DAPT: 12 vs 30 Months of Dual AntiPlatelet Therapy after Drug-Eluting Stents [1]

BOTTOM LINE

- In **DAPT**, a group of highly selected patients 56% excluded at randomization who received a drug-eluting stent (DES) 27% paclitaxel & dual antiplatelet therapy (DAPT, i.e. ASA + thienopyridine) beyond 1 year (30 months in total) had:
  - ↓ risk of stent thrombosis (NNT=100) and ↓ risk major adverse cardiovascular & cerebrovascular event (MACCE) (NNT=63) but ↑ risk of moderate-severe bleeding (NNH=112)
  - ↑ risk of all-cause mortality trend at 30 months, statistically significant at 33 months, NNH=200 (primarily driven by non-cardiovascular death)
- The ideal duration of DAPT therapy is still unknown. Extended DAPT therapy may be of most benefit in those who are at a very high risk of ischemic events & low risk of bleeding; however, high risk patients were excluded from **DAPT** (randomization phase).

BACKGROUND [1,2,3,4,5,6,7,8,9]

- DAPT is recommended after bare-metal stent (BMS) & DES placement to ↓ the risk of stent thrombosis & MACCE.
- Compared to BMS, DES ↓ the risk of restenosis & the need for target vessel revascularization procedures; however, DES may ↑ the risk of stent thrombosis, depending on the type:
  - 1st generation DES (G_1DES; paclitaxel, sirolimus): ↑ risk of very late stent thrombosis (i.e. >1 year after PCI) compared to BMS.
  - Newer generation DES (e.g. everolimus, zotarolimus): similar rate of very late stent thrombosis as BMS.
- The **Canadian Cardiovascular Society 2012 Antiplatelet Guidelines** recommend DAPT x 12 months after a coronary stent has been inserted. The committee also suggests that DAPT may be continued beyond 12 months in patients who have a high risk of thrombosis & a low bleeding risk (conditional recommendation, low-quality evidence).[4]
- Several other clinical practice guidelines make similar statements with extended DAPT, which is based on observational studies that suggested DAPT beyond 1 year ↓ the risk of very late stent thrombosis with G_1DES.[5,6,7] The Food & Drug Administration (FDA) requested that a large randomized controlled trial be conducted to address this issue.
- Three randomized controlled trials have evaluated extended vs standard (12 months) DAPT – **DES-LATE**, **ARTIC-Interruption**, **DAPT**. All three studies excluded patients with a high thrombosis or bleed risk. Patients could only be randomized to extended DAPT if they were 'event-free' after 12 months of DAPT (i.e. no major adverse cardiac or cerebrovascular events, or major bleeding).
  - **ARTIC-Interruption** (2014, France):[8] n=1,259 patients with DES (~40% G_1DES), open-label DAPT x 12 months vs 18 to 30 months (90% clopidogrel, 10% prasugrel). Primary endpoint (death, MI, stent thrombosis, stroke or urgent revascularization): NS. Major bleeding (STEEPLE): NS; major & minor bleeding: ↑ risk with extended DAPT, NNH=100
  - **DES-LATE** (2014, Korea):[9] n=5,045 patients with DES (~64% G_1DES), open-label DAPT 12 months vs 36 months (100% clopidogrel). Primary endpoint (death from CV causes, MI, stroke): NS; stent thrombosis: NS. Major bleeding (TIMI): NS
- Of note, because very late stent thrombosis is rare (0.3% with G_1DES, 0.04% with newer generation DES), it is estimated that approximately 10,000 individuals would need to be recruited in order to evaluate extended DAPT for this outcome.

TRIAL BACKGROUND [1,2]

DESIGN: international 11 countries, multi-centre 452 sites, prospective, open-label followed by a randomized, double-blinded, placebo controlled trial. ITT & superiority for efficacy outcomes. Concealed allocation. Funding: 8 stent and pharmaceutical manufacturers, including the manufacturers of clopidogrel (Bristol Myers Squibb, Sanofi) and prasugrel (Eli Lilly), & the Harvard Clinical Research Institute. Enrolment period: August 2009 - July 2011.

