Cardiovascular disease is the largest cause of death and disability in developed countries. A common component of the end stage of these diseases is thromboembolic disorders which account for over 50% of cardiovascular related deaths. This large unmet medical need resulted in intense activity to discover and develop new antithrombotic drugs. Over the past few decades, drug discovery directed at the treatment and prevention of thromboembolic diseases has been challenged by the need to balance robust efficacy with exquisite safety. Perhaps the most impactful advance to date in the area of oral anticoagulants, has been the recent introduction into clinical practice of the new class of orally bioavailable small molecule factor Xa (FXa) inhibitors. At Bristol-Myers Squibb our efforts culminated in the discovery of Eliquis® (apixaban), a novel oral FXa inhibitor. This presentation will highlight the key learnings from the discovery efforts which led to Eliquis, and applications of these learnings to the design of small molecule Factor XIa inhibitors.