

What's New with the Use of Anti-platelet Therapy in Acute Coronary Syndromes?

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Objectives

After the completion of this program, the pharmacist, pharmacy technician, or pharmacy intern will be able to:

- Describe the role of anti-platelets in acute coronary syndromes.
- Compare the mechanism of action, pharmacokinetics, and side effect profile for each medication presented.
- Identify medication safety issues associated with clopidogrel, prasugrel, and ticagrelor and discuss how the pharmacy plays a role to make these medications safe.

Table 1. Clinical Outcome Studies Describing Potential Drug Interaction Between Clopidogrel and Proton Pump Inhibitors (PPI).

Study	Primary Endpoint	Results	Comments
Rassen, et al. ¹ N=18,565	MI hospitalization or death	Propensity score-adjusted rate ratio of users of PPIs vs. Non-users (95% CI): -Combined endpoint: 1.22 (0.99-1.51) -MI 1.22 (0.95-1.57) -Death: 1.20 (0.84-1.70) -Revascularization: 0.97 (0.79-1.21)	-Meta-analysis of 3 large cohort studies -Did not find a major clinical relevant drug interaction between PPIs and clopidogrel
O'Donoghue, et al. ² N=13,608	Composite (CV death, MI, or stroke)	PPI use was not associated with an increase in the composite endpoint with clopidogrel (11.8% vs. 12.2%, p=0.8) or prasugrel (10.2% vs. 9.7%, p=0.58)	-All PPIs were included -Post hoc analysis of a large randomized controlled trial -Varying durations of PPI use
Juurink, et al. ³ N=2791	Rates of readmission to the hospital for acute MI (current, previous, remote PPI use, H ₂ RA use, or pantoprazole use)	Readmission for acute MI, adjusted OR (95% CI) -Current use: 1.27 (1.03-1.57) -Previous use: 0.86 (0.63-1.19) -Remote use: 0.81 (0.46-1.41) -H ₂ RA use: 0.94 (0.63-1.40) -Pantoprazole: 1.02 (0.70-1.47)	-Nested case-control -Positive association between PPI current use and MI -Omeprazole accounted for as it is not OTC in Canada
Ho, et al. ⁴ N=8205	All-cause mortality or rehospitalization for ACS	Death or rehospitalization was higher in the patients prescribed a PPI vs. patients with no PPI (29.8% vs. 20.8%), Adjusted OR 1.25 (1.11-1.41)	-All PPIs were included, however 60% were taking omeprazole -Patients in the PPI group resulted in less

MI: Myocardial Infarction; CV: Cardiovascular; CI: Confidence Interval; H₂RA: Histamine₂ receptor antagonist; OR: Odds ratio; OTC: Over-the-counter

ADEs associated with bleeding

Table 2. Clinical Studies Evaluating the Role of Prasugrel in Acute Coronary Syndromes.

Study	Primary Endpoint	Results	Comments
Wiviott, et al.⁵ N= 13, 608	Composite (rate of death from CV causes, nonfatal MI, or nonfatal stroke)	Composite endpoint was decreased in the prasugrel group vs. the clopidogrel group (9.9% vs 12.1%, p<0.001)	-Greater benefit seen in diabetic patients -Higher rates of major hemorrhage, life-threatening bleeding, and non-fatal bleeding -Post hoc analysis showed three populations with increased bleeding (previous stroke or TIA, age >75, weight <60 kg)
Wiviott, et al.⁶ N=201	Inhibition of platelet aggregation (IPA) at 6 hrs and 14 days	Prasugrel showed a greater antiplatelet effect (Loading dose (6hrs) prasugrel 74.8% vs. clopidogrel 31.8%, p<0.001) and (maintenance dose (14 days) prasugrel 61.3% vs. clopidogrel 46.1%, p<0.001)	-Loading dose of clopidogrel was 600 mg; maintenance dose was 150 mg (higher than what is commonly used in practice) -Bleeding rates were low in both groups
Murphy, et al.⁷ N=13, 608	Recurrence of CV death, MI, or stroke	Reduction in recurrent events with prasugrel vs. clopidogrel for CV death, MI or stroke (HR 0.65; 95% CI 0.46-0.92, p=0.016)	-Analyzed data from the TRITON-TIMI 38 trial -Less total events with prasugrel than with clopidogrel
Morrow, et al.⁸ N=13, 608	Occurrence of an MI	Prasugrel reduced the risk of MI at 30 days compared to clopidogrel (7.4% vs. 9.7%, p<0.0001)	-Reduced the risk of MI with procedure based and non-procedure based MI's -Reduced risk across MI size

MI: Myocardial Infarction; CV: Cardiovascular; TIA: Transient Ischemic Attack; HR: Hazard Ratio; CI: Confidence interval;

Table 3. Clinical Studies Evaluating the Role of Ticagrelor in Acute Coronary Syndromes.

Study	Primary Endpoint	Results	Comments
Cannon, et al.⁹ N=984	Bleeding events (major and minor) within the first 4 weeks of treatment	No difference was found between the clopidogrel and AZD6140 groups: -Clopidogrel (8.1%) -AZD6140 90 mg (9.8%, p=0.43) -AZD6140 180 mg (8%, p=0.96)	-No difference in clinical end points (small number of patients) -Side effects noted included dyspnea, hypotension, and nausea (4% discontinuation versus 1% with clopidogrel)
Wallentin, et al.¹⁰ N=18,624	Composite (death from vascular causes, MI, or stroke)	Events in the composite end point occurred less with ticagrelor (9.8%) vs. clopidogrel (11.7%) at 12 months HR, 0.84(95% CI 0.77-0.92; p<0.001)	-Bleeding rates were similar between both groups, (ticagrelor showed a higher rate of non-CABG related major bleeding) -More dyspnea with ticagrelor was noted
Grubel, et al.¹¹ N=123	ONSET: IPA at 2 hours OFFSET: slope of IPA between 4 and 72 hours after the last dose of study drug	ONSET: IPA was greater for ticagrelor than for clopidogrel (88% vs. 38%, p<0.0001) OFFSET: Greater slope of IPA in the ticagrelor group than in the clopidogrel group (-1.04 vs. -0.48 IPA %/hr, p<0.0001)	-The onset of platelet inhibition is rapid (within 30 minutes) and greater than 600 mg of clopidogrel when ticagrelor is given -Greater anti-platelet effect was sustained throughout the maintenance period with ticagrelor -The rate of offset was greater than clopidogrel, with return to baseline quicker with ticagrelor
Grubel, et al.¹² N=98	Estimation of the proportion of clopidogrel nonresponders who responded to ticagrelor after steady state dosing based on platelet aggregation measurements taken 4 hours after the last dose	Proportion of patients who responded to ticagrelor was higher than those who responded to clopidogrel (p=0.005)	-Ticagrelor therapy was associated with greater platelet inhibition with clopidogrel responders and non-responders -Ticagrelor produced a rapid increase in platelet inhibition in both clopidogrel responders and non-responders

MI: Myocardial Infarction; CV: Cardiovascular; HR: Hazard Ratio; CI: Confidence interval; IPA: Inhibition of platelet aggregation

References

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