# 2016 Duration of Dual Antiplatelet Therapy Guideline Focused Update Data Supplement

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| **Studies of shorter (3-6 mo) vs. 12 mo duration of DAPT** | | | | | |
| ISAR-SAFE Schulz-Schupke S, et al., 2015 (1) 25616646 | **Aim:** Test if 6 mo DAPT is noninferior to 12 mo DAPT<br><br>**Study type:** RCT, noninferiority trial<br><br>**Size:** 6,000 pts (4,005 pts actually enrolled, 4,000 pts analyzed) | **Inclusion criteria:** Pts being treated with DAPT 6 mo after DES<br><br>**Exclusion criteria:** Left main PCI, MI in the initial 6 mo after stent, previous stent thrombosis | **Intervention:** 6 additional mo DAPT after initial 6 mo of DAPT (n=2,003)<br><br>**Comparator:** No further clopidogrel after initial 6 mo (n=1,997) | **1° endpoint:** Composite endpoint of death, MI, stent thrombosis, CVA, or TIMI major bleeding 9 mo after randomization (15 mo after stent)<br>• 1.5% with no additional DAPT (6 mo total) vs. 1.6% with 6 additional mo DAPT (12 mo total) (p<0.001 for noninferiority) | • Trial stopped early due to slow recruitment<br>• Lower than expected event rates<br>• Stent thrombosis and TIMI major bleeding rates low and not statistically different |
| SECURITY Colombo A, et al., 2014 (2) 25236346 | **Aim:** Test noninferiority of 6 vs. 12 mo DAPT after 2nd generation DES<br><br>**Study type:** RCT, noninferiority trial<br><br>**Size:** 1,399 pts | **Inclusion criteria:** Pts with stable angina, unstable angina, or silent ischemia<br><br>**Exclusion criteria:** Recent STEMI or NSTEMI, left main PCI, SVG PCI, CKD, active bleeding or significant bleeding risk | **Intervention:** 6 mo DAPT (n=682)<br><br>**Comparator:** 12 mo DAPT (n=717) | **1° endpoint:** Cardiac death, MI, CVA, stent thrombosis or BARC type 3 or 5 bleeding<br>• 4.5% with 6 mo DAPT vs. 3.7% with 12 mo DAPT (risk difference 0.8%; 95% CI: -2.4%–1.7%; p=0.469)<br>• p<0.05 for noninferiority | • Stent thrombosis rates low and not significantly different<br>• Relatively low-risk population enrolled |
| OPTIMIZE Feres, et al., 2013 (3) 24177257 | **Aim:** Assess whether 3 mo of DAPT is clinically noninferior to 12 mo in pts undergoing PCI with ZES<br><br>**Study type:** RCT, noninferiority trial<br><br>**Size:** 3,211 pts | **Inclusion criteria:** Stable angina, low-risk ACS<br><br>**Exclusion criteria:** STEMI for primary or rescue PCI, PCI with BMS in nontarget lesion <6 mo prior to index procedure, previous DES Rx., schedule elective surgery within 12 mo after index procedure, any contraindication to ASA and clopidogrel, SVG lesion, DES stenosis | **Intervention:** 3 mo DAPT (1,605)<br><br>**Comparator:** 12 mo DAPT (1,606) | **1° endpoint:** NACCE. At 1 y follow-up<br>• 93 pts with 3 mo Rx vs. 90 pts with 12 mo Rx (95% CI: 1.52–1.86)<br>• p=0.002 for noninferiority<br><br>**Safety endpoint:** GUSTO major bleeding<br>• 0.2% with 3 mo Rx vs. 0.4% with long term Rx (HR: 0.50, 95% CI: 0.16–1.11) | • Stent thrombosis (5 pts in short term vs. 4 pts in long term)<br>• Study not powered to detect small differences in ischemic and bleeding events after 90 d.<br>• Overall event rate for NACCE was lower than anticipated. |

