

# **ELEVATE-TIMI 56: Discussion**

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# What Is Already Known

- Clopidogrel must render plasma active metabolite levels for *in vivo* anti-platelet function
- Mechanistically CYP2C19 is primarily responsible for producing active metabolite from clopidogrel
- Patients who carry nonfunctional alleles of CYP2C19 such as \*2 have (replicated numerous times):
  - Reduced plasma active metabolite levels
  - Increased risk of *ex vivo* residual platelet activity
  - Greater risk of cardiac events, i.e. stent thrombosis

## Summary and Analysis: Strengths or What This Study Adds

- **Patients:** stable CAD, at SS on 75 mg/day, studied longitudinally between 4-24 wks post-MI or PCI
  - Relative % of post-MI or PCI not specified
- **N of 333:** 74% non-carriers (\*1/\*1), 24% (\*1/\*2) and 1.8% (\*2/\*2), robust p values
- **PFT:** 14 days after dose, VASP and VerifyNow P2Y<sub>12</sub>, assumed to relate to clinical events (not reported)
- **Actionable information:** clear dose information for difficult subgroup (IM, \*1/\*2) with VASP PRI-matching to 75 mg in EM subgroup (\*1/\*1). Avoid clopidogrel in PMs. No cost to ADRs.

# Summary and Analysis: Weaknesses or Limitations

- Age and sex-match between non-carriers and carriers not clear (RPA independent of genetics)
- Race of trial participants not described although 5-10% of Asians are \*3 carriers (not measured)
- CYP2C19\*17 carrier status not reported (10-20%)
- Absence of plasma active metabolite levels to confirm diminished clopidogrel conversion
- Significant variability in CYP2C19 \*2/\*2 VASP PRI as a function of dose (2X at 300 mg), small N (6)
- Potential effects, if any, of polymorphisms in efflux pump (PGP) on absorption

## Summary and Analysis: Weaknesses or Limitations

- **Concomitant medicines** not reported but low dose ASA, statins, PPIs and antidiabetic drugs of interest
  - Known modulators of 2C19 activity through DDI
  - Differential effects non-carriers and \*1/\*2, \*2/\*2
- **Concomitant diseases** not reported but diseases such as Type 2 diabetes & obesity affect platelet function

*Implications: confirmed previous reports of higher platelet reactivity between non-carriers and carriers. Results support higher doses of clopidogrel in \*1/\*2 genotypes (IM) but not \*2/\*2 (PM) relative to \*1/\*1 (EM)*