Does Clopidogrel **PLAVIX** + ASA **ASPRIN** impact mortality?

The purpose of this Q&A is to help clarify some of the misconceptions surrounding recent publications.

**BOTTOM LINE**

- Compared to ASA alone, dual antiplatelet therapy (DAPT) with clopidogrel + ASA does **not** ↑ or ↓ cardiovascular (CV) mortality, regardless of indication. However, the effect on **all-cause mortality** is less clear.
- Two meta-analyses of clopidogrel + ASA studies across multiple indications did not detect an ↑ risk in **all-cause mortality**. However, 8 meta-analyses which focused on DAPT post drug-eluting stent (primarily with clopidogrel + ASA) had mixed results.
- In the largest DAPT post drug-eluting stent study to date, the potential ↑ risk of **all-cause mortality** was driven by non-CV death, specifically cancer-related death, not fatal bleeding.
- If there is an ↑ risk in **all-cause mortality**, the absolute risk is small & it appears to only be associated in individuals with a coronary stent who are on clopidogrel + ASA longer than 1 year e.g. ≥12 vs 12 months ARI 0.4%, NNH=250. The benefits of clopidogrel + ASA in these individuals includes ↓ in MI NNT=71-100 & stent thrombosis NNT=143-167.
- Until additional data is available, DAPT >1 year in patients with advanced cancer & coronary stent should be used cautiously.
- Discussion limited to clopidogrel, which has the most data. Ticagrelor & prasugrel have less safety data.

**BACKGROUND**

In November 2015, the U.S. Food & Drug Administration (FDA) released a statement that long-term use of clopidogrel does not ↑ or ↓ the overall risk of death in patients with, or at risk for, heart disease based on their meta-analysis that was prompted by the DAPT study. The meta-analysis also suggested that clopidogrel does not ↑ the risk of cancer or death from cancer.

**DAPT (Dual AntiPlatelet Therapy) Trial** (see RxFiles Trial Summary)

- The DAPT study (drug-eluting stent [DES] analysis) compared 12 versus 30 months of DAPT post coronary stent.
- In a group of highly selected patients 56% excluded at randomization, those who were on DAPT (i.e. ASA + thienopyridine 65% clopidogrel, 35% prasugrel) for 30 months had:
  - ↓ risk of stent thrombosis (NNT=100) & ↓ risk major adverse cardiovascular & cerebrovascular event (MACCE) (NNT=63) but ↑ risk of moderate-severe bleeding (NNH=112)
  - At 30 months, there was a trend of ↑ risk of **all-cause mortality** (2% vs 1.5%, p=0.05) with longer DAPT - this was driven by non-CV deaths (1% vs 0.5%, p=0.02)
- Between months 30 and 33, study medication was discontinued & all patients received open-label ASA. The difference in **all-cause mortality** reached a statistical significant increase (2.3% vs 1.8%, p=0.04) with a NNH=200/33 months for longer DAPT.
  - This was again driven by **non-CV deaths** (1.1% vs 0.6%, p=0.01).
  - **Non-CV death** was divided into 3 types: bleeding, trauma & cancer-related death (not mutually exclusive).
  - The ↑ risk of **non-CV death** was driven by **cancer-related deaths** (31/5020 [0.6%] vs 14/4941 [0.3%], p=0.02), not bleeding.
  - Of note, in the extended DAPT treatment arm, there was 22 more patients with a history of cancer at enrollment (488 vs 466, p=NS). Nine patients (8 vs 1) with **cancer-related deaths** had a diagnosis of cancer prior to enrollment; when these individuals were excluded from the analysis, mortality was no longer statistically significant.
- The DAPT investigators also conducted a separate analysis for those who received bare-metal stents (BMS), with the same trial design (i.e. 12 vs 30 months of DAPT). There was neither a ↓ in thrombosis, nor an ↑ in harm, but the study was underpowered.
- The investigators subsequently combined their DES (85.5%) and BMS (14.5%) analyses to review the risk of mortality. All-cause mortality was NS, but non-CV death was higher in the extended DAPT treatment arm (0.9% vs 0.5%, p=0.01).
- Kaplan-Meier curves for **all-cause mortality** separated at 24 months, and continued to separate up until month 33.