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| **RESET**<br>Kim BK, et al., 2012<br>(4)<br>22999717 | **Aim:** Evaluate noninferiority of shorter DAPT after DES<br><br>**Study type:** RCT, open label, noninferiority trial<br><br>**Size:** 2,117 pts | **Inclusion criteria:** Pts undergoing DES implantation<br><br>**Exclusion criteria:** Contraindication to antiplatelet agents, bleeding, STEMI within 48 h or cardiogenic shock, left main PCI | **Intervention:** 3 mo DAPT with E-ZES (n=1059)<br><br>**Comparator:** 12 mo DAPT with other DES (n=1058) | **1° endpoint:** CV death, MI, stent thrombosis, TVR, bleeding at 1 y.<br>• 4.7% with 3 mo DAPT/E-ZES vs. 4.7% with 12 mo DAPT/other DES (difference 0.0%; 95% CI: -2.5–2.5; p=0.84)<br>• p<0.001 for noninferiority | • No significant differences in rates of stent thrombosis, bleeding or TVR<br>• Study underpowered due to low event rates<br>• Same stents not used in the 2 randomization arms |
| **EXCELLENT**<br>Gwon HC, et al., 2012<br>(5)<br>22179532 | **Aim:** Evaluate whether 6 mo DAPT would be noninferior to 12 mo DAPT after DES<br><br>**Study type:** RCT, open label, noninferiority trial<br><br>**Size:** 1,443 pts | **Inclusion criteria:** >50% lesion with evidence of myocardial ischemia or >75% lesion (with or without documented ischemia)<br><br>**Exclusion criteria:** MI within 72 h, LVEF<25% or cardiogenic shock, recent major bleeding or surgery | **Intervention:** 6 mo DAPT after DES (n=722)<br><br>**Comparator:** 12 mo DAPT after DES (n=721) | **1° endpoint:** Target vessel failure (cardiac death, MI, ischemia-driven TVR) at 12 mo<br>• 4.8% with 6 mo DAPT vs. 4.3% with 12 mo DAPT (p=0.001 for noninferiority) | • Stent thrombosis 0.9% with 6 mo DAPT vs. 0.1% with 12 mo DAPT (HR: 6.02; 95% CI: 0.72–49.96; p=0.10)<br>• TIMI major bleeding 0.3% with 6 mo DAPT vs. 0.6% with 12 mo DAPT (HR: 0.50; 95% CI: 0.09–2.73; p=0.42)<br>• Target vessel failure occurred more frequently with 6 mo DAPT in diabetic pts<br>• Study underpowered for death or MI |
| **Studies of shorter (6 mo) vs. 24 mo duration of DAPT** | | | | | |
| **ITALIC**<br>Gilard M, et al., 2015<br>(6)<br>25461690 | **Aim:** Evaluate noninferiority of 6 mo DAPT vs. 24 mo DAPT with newer generation (Xience) DES<br><br>**Study type:** RCT, open label, noninferiority trial<br><br>**Size:** 2,031 pts (actual 1,850 pts) | **Inclusion criteria:** Pts undergoing PCI<br><br>**Exclusion criteria:** Primary PCI for STEMI, left main PCI, ASA nonresponder | **Intervention:** 6 mo DAPT (n=926)<br><br>**Comparator:** 24 mo DAPT (n=924) | **1° endpoint:** Death, MI, urgent TVR, CVA, major bleeding at 12 mo post-stenting<br>• 1.6% with 6 mo vs. 1.5% with 24 mo (p=0.85)<br>• p<0.00002 for noninferiority (absolute risk difference 0.11%; 95% CI: -1.04–1.26%) | • Study terminated early due to recruitment problems<br>• No significant differences in stent thrombosis or bleeding complications<br>• Low event rates (lower than expected) |
| **PRODIGY**<br>Valgimigli M, et al., 2012<br>(7)<br>22438530 | **Aim:** To evaluate the impact of up 6 or 24 mo DAPT after BMS or DES<br><br>**Study type:** RCT<br><br>**Size:** 2,013 pts (1970 eligible for randomization at 30 d) | **Inclusion criteria:** SIHD or ACS pts undergoing PCI<br><br>**Exclusion criteria:** Bleeding diathesis, bleeding or stroke within 6 mo, oral anticoagulant therapy | **Intervention:** 24 mo DAPT (n=987)<br><br>**Comparator:** 6 mo DAPT (n=983) | **1° endpoint:** Death, MI or CVA at 2 y<br>• 10.1% with 24 mo DAPT vs. 10.0% with 6 mo DAPT (HR: 0.98; 95% CI: 0.74–1.29; p=0.91)<br><br>**1° Safety endpoint:** BARC type 2, 3 or 5 bleeding<br>• 7.4% with 24 mo DAPT vs. 3.5% with 6 mo DAPT (HR:0.46; 95% CI 0.31–0.69; p=0.00018) | • Stent thrombosis rates low and not significantly different between treatment groups |

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ACS indicates acute coronary syndrome; ASA, aspirin; BARC, Bleeding Academic Research Consortium; BMS, bare metal stent; CKD, chronic kidney disease; CVA, cerebrovascular accident; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NACCE, Net Adverse Clinical and Cerebral Events; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; Rx, prescription; STEMI, ST-elevation myocardial infarction; SIHD, stable ischemic heart disease; SVG, saphenous vein graft; TIMI, Thrombolysis In Myocardial Infarction; and TVR, target-vessel revascularization.

## Data Supplement 2. RCTs of Prolonged/Extended (>12 Month) Duration of DAPT in Patients Treated With Stent Implantation

