et al.<sup>3,5</sup>; had the study been included there would have been no changes in the association of lower extremity peripheral arterial disease (PAD) prothrombin G20210A (pooled random effect odds ratio 1.68 [95% confidence interval 0.94–3.00];  $I^2$  52.1%;  $p = .08$ ). Furthermore, the addition of the study by Bérard et al. does not modify the association between prothrombin G20210A and critical limb ischemia secondary to PAD (even in the absence of positive cases).<sup>3</sup> Finally, we agree that well-designed prospective cohort studies are needed to evaluate the role of prothrombin G20210A in the progression and outcome of patients with PAD.

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### Re: 'Association of Venous Disorders with Leg Symptoms: Results from the Bonn Vein Study 1'

In their well defined population based cross sectional study, Wrona et al.<sup>1</sup> have evaluated the association between chronic venous disorders like varicose veins and chronic venous insufficiency, and leg symptoms. Symptoms such as tightness, feeling of heaviness, swelling, itching, and pain after standing or sitting have been found to be associated with varicose veins and chronic venous insufficiency. However, muscle cramps and pain during walking have been found to be associated with varicose veins but not with chronic venous insufficiency. Restless legs and muscle cramps are not, or less associated, with varicose veins, chronic venous insufficiency, or C class. Finally, they have concluded that restless legs and muscle cramps should no longer be considered as "venous leg symptoms".

Assessment of venous symptoms and making a differential diagnosis in patients suffering from a variety of

symptoms is a big challenge in daily clinical practice. In accordance with Wrona et al.,<sup>1</sup> the general agreement is that these symptoms themselves show poor sensitivity and specificity for venous insufficiency but are ordinarily recognized as symptoms of a functional disorder.<sup>2,3</sup>

Several factors might play role in the diagnostic inefficacy of venous symptoms. Firstly, studies have mostly focused on either the prevalence of varicose veins or duplex scanning in assessing venous insufficiency irrespective of symptoms.<sup>4</sup> Secondly, a high co-existence rate of co-morbid disease, such as peripheral artery disease, arthrosis, and obesity, makes the assessment of lower limb symptoms more complex. Diabetes mellitus, which has never been mentioned in the literature, is likely to play a role as an underlying cause in the pathogenesis of aching legs, burning sensation, swelling, or itching.<sup>5</sup> Likewise neither population based nor symptom oriented studies have ever included patients' medication in their analysis. Someone would expect to see the positive or the negative influence of drugs received such as diuretics, calcium antagonists, oral anti-diabetic medications, and painkillers on venous symptoms.

In this regard, it is too early to state that muscle cramps, and restless legs should no longer be considered as venous leg symptoms. Instead of evaluating each symptom individually, a comprehensive scoring system is needed for assessing or combining symptoms as a whole.

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