INTERVENTION: DAPT (ASA + $P2Y_{12}$ receptor inhibitor) 12 months vs 30 months

- **Enrollment:** all participants received open-label DAPT x 12 months (months 0-12)
  - ASA 75-325mg daily x 6 months, then 75-162mg daily + clopidogrel 300-600mg x 1, then 75mg daily, **or** + prasugrel 60mg x 1, then 5-10mg daily (5mg daily if <60kg)
- **Randomization:** eligible patients were randomized to DAPT or placebo + ASA x 18 months (months 12-30)
- **Observational follow-up:** open-label ASA only x 3 months (months 30-33)
- Stent type, choice of thienopyridine, and dose of ASA was left to the discretion of the clinician overseeing care.

INCLUSION: Enrollment: age >18 years, undergoing PCI with DES or BMS stent (only DES data presented here)

- **Randomization:** "12 Month Clear" i.e. DAPT x 12 months, event free (i.e. no death, MI, stroke, repeat coronary revascularization, stent thrombosis, & moderate or severe GUSTO bleeding) and adherent to therapy (80-120% of doses during months 0-6 and without interruption of therapy >14 days during months 6-12)

EXCLUSION:

- **Enrollment:** stent diameter <2.25 or >4.0mm, pregnant women, planned surgery requiring discontinuation (>14 days) of antiplatelet therapy within 30 months post PCI, current medical condition with a life expectancy <3 years, on warfarin or similar anticoagulant, treated with both DES and BMS
- **Randomization:** switched thienopyridine type or dose within 6 months before randomization, PCI or cardiac surgery between 6 weeks post-index procedure and randomization, planned surgery requiring the discontinuation (>14 days) of antiplatelet therapy within 21 months after randomization

POPULATION at randomization: n=9961 of 22,866 who received a DES

- mean age ~62 years, ~75% ♂, 88% Caucasian, 89.5% from North America
- mean body weight 91.5kg (±19.5kg), BMI 30.5kg/m^2 (±5.8kg/m^2)
- 75% HTN 75.8% DAPT vs 74% placebo + ASA, p=0.03, 30.6% DM, ~25% smoker current or within past year, ~22% MI, ~3% stroke/TIA, ~5% HF, ~6% PAD
- ~30% prior PCI, ~11.5% prior CABG, ~51% had risk factor(s) for stent thrombosis e.g. STEMI, NSTEMI, renal failure, LVEF<30%, >2 vessels stented, etc
- **Indication for PCI:** ~38% stable angina, ~20% "other", ~17% unstable angina, 15.5% NSTEMI, ~10.5% STEMI
- **Type of thienopyridine:** ~65% clopidogrel, ~35% prasugrel; 22% were on a proton-pump inhibitor at randomization [3]
- **Type of DES:** ~47% everolimus, ~27% paclitaxel, ~13% zotarolimus, ~11% sirolimus & 2% >1 type
- Mean number: treated lesions 1.3, treated vessels 1, stents 1.5, stent length 27.5mm
- 53% stent diameter ≥3mm, 97% native coronary artery lesions (~40% left anterior descending), 43% modified ACC-AHA lesion B2 or C

