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NEW RESEARCH PAPER

$P2Y_{12}$ Receptor Function and Response to Cangrelor in Neonates With Cyanotic Congenital Heart Disease

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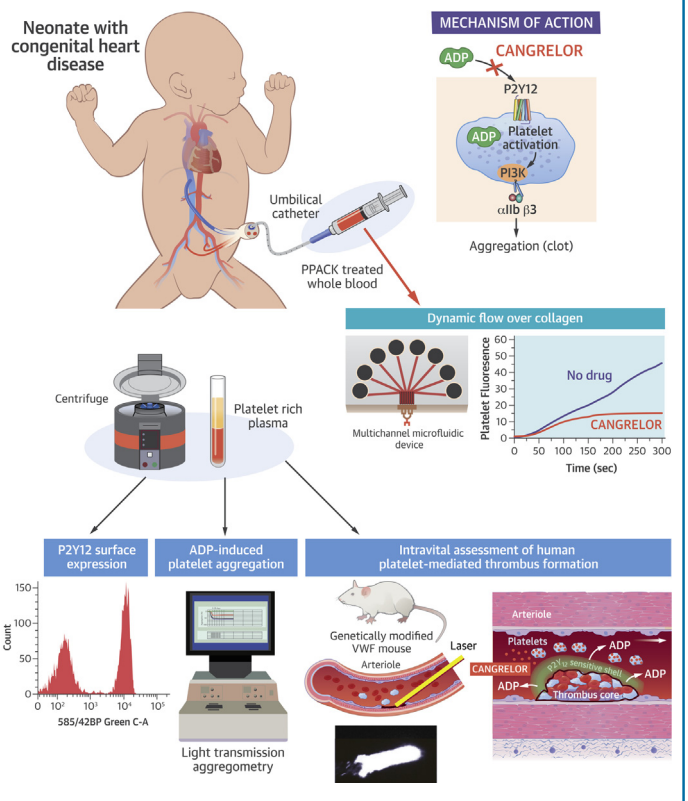
VISUAL ABSTRACT



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HIGHLIGHTS

- **Platelets from neonatal patients with cyanotic congenital heart disease have a nearly identical response to adenosine diphosphate activation and $P2Y_{12}$ receptor blockade with cangrelor as their adult counterparts.**
- **Integrating high-throughput technologies with unique biological platforms can provide considerable insight into the potential clinical use of antiplatelet agents for neonatal and pediatric patients at risk for thrombosis.**
- **Cangrelor may prove to be an effective antithrombotic drug with pharmacological properties well suited for use in the immediate post-operative period for neonates palliated with systemic-to-pulmonary artery shunts.**

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ABBREVIATIONS AND ACRONYMS

ADP = adenosine diphosphate

ATE = acute thromboembolic events

CHD = congenital heart disease

EC_{50} = the concentration of a drug that gives half-maximal response

IC_{50} = the concentration of an inhibitor where the response (or binding) is reduced by one-half

LTA = light transmission aggregometry

PCI = percutaneous coronary intervention

PD = pharmacodynamic

PK = pharmacokinetic

VWF = von Willebrand factor

SUMMARY

Shunt thrombosis remains a major cause of morbidity and mortality, especially during the initial palliation for single-ventricle physiology. The authors present evidence that the $P2Y_{12}$ inhibitor cangrelor may fill a therapeutic void in thromboprophylaxis. They base this theory on results showing that platelets from neonatal patients with cyanotic congenital heart disease have a robust response to adenosine diphosphate and are amenable to $P2Y_{12}$ inhibition with cangrelor. Unique to this study was their ability to establish drug efficacy in an avatar mouse model that permits the in vivo evaluation of human platelet–mediated thrombus formation illustrating that this $P2Y_{12}$ inhibitor yields the intended biological response. (J Am Coll Cardiol Basic Trans Science 2017;■:■–■)

Acute thromboembolic events (ATEs) are rapidly becoming the new epidemic in centers that care for critically ill neonates due to an increase in invasive monitoring, life-saving technologies such as extracorporeal membrane oxygenation, and new surgical techniques and graft materials used to repair complex congenital heart disease (CHD) (1,2). In the latter case, infants (aged <6 months) constitute the major proportion (approximately 70%) of patients seen in tertiary care centers with ATEs (3). In particular, those with single-ventricle physiology who require placement of a systemic-to-pulmonary artery shunt (e.g. modified Blalock-Taussig or central shunts) are at greatest risk, especially in the early post-operative period (3–5). Consequently, this scenario has resulted in suboptimal post-operative outcomes as exemplified in a retrospective review of 2,058 neonates who underwent palliation with a systemic-to-pulmonary artery shunt at multiple centers; discharge mortality and complication rates were around an aggregate of 6.7% and 12.3%, respectively (6). Early institution of aspirin, an irreversible inhibitor of platelet cyclooxygenase, is believed to be beneficial in reducing the risk of shunt occlusion and death (7,8), but controversy remains regarding its overall effectiveness. In fact, it has been reported that aspirin alone may not be sufficient to fully inhibit platelet function in the immediate post-operative period (9). Thus, an urgent need remains for additional pharmacological protection to provide adequate thromboprophylaxis for these critically ill patients.

Clopidogrel (a thienopyridine derivative) is an antiplatelet agent that targets the adenosine diphosphate (ADP) receptor $P2Y_{12}$ and is known to reduce the risk of ischemia and thrombosis in adult patients during and after percutaneous coronary intervention (PCI) (10,11). It does so by impairing $P2Y_{12}$ potentiation of platelet-dense granule secretion in response to strong agonists, stabilization of platelet aggregates by contributing to the activation of αIIbβ3, and inhibition of the antiplatelet effects of prostacyclin (12). Despite its proven clinical efficacy in adults with cardiovascular disease, clopidogrel has several major drawbacks that would limit its use in the immediate post-operative period for neonatal cardiac patients. These drawbacks include the requirement for oral administration that may result in erratic absorption (particularly in bypass cases), delay in the onset of action due to the need for conversion of the pro-drug to an active metabolite, and irreversible inhibition of the $P2Y_{12}$ receptor that would necessitate platelet transfusion(s) if bleeding occurred (13). Interestingly, a previous clinical trial evaluating clopidogrel therapy in infants with cyanotic CHD who underwent palliation with a systemic-to-pulmonary artery shunt failed to show any benefit in reducing the rate of death or shunt-related morbidity in drug-treated patients (14). This outcome was somewhat surprising as the supraphysiologic shear rates (in excess of 15,000 s^{-1}) and shearing forces predicted to occur in artificial conduits connecting the systemic circulation to the pulmonary artery would favor $P2Y_{12}$-mediated platelet activation and aggregation (15). However, potential shortcomings of this trial were the low

(Dr. Prats and Ms. Evans) are employed by the company whose product was studied in the present research. Dr. Prats has also received consulting fees from the current sponsor of the study product (cangrelor [Chiesi USA, Inc.]). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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