

Antiplatelet Development: The Search for America's Next Top Agent

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Editorial

Cardiovascular disease continues to remain a focal theme in the healthcare industry today. Although death rates related to cardiovascular disease (CVD) have declined since the end of the 20 century, CVD still accounts for 1 out of every 3 deaths with costs well over 300 billion annually in the United States (U.S.) [1]. As a result, there continues to be a high number of inpatient cardiovascular procedures and operations. In fact, estimates from the American Heart Association show that more than half of the 1.2 million hospital stays for coronary artery disease (CAD) were among patients who received a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) [1].

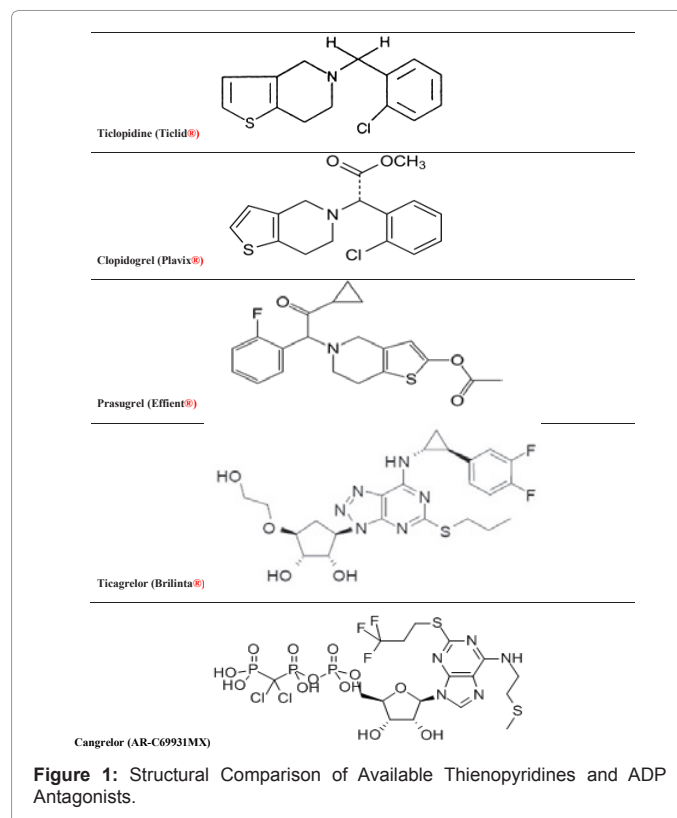
Given the evolution of coronary stents over the past couple of decades and the support of guidelines, the use of PCI with stenting will continue to remain at the forefront of treating those with an acute coronary syndrome (ACS) [2-9]. However, stenting poses an increased risk of thrombosis which begins during the periprocedural period and persists over the long-term due to exposure of foreign material within the coronary vasculature and other factors [10]. Historically, dual antiplatelet therapy (DAPT) consisting of aspirin and a thienopyridine was used to mitigate any negative consequences including stent thrombosis and recurrent cardiovascular events. Ticlopidine (Ticlid®) was the first agent to show a benefit in reducing cardiac endpoints but its use was limited because of a higher incidence of blood dyscrasias particularly neutropenia [11,12].

Subsequently, Clopidogrel (Plavix®) was developed and established as the cornerstone of DAPT based on its improved safety profile and efficacy in a wide range of clinical applications [11-16]. Multiple clinical trials have been published in support of its use with PCI making it the benchmark agent for comparison [17-19]. Although Clopidogrel has traditionally endured success as aspirin's chief partner, its associated shortcomings eventually led to the development of other oral antiplatelet agents such as Prasugrel (Effient®) and Ticagrelor (Brilinta®) (Figure 1). Because Clopidogrel requires a complex metabolic transformation to its active form, it was predisposed to multiple drug interactions and genetic polymorphisms that hindered its ability to fully inhibit platelet aggregation [20-24]. Prasugrel was designed to undergo active conversion through a more efficient pathway with the intent of establishing greater bioavailability and platelet inhibition. Until recently though, Prasugrel was primarily limited to those undergoing PCI for an ACS based on data from the TRITON-TIMI 38 trial but it has now been shown to maintain its benefit regardless of PCI strategy [25,26]. Ticagrelor, on the other hand,

receptors but was developed as an orally active drug that does not require active metabolism like the previously described prodrugs. Both newer agents, however, have been associated with a higher incidence of certain types of bleeding and require more research before their use can be extrapolated to other indications [25-27]. Furthermore, these agents are recommended to be withheld at least 5 days before CABG.

As personalized medicine strives forward, clinicians and researchers may continue to find themselves improving upon the shortcomings of previously developed agents in an effort to fine tune

the balance between safety and efficacy. The newest antiplatelet agent in development, Cangrelor (AR-C69931MX, Medicines Company), has been designed as an intravenous agent with rapid and reversible platelet inhibition in order to allow providers to take advantage of unique clinical situations where oral administration or absorption may not be practical. It was designed by changing the chemical structure of adenosine triphosphate through the replacement of anhydride groups with methylene groups and a halogen as well as through the addition of nonpolar moieties and sulfide linked chains [28]. More Phase III studies are needed to establish its role around the current agents but until then, it is likely that the search for the next cornerstone of therapy will continue.



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