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

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 (NHH=112)
  - ↑ risk of all-cause mortality trend at 30 months, statistically significant at 33 months, NHH=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
- 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 (G1DES; 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 G1DES.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)^6; n=1,259 patients with DES (~40% G1DES), 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, NHH=100
  - DES-LATE (2014, Korea)^1; n=5,045 patients with DES (~64% G1DES), 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 G1DES, 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
- 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.
- Enrolment: 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 overseen 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% white, 88% Caucasian, 89.5% from North America
  - mean body weight 91.5kg (±19.5kg), BMI 30.5kg/m² (±5.8kg/m²)
  - 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, ~5% 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
  - 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
In a separate analysis, the DAPT investigators evaluated extended DAPT in patients who had a BMS inserted. 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 adjudication 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.
- Only 43.6% (9961/22,866) of the enrolled participants who received a DES were randomized at 12 months. 11.5% (2638/22,866)
- 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.
- Excluded from the randomization phase.  Only 22% of the study population was on a proton-pump inhibitor at randomization.
- Clinical endpoints (stent thrombosis, MACCE [including death], bleeding) with ITT analysis for efficacy outcomes.

**UNCERTAINTIES:**
- 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).
REFERENCES:


