“Proton Pump Inhibitors increase Cardiovascular risk in patient taking Clopidogrel”

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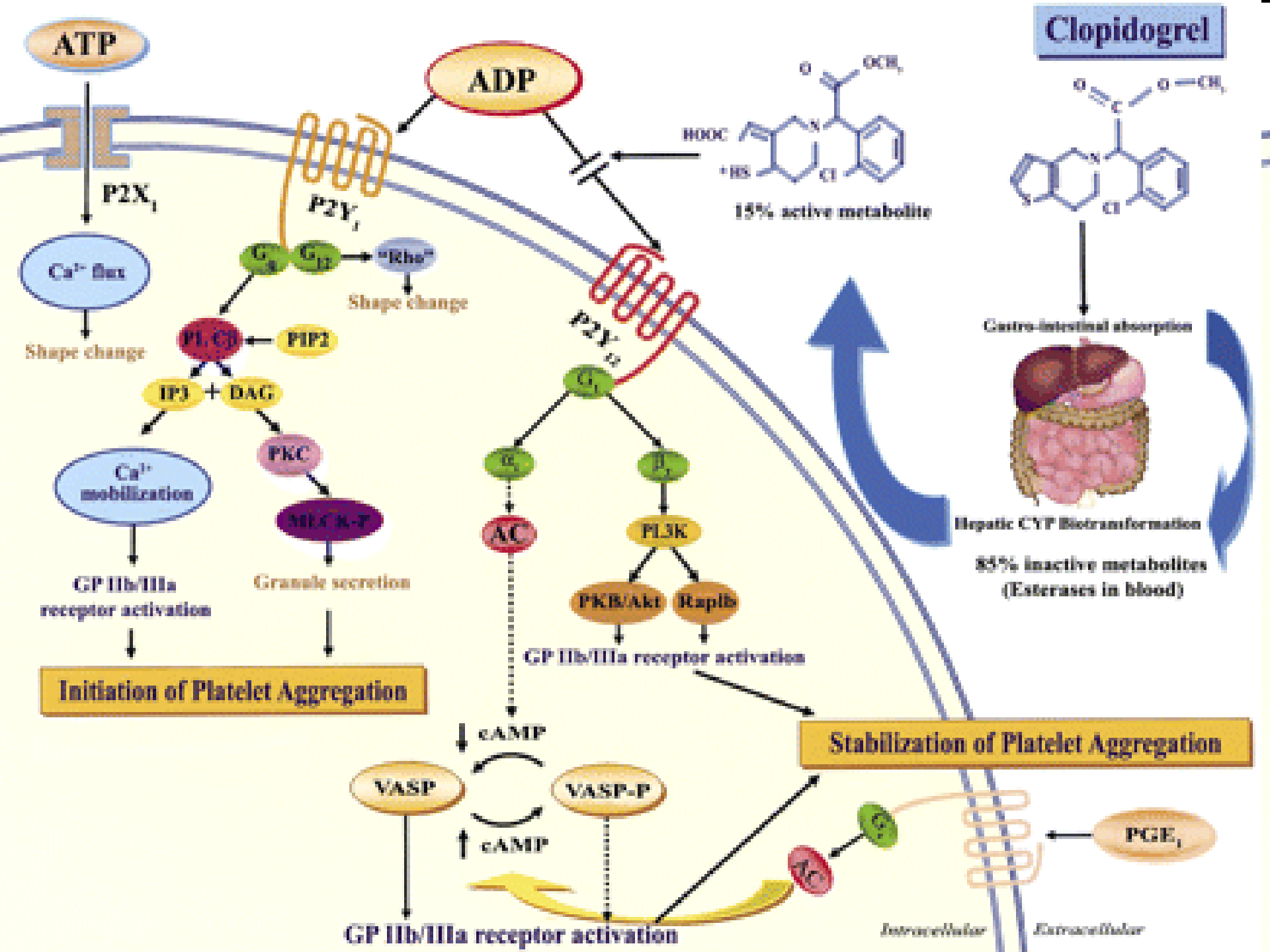
Clopidogrel Metabolism

- Clopidogrel is an inactive prodrug that is converted to its active metabolite by cytochrome P450 (CYP) enzyme 2C19 ,leading to inhibition of ADP-induced platelet aggregation by irreversible blockade of the platelet P2Y12 receptor .

- Both clopidogrel and its active metabolite are relatively short lived in plasma. With repeated 75mg daily doses, plasma concentrations of the parent compound and its active metabolite fall below the lower limit of quantification after 2hr.