**Meta-Analyses**

- The DAPT study prompted multiple meta-analyses see Table on page 2.
- The FDA & DAPT investigators conducted MA focusing on the potential ↑ risk of mortality with clopidogrel, & included studies that spanned multiple indications. Both groups concluded there was no ↑ risk of mortality with long-term clopidogrel use.
- Multiple other MA were generated to compare the overall benefits & harms associated with various DAPT treatment durations. These 8 meta-analyses focused on the use clopidogrel + ASA post-coronary stent; all-cause mortality results were mixed.
  - Approximately half of the MA concluded there was an ↑ risk of **all-cause mortality** with extended DAPT >12 months. The risk, in absolute terms, was small & varied based on the durations evaluated (absolute risk ↑ of 0.3-0.4%, NNH=250 to 334). There was no ↑ risk when abbreviated DAPT ≤6 months was compared to standard DAPT 12 months.
**TABLE: COMPARISON OF THE META-ANALYSES CONDUCTED SINCE THE DAPT STUDY**

<table>
<thead>
<tr>
<th>See all published in 2015</th>
<th>U.S. FDA†</th>
<th>DAPT Investigators ‡</th>
<th>Meta-Analyses on DAPT for Coronary Stents ¹³⁻¹⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials</td>
<td>12</td>
<td>14</td>
<td>ranged from 9 to 11</td>
</tr>
<tr>
<td>Number of patients</td>
<td>56,799</td>
<td>69,644</td>
<td>29,531 to 32,372</td>
</tr>
</tbody>
</table>

### Included indications

| Atrial fibrillation: ACTIVE-A | ✓ | ✓ | ✓ | - |
| CAD after ACS: CURE | ✓ | ✓ | ✓ | - |
| CVD confirmed or high-risk: CHARISMA | ✓ | ✓ | ✓ | - |
| Lacunar stroke: SP53 | ✓ | ✓ | ✓ | - |
| PAD revascularization: CASPAR | ✓ | ✓ | ✓ | - |
| CAD + elective PCI: CREDO | ✓ | ✓ | ✓ | - |
| CAD + PCI: ARTIC-Interruption | - | ✓ | ✓ | - |
| ASA-171 | - | - | ✓ | - |
| DAPT | - | - | ✓ | - |
| DES-LATE | ✓ | ✓ | ✓ | - |
| EXCELLENT | ✓ | ✓ | ✓ | - |
| ISAR-SAFE | - | - | ✓ | - |
| ITALIC | - | - | ✓ | - |
| OPTIMIZE | ✓ | ✓ | ✓ | - |
| PRODIGY | ✓ | ✓ | ✓ | - |
| RESET | ✓ | ✓ | ✓ | - |
| SECURITY | ✓ | ✓ | ✓ | - |

### Mortality Results

<table>
<thead>
<tr>
<th>Risk of all-cause mortality</th>
<th>NS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of cardiovascular mortality</td>
<td>-</td>
<td>NS</td>
</tr>
</tbody>
</table>

† full meta-analysis has not been published

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### Clopidogrel does not decrease the risk of mortality... but this is not breaking news

- **In the studies that assessed DAPT with clopidogrel, a ↓ in mortality** was only statistically significant together with the other composite endpoint components, which was driven by the reduction in MI.¹⁻⁷ Exception: COMMIT, which was a study conducted in China.²¹

- **Mortality** (all-cause or cardiovascular), as a secondary endpoint was NS,¹⁻⁷ or as in the case of the DAPT study, potentially ↑.¹⁸

### What about Ticagrelor & Prasugrel?

- **In the “Additional Information” section of the FDA announcement, it is noted that prescribers should consider that prasugrel & ticagrelor have been shown to be superior to clopidogrel when used in this patient population [i.e. DAPT post PCI]. In addition, in patients with a history of MI 1 to 3 years prior to study enrollment, ticagrelor has also been shown to reduce the risk of cardiovascular death, MI, & stroke.**⁸

- The above statements are based on clinical trial data, not the FDA meta-analysis (only included clopidogrel).⁸

- **Both Canadian & American guidelines recommend prasugrel or ticagrelor, over clopidogrel, in ACS patients with coronary stents.**²⁵⁻²⁷

- **Prasugrel:** ↓ the risk of CV death as part of the composite endpoint in ACS patients undergoing PCI. Neither all-cause mortality nor CV death was statistically significant as individual secondary endpoints TRITON-TIMI (22), PLATO (23), PEGASUS (24).

- **Ticagrelor:**
  - **In PEGASUS, patients who had a MI 1-3 years prior to study enrollment, both ticagrelor 60mg BID & 90mg BID ↓ mortality as part of the composite endpoint, compared to placebo.**²⁴ However, this was primarily driven by a ↓ in MI.²⁴
  - Ticagrelor 90mg BID is the only P2Y₁₂ inhibitor that showed a ↓ in mortality – i.e. death from vascular causes (NNT=91/9 months) PLATO (23) & death from coronary heart disease (NNT=182/3 years) PEGASUS (24) but both were secondary endpoints (i.e. underpowered).
  - As of March 2016, ticagrelor has not been approved in Canada for patients with a history of MI in the previous 3 years. Ticagrelor 60mg BID is also not currently available on the Canadian market (only 90mg BID).
REFERENCES:


