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.[1-7] 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**.[8,9] However, 8 meta-analyses which focused on **DAPT post drug-eluting stent** (primarily with clopidogrel + ASA) had mixed results.[10-17]
- 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.[18]
- 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.[10-17] The benefits of clopidogrel + ASA in these individuals includes ↓ in MI NNT=71-100 & stent thrombosis NNT=143-167.[10-17]
- 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.[8, 18] The meta-analysis also suggested that clopidogrel does not ↑the risk of cancer or death from cancer.[8]

DAPT (Dual AntiPlatelet Therapy) Trial [18] (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.[19]
- The investigators subsequently combined their DES (85.5%) and BMS (14.5%) analyses to review the risk of mortality.[20]
  - **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.[8-17]
- The FDA & **DAPT** investigators conducted MA focusing on the potential ↑ risk of mortality with clopidogrel, & included studies that spanned multiple indications.[8,9] Both groups concluded there was no ↑ risk of **mortality** with long-term clopidogrel use.[8,9]
- Multiple other MA were generated to compare the overall benefits & harms associated with various DAPT treatment durations.[10-17] These 8 meta-analyses focused on the use clopidogrel + ASA post-coronary stent; all-cause mortality results were mixed.[10-17]
  - 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 all published in 2015

	U.S. FDA† [8]	DAPT Investigators [9]	Meta-Analyses on DAPT for Coronary Stents [10-17]
Number of trials	12	14	ranged from 9 to 11
Number of patients	56,799	69,644	29,531 to 32,372
Included indications			
Atrial fibrillation: **ACTIVE-A**	✓	✓	-
CAD after ACS: **CURE**	✓	✓	-
CVD confirmed or high-risk: **CHARISMA**	✓	✓	-
Lacunar stroke: **SPS3**	✓	✓	-
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			
Risk of all-cause mortality	NS	NS	• Study-defined longer 12, 18, 24, 30, 36 months vs shorter DAPT 3, 6, 12 months: - 4 MA: ↑ risk of **all-cause mortality** (ARI 0.3%, NNH=334) [10,11,,14,15] - 2 MA: **all-cause mortality** NS (1 MA p=0.05) [12,17] • Extended DAPT >1 year vs standard DAPT 1 year: - 5 MA: ↑ risk of **all-cause mortality** (ARI 0.4%, NNH=250) [10,11,13,14,16] - 2 MA: **all-cause mortality** NS (1 MA p=0.05) [12,17] • Abbreviated ≤6 months vs standard DAPT 1 year: - **all-cause mortality** NS
Risk of cardiovascular mortality	-	NS	NS

Different population, wide variance

Narrower population, all PCI

† full meta-analysis has not been published

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, **TRITON-TIMI** (22), **PLATO** (23), **PEGASUS** (24) not the FDA meta-analysis (only included clopidogrel).
- 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)
- **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 $P2Y_{12}$ 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 available on-line www.RxFiles.ca

ACS=acute coronary syndrome **ARI**=absolute risk increase **ASA**=acetylsalicylic acid **BMS**=bare metal stent **CAD**=coronary artery disease **CV**=cardiovascular **CVD**=cardiovascular disease **DAPT**=dual antiplatelet therapy **DES**=drug-eluting stent **FDA**=Food & Drug Administration **MA**=meta-analysis/meta-analyses **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-statistically significant **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention

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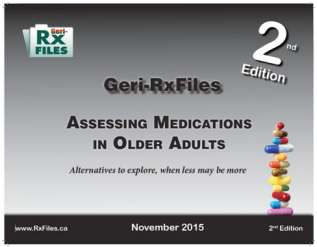

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