RESULTS

follow-up: 30 and 33 months

TABLE 1: EFFICACY & SAFETY

PRIMARY ANALYSIS PERIOD: ITT & superiority

MONTHS 12 TO 30

CLINICAL ENDPOINTS	DAPT n=5020	PLACEBO + ASA n=4941	HAZARD RATIO (95% CI)	P-VALUE	NNT/NNH	COMMENTS
CO-PRIMARY EFFICACY ENDPOINTS						
Stent thrombosis	0.4%	1.4%	0.29 (0.17-0.48)	<0.001	100/30 MONTHS	- **MACCE** rates primarily driven by MI - **MI not related to stent thrombosis:** DAPT 1.8% vs placebo + ASA 2.9%, HR 0.59, p<0.001 - **All-cause mortality** was primarily driven by non-cardiovascular death - **Cancer-related deaths** DAPT n=31 vs placebo + ASA n= 14, p=0.02 - **Discontinuation Rate:** DAPT 21.4% vs placebo + ASA 20.3%, NS
MACCE (death, MI, stroke)	4.3%	5.9%	0.71 (0.59-0.85)		63/30 MONTHS	
SECONARY EFFICACY ENDPOINTS						
Myocardial Infarction	2.1%	4.1%	0.47 (0.37-0.61)	<0.001	50/30 MONTHS	
Stroke	0.8%	0.9%	NS	0.32	-	
All-Cause Mortality	2%	1.5%	1.36 (1.00-1.85)	0.052	-	

SECONDARY ANALYSIS PERIOD: ITT & superiority

MONTHS 12 TO 33

CLINICAL ENDPOINTS	DAPT x 30 MONTHS THEN ASA x 3 MONTHS n=5020	PLACEBO + ASA n=4941	HAZARD RATIO (95% CI)	P-VALUE	NNT/NNH
Stent thrombosis	0.7%	1.4%	0.45 (0.29-0.69)	<0.001	143/33 MONTHS
MACCE (death, MI, stroke)	5.6%	6.5%	0.82 (0.7-0.97)	0.02	112/33 MONTHS
Myocardial Infarction	3%	4.5%	0.61 (0.49-0.76)	<0.001	67/33 MONTHS
Stroke	1%	1.1%	NS	0.48	-
All-Cause Mortality	2.3%	1.8%	1.36 (1.02-1.82)	0.04	200/33 MONTHS

PRIMARY SAFETY ENDPOINT: patients who could be evaluated; superiority & non-inferiority

MONTHS 12 TO 30

CLINICAL ENDPOINTS	DAPT n=4710	PLACEBO + ASA n=4649	HAZARD RATIO (95% CI)	P-VALUE	NNT/NNH
GUSTO moderate or severe bleeding	2.5%	1.6%	1.61 (1.21-2.16)	0.001 NS for non-inferiority	112/30 MONTHS

SECONDARY SAFETY ENDPOINTS: patients who could be evaluated

CLINICAL ENDPOINTS	DAPT n=4710	PLACEBO + ASA n=4649	RISK DIFFERENCE % (95% CI)	P-VALUE	NNT/NNH 30 MONTHS
GUSTO severe bleeding Intracranial bleed or hemodynamic compromise requiring intervention	0.8%	0.6%	0.2 (-0.1-.06)	0.15	-
GUSTO moderate bleeding transfusion, but hemodynamically stable	1.7%	1%	0.7 (0.2-1.2)	0.004	143
BARC Type 2, 3 or 5	5.6%	2.9%	2.6 (1.8-3.5)	<0.001	37
BARC Type 2 overt, actionable bleed	3.1%	1.5%	1.5 (0.9-2.1)		63
BARC Type 3 overt bleed, ↓Hgb & transfusion	2.6%	1.5%	1.1 (0.6-1.7)		91
BARC Type 5 fatal bleed	0.15%	0.09%	0.1 (-0.1-0.2)	0.38	-

Events 3 Months After Discontinuing DAPT:*

DAPT Arm (last 3 months of tx vs 3 months after)
- Stent thrombosis: HR 0.12 (0.01-0.22) → 0.31 (0.13-0.50)
- MACCE: HR 0.8 (0.53-1.07) → 1.59 (1.2-2)
- MI: HR 0.43 (0.23-0.63) → 1.12 (0.8-1.5)

DAPT vs Placebo + ASA (months 12-15, p<0.001)
- Stent thrombosis: HR 0.05 (0.01-0.39)
- MACCE: HR 0.38 (0.25-0.59)
- MI: HR 0.24 (0.13-0.42)

