

### **Thromboprophylaxis in Medically Ill**

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in hospitalized medically ill patients. It is estimated that in the US and EU alone, approximately 650,000 VTE-related deaths can be attributed to recent hospitalization in the medically ill population, where rates of VTE linked to hospitalization are estimated to be 35-fold higher than those non-hospital related. Although multifactorial risk factors for VTE have been recognized for some time in this population and linked to both intrinsic (patient-related) and extrinsic (disease-related) causes, it is only recently that evidence-derived, scored, and validated VTE risk models such as the IMPROVE VTE score have been applied to the medically ill population. These models help to assess how individual VTE risk factors can be weighted and combined to determine the overall VTE risk in a particular patient at the bedside.

Anticoagulant-based primary thromboprophylaxis with either unfractionated heparin, low molecular weight heparin (LMWH), or the pentasaccharide fondaparinux in the medically ill population has been shown from data that is nearly 20 years old to produce a 50-60% reduction in total VTE risk when given in-hospital. Initial large clinical trials studying extended thromboprophylaxis for 4 weeks or more in medically ill with either LMWH or the direct oral anticoagulants (DOACs) have shown mostly benefit but with an increased risk of major and clinically relevant non-major bleeding, producing an overall unfavorable net clinical benefit in this population. More recently large clinical trials of extended thromboprophylaxis with the DOACs betrixaban and rivaroxaban have finally shown an improved safety profile by careful patient selection, thus making a strategy of extended thromboprophylaxis beneficial. If this extended thromboprophylaxis strategy is applied to the 25-30% of medically ill patients - as modeling estimates suggest - that have a high enough VTE risk to benefit from such a strategy, then there is potential from a populational perspective to reduce the burden of VTE, including VTE-related death, in tens of thousands of patients in the US and EU.

### **The Perioperative Management of Patients with Atrial Fibrillation on Direct Oral Anticoagulants**

It is estimated worldwide that 1 in 6 patients on chronic oral anticoagulation with atrial fibrillation, or approximately 6 million patients per year, will require temporary interruption of their anticoagulant therapy for an elective procedure or surgery. Direct oral anticoagulants or DOACs have recently surpassed warfarin as the oral anticoagulant of choice in patients with atrial fibrillation. However, the management of such patients in perioperative situations remains uncertain, including the timing of their interruption, the necessity of using heparin bridging therapy as temporary anticoagulation, and the routine need of preoperative coagulation testing.

Recent data to inform management principles of the DOACs suggest that any periprocedural management strategy should consist of an estimation of the procedural bleeding risk, patient renal function, and pharmacokinetic characteristic of each DOAC. Using these simple principles, the clinician can expect a very low 30-day periprocedural adverse outcome event rate of thrombotic and bleeding complications that is similar to, and in some instances safer, than that with warfarin. Consistent clinical data also points to the fact that the use of heparin bridging therapy with DOACs lead to a multifold increased risk of major bleeding without an accompanying reduction in the risk of stroke or systemic embolism. The recently completed large multicenter, multinational PAUSE trial assessed clinical outcomes with DOACs in atrial fibrillation patients undergoing elective procedures using a simple, standardized DOAC protocol based on DOAC pharmacokinetic properties and bleeding risks associated with the procedure/surgery. This trial will provide for the first time high quality data as to the optimal periprocedural management of this population with the DOACs.