- Despite a short half-life, the irreversible binding of clopidogrel's active metabolite to the platelet receptor leads to a prolonged pharmacodynamic effect. Inhibition of platelet aggregation by clopidogrel lasts for several days, with platelet function returning to baseline about 5 days after stopping the drug.


ATP
ADP
Clopidogrel
P2X1
P2Y1
P2Y12
Ca2+ flux
Shape change
Gq
G12/13
"Rho"
Shape change
PLCβ
PIP2
IP3 + DAG
Ca2+ mobilization
PKC
MLC K-P
GP IIb/IIIa receptor activation
Granule secretion
Initiation of Platelet Aggregation
Gi
α
βγ
AC
PI3K
PKB/Akt
Rap1b
GP IIb/IIIa receptor activation
15% active metabolite
Gastro-intestinal absorption
Hepatic CYP Biotransformation
85% inactive metabolites
(Esterases in blood)
cAMP
VASP
VASP-P
cAMP
GP IIb/IIIa receptor activation
Stabilization of Platelet Aggregation
PGE1
Intracellular
Extracellular

PPI Metabolism

- PPIs are also prodrugs transformed in the acid environment of gastric parietal cells nonenzymatically to active derivatives, which bind covalently to H+ K+-ATPase (proton pump) . This irreversible inhibition of the proton pump leads to long-term acid suppression for up to 36hr, despite very short plasma half-lives of ~0.5 to 2h .

- Recent studies show that PPIs reduce the ex vivo inhibition of platelet aggregation achieved during treatment with clopidogrel.

- From the National Patient Registry, all consecutive patients older than 30 years hospitalized with acute myocardial infarction between 2000 and 2006 in Denmark were considered.

- The primary outcome was a composite of rehospitalization for myocardial infarction or stroke or cardiovascular death.

- Two statistical methods were used to estimate the risk associated with PPI treatment with or without concomitant use of clopidogrel.
- Cox proportional hazards model was used to derive hazard ratios (HRs) and 95% CIs.

- Clopidogrel was associated with lower event rates, and PPIs were associated with higher event rates.
- The event rates were highest among patients who received a PPI but not clopidogrel.

Cox Proportional Hazards Regression Analysis

- The time-dependent Cox proportional hazards regression analysis , based on patients who filled prescriptions for clopidogrel within 30 days of discharge, demonstrated an increased risk for the primary end point (cardiovascular death or rehospitalization for myocardial infarction or stroke) among patients who received both clopidogrel and a PPI (HR, 1.29 [95% CI, 1.17 to 1.42]; $P < 0.001$) compared with those who did not receive a PPI.

Time-Dependent, Propensity Score–Matched Cox Proportional Hazards Regression Analysis

- The propensity score–matched Kaplan -Meier analysis depicts the elevated risk for cardiovascular death or rehospitalization for myocardial infarction or stroke for patients who received PPIs with or without clopidogrel.

Additional Analyses

- An unmeasured confounder would have to elevate risk by 2.5 to 3 to fully explain the increased risk for cardiovascular events observed with either PPI or clopidogrel and PPI.

- A post hoc analysis of the randomized CREDO (Clopidogrel for the Reduction of Events During Observation) trial also found baseline PPI use to be associated with increased cardiovascular events, regardless of whether clopidogrel was used.

- These studies were based on selected patients eligible for randomized trials, who were usually younger and less likely to have significant comorbid conditions than many patients who are prescribed both clopidogrel and a PPI.

- PPIs seem to be associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use. Increased cardiovascular risk associated with PPI use independent of clopidogrel is caused by unmeasured confounders.

- Clopidogrel is converted to its active metabolite by cytochrome P450 (CYP) enzymes. Clopidogrel users with decreased CYP2C19 function have less inhibition of platelet aggregation and increased cardiovascular (CV) events.

- As PPI metabolism also involves CYP2C19, competition by PPIs might interfere with clopidogrel ’s action. Omeprazole, but not other PPIs, worsens surrogate markers of clopidogrel efficacy. Some observational studies show that clopidogrel users prescribed PPIs have increased risks of CV events (hazard / odds ratios = 1.25 – 1.5).

- Recent studies and the ensuing media coverage have raised concerns among health-care providers and patients that an interaction of PPIs and clopidogrel could increase CV events such as coronary artery stent thrombosis and myocardial infarction (MI).

Thank You