induced anticoagulation and allows reinitiation of dabigatran etexilate treatment 24 h after a surgical intervention or after major bleeding to reduce thromboembolic risk. Alternatively, other antithrombotics could be introduced at any time since idarucizumab binding is dabigatran-specific.

Safety and efficacy of idarucizumab re-exposure was assessed ~2 months later in 3 male and 3 female subjects who initially received 2.5 g idarucizumab. As described, dabigatran etexilate 220 mg twice a day for 3.5 days was followed by 2.5 g idarucizumab 1 h 55 min after the last dose. Reduction in unbound dabigatran concentrations and reversal of anticoagulation (**Figure 1B**) were similar to the first idarucizumab treatment, with no adverse events indicative of allergic/immunologic reactions. No anti-idarucizumab antibodies were detected prior to re-exposure with idarucizumab. After re-exposure, 1 of 6 subjects tested positive with a low titer at 3 months. Thus, a second administration of idarucizumab appears safe and effective and could be given to patients requiring this for life-threatening bleeds or urgent surgery.

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Usual Blood Pressure and New-Onset Diabetes Risk

Evidence From 4.1 Million Adults and a Meta-Analysis

Emdin et al. (1) indicated that increased blood pressure was a significant risk factor for developing type 2 diabetes (T2DM), and concluded that "further investigation is needed to determine whether this association is causal." In response, we propose that there is considerable evidence that insulin resistance (IR) is the causal link between hypertension and increased risk of T2DM.

Insulin resistance is characteristic of patients with T2DM, and T2DM develops when pancreatic β-cells do not secrete enough insulin to overcome the IR (2). Normotensive, first-degree relatives of patients with hypertension are insulin resistant, prospective studies have shown that hyperinsulinemia predicts development of hypertension, and IR is increased in patients with hypertension (3,4). Given these relationships, and the importance of IR in T2DM, it is not surprising that patients with hypertension are at increased risk of incident T2DM. However, as emphasized by Emdin et al. (1), previous studies have not yielded consistent support of this relationship. One explanation is that essentially all patients with T2DM have IR, whereas only approximately 50% of patients with hypertension are insulin resistant and at enhanced risk of T2DM (5). Given this degree of variability of IR in patients with hypertension, it is not surprising that the causal link between hypertension and T2DM is not easily discerned. The huge database analyzed by Emdin et al. (1) increased the likelihood that increases in blood pressure would be shown to predict incident T2DM. We suggest that further research into the relationship between hypertension and T2DM take into account the substantial metabolic heterogeneity that exists between subpopulations subsumed under the rubric of hypertension.

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Search for Evidence-Based Medicine for Brugada Syndrome

The paper by Nademanee et al. (1) is so excellent—it demonstrated that the proposed diagnosis of idiopathic origin for the so-called Brugada syndrome must be dismissed.

There are 2 minor criticisms: one is that not one of the patients submitted to necropsy had an electrocardiogram (ECG) performed during life, so it is possibly but not definitely sure that they have the complete phenotypic traits. It is also confusing why, because this lethal syndrome has been proposed to be the "mother" of a relevant number of sudden deaths, it has been so difficult to perform detailed necropsy studies in patients who have died because of the syndrome, and why those published have been so rarely discussed (see Table 1 of Martini et al. [2]).

As a second comment, I find it unfair in this paper that the humble but first discoverer of the syndrome (and its underlying structural abnormalities), Professor Andrea Nava from Padova, was not even cited. Nava described the complete syndrome in 1987/1998 (1–3) and by a simple analysis of the ECG demonstrated that the ECG pattern was due to a right ventricular conduction disturbance linked to a structural abnormality of the right ventricle. These evidence-based theories received a lot of heavy criticism (and other unfair definitions and boycott), because experts have insisted the syndrome was idiopathic, linked to ion channel abnormalities in a totally normal heart. The unjustified abuse of this non-evidence-based assumption has led to devastating (and high-cost) therapy in asymptomatic and healthy young people (4), which could have been avoided if the structural heart abnormalities underlying the true patients described 30 years ago had been heeded, and not the functional phantoms and the genetic purgatory had been investigated (5). I hope that starting from now efforts will be made to improve the knowledge of what is evidence based rather than to search different confusing pathways that slow the correct identification and risk stratification of the syndrome and its underlying disease.

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The Complex Network of the Brugada Syndrome

I read the paper by Nademanee et al. (1) with great interest and congratulate the authors on their excellent work. As the authors correctly state, Brugada