*HR/day

In a separate analysis, the DAPT investigators evaluated extended DAPT in patients who had a **BMS** inserted.[10] The authors concluded there was no benefit or harm, but the study was underpowered.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Largest randomized controlled trial assessing DAPT therapy beyond 1 year of stent placement.
- Clinically meaningful endpoints (stent thrombosis, MACCE [including death], bleeding) with ITT analysis for efficacy outcomes.
- Blinded adjucation of clinical outcomes (and unblinded, independent safety committee).
- Extended follow-up. Patients were followed for 3 months after discontinuation of their thienopyridine to assess for rebound ischemia. There was an increased risk of stent thrombosis & MACCE in both groups after discontinuation.
- Only ~5% of patients lost to follow-up.

LIMITATIONS:
- Only 43.6% (9961/22,866) of the enrolled participants who received a DES were randomized at 12 months. 11.5% (2638/22,866) had an event(s) during the first 12 months of therapy and approximately 2/3 (61%, 1620/2638) of these individuals required revascularization. 25.4% (5808/22,866) withdrew consent.
- Low risk compliant patient population, i.e. those who had an event (thrombosis, bleed, death) or were non-compliant were excluded from the randomization phase. Only 22% of the study population was on a proton-pump inhibitor at randomization.

UNCERTAINITIES:
- Benefits & risks in a higher-risk population
- Potential increase in non-cardiac deaths, e.g. cancer-related, fatal trauma
- Outcomes with other stent types or non-thienopyridine P2Y12 inhibitors (e.g. ticagrelor)
- **Difference in outcomes for 1st vs 2nd generation DES**
  - The risk of stent thrombosis is thought to be higher with 1st generation DES (e.g. paclitaxel, 27% of patient population). When these individuals were excluded for a post-hoc analysis, the difference in stent thrombosis between groups lessened (months 12-30: DAPT 0.23% vs placebo + ASA 0.72%, HR 0.33 [95% CI 0.15-0.72], p=0.004, ARR=0.49%, NNT=205).[3]

RxFILES RELATED LINKS

- Duration of DAPT & Triple Therapy RxFiles Chart
- **PCI-CLARITY** RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CLARITY%20Trial%20Summary.pdf
- **PCI-CURE** RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CURE%20Trial%20Summary.pdf
- **PLATO** RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/PLATO%20Trial%20Summary.pdf
- **TRITON-TIMI** RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf

♂=male **ACS**=acute coronary syndrome **ARI**=absolute risk increase **ASA**=acetylsalicylic acid **BARC**=Bleeding Academic Research Consortium criteria **BMI**=body mass index **BMS**=bare-metal stent **CABG**=coronary artery bypass graft **CI**=confidence interval **CV**=cardiovascular **DAPT**=dual antiplatelet therapy **DES**=drug-eluting stent **DM**=diabetes mellitus **G_1DES**=1st generation DES **GUSTO**=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria **HF**=heart failure **HR**=hazard ratio **HTN**=hypertension **ITT**=intention to treat **LVEF**=left ventricular ejection fraction **MACCE**=major adverse cardiovascular and cerebrovascular events (composite of death, MI, stroke) **MI**=myocardial infarction **mos**=months **NNT**=number needed to treat **NNH**=number needed to harm **NS**=non-statistically significant **NSTEMI**=non-ST elevated MI **P2Y12 inhibitor**=platelet receptor inhibitor **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention **STEMI**=ST elevated MI **sx**=surgery **TIA**=transient ischemic attack **tx**=treatment

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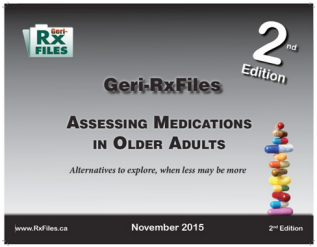

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