| Study Acronym Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
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| OPTIDUAL Helft G, et al., 2015 (8) 26364288 | **Aim:** Evaluate hypothesis that continuing clopidogrel would be superior to stopping clopidogrel at 12 mo following DES<br><br>**Study type:** RCT, open label, superiority trial<br><br>**Size:** 1,966 pts (1385 included in ITT analysis) | **Inclusion criteria:** Pts (SIHD or ACS) undergoing PCI with DES free of MACCE or major bleeding after 12 mo DAPT<br><br>**Exclusion criteria:** Need for oral anticoagulation, unprotected left main PCI, life expectancy <2 y | **Intervention:** Additional 36 mo DAPT (n=695)<br><br>**Comparator:** ASA therapy alone (n=690) | **1° endpoint:** Net adverse clinical events (death, MI, CVA or major bleeding)<br>• 5.8% with additional 36 mo DAPT vs. 7.5% with ASA alone (HR: 0.75; 95% CI: 0.50–1.28; p=0.017) | • Study terminated early due to slow recruitment<br>• Actual median follow-up 33.4 mo<br>• Rates of death 2.3% with extended DAPT vs. 3.5% with ASA alone (HR: 0.65; 95% CI: 0.34–1.22; p=0.18)<br>• Rates of major bleeding identical at 2.0% (p=0.95)<br>• Post hoc analysis of MACCE (death, MI or CVA) found rates of 4.2% with extended DAPT vs. 6.4% with ASA alone (HR: 0.64; 95% CI: 0.40–1.02; p=0.06) |
| ITALIC Gilard M, et al., 2015 (6) 25461690 | **Aim:** Evaluate noninferiority of 6 mo DAPT vs. 24 mo DAPT with newer generation (Xience) DES<br><br>**Study type:** RCT, open label, noninferiority trial<br><br>**Size:** 2,031 pts (actual 1850 pts) | **Inclusion criteria:** Pts undergoing PCI<br><br>**Exclusion criteria:** Primary PCI for STEMI, left main PCI, ASA nonresponder | **Intervention:** 6 mo DAPT (n=926)<br><br>**Comparator:** 24 mo DAPT (n=924) | **1° endpoint:** Death, MI, urgent TVR, CVA, major bleeding at 12 mo post-stenting<br>•1.6% with 6 mo vs. 1.5% with 24 mo (p=0.85)<br>• p<0.00002 for noninferiority (absolute risk difference 0.11%; 95% CI: -1.04–1.26%) | • Study terminated early due to recruitment problems<br>• No significant differences in stent thrombosis or bleeding complications<br>• Low event rates (lower than expected) |

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| **DAPT**<br>Mauri L, et al., 2014<br>(9)<br>25399658 | **Aim:** To assess benefits and risks of >12 mo DAPT after BMS or DES<br><br>**Study type:** RCT, placebo-controlled<br><br>**Size:** 9,961 pts | **Inclusion criteria:** Pts treated with BMS or DES, but only DES-treated pts included in this report<br><br>**Exclusion criteria:** MI, CVA, repeat revascularization, stent thrombosis, or moderate-severe bleeding during the 1st 12 mo DAPT after DES (before randomization); oral anticoagulant use | **Intervention:** Additional 18 mo of DAPT after initial 12 mo<br><br>**Comparator:** Placebo thienopyridine after initial 12 mo DAPT | <u>Co-1° endpoints (after additional 18 mo Rx)</u>:<br>• Stent thrombosis: 0.4% with continued DAPT vs. 1.4% with placebo thienopyridine (HR: 0.29; 95% CI: 0.17–0.48; p=0.001)<br>• MACCE (death, MI, CVA): 4.3% with continued DAPT vs. 5.9% with placebo thienopyridine (HR: 0.71; 95% CI: 0.59–0.85; p<0.001)<br><br>**1° Safety endpoint:** GUSTO moderate or severe bleeding<br>• 2.6% with continued DAPT vs. 1.6% with placebo thienopyridine (p=0.001) | • All-cause death 2.0% with continued DAPT vs. 1.5% with placebo thienopyridine (HR: 1.36; 95% CI:1.00–1.85; p=0.05)<br>• Increased death due to more non–CV deaths<br>• Only DES-treated pts included in this report<br>• DES included 1st and 2nd generation stents |
| **ARCTIC-Interruption**<br>Collet JP, et al., 2014<br>(10)<br>25037988 | **Aim:** To demonstrate superiority of continued (>12 mo) vs. interrupted (12 mo) DAPT<br><br>**Study type:** Planned extension of ARTIC-Monitoring trial. Pts treated with 1 y DAPT randomized to interrupt (stop) therapy or continue therapy. RCT, open label.<br><br>**Size:** 1,259 pts | **Inclusion criteria:** Pts prior enrolled in ARCTIC-Monitoring trial without an event at 12 mo<br><br>**Exclusion criteria:** Primary PCI, bleeding diathesis, chronic anticoagulation use | **Intervention:** Interruption (cessation) of DAPT after 12 mo Rx (n=624)<br><br>**Comparator:** Continuation of DAPT after 12 mo Rx for an additional 6-18 mo (n=635) | **1° endpoint:** Death, MI, stent thrombosis, CVA or urgent TVR<br>• 4% of interruption group vs. 4% of continuation group (HR: 1.17; 95% CI: 0.68–2.03; p=0.58)<br><br>**1° Safety endpoint:** STEEPLE major bleeding<br>• <0.5% of interruption group vs. 1% of continuation group (HR: 0.15; 95% CI: 0.02–1.20; p=0.073) | • High-risk pts not enrolled<br>• No differences in secondary endpoints, including stent thrombosis |
| **DES-LATE**<br>Lee CW, et al., 2014<br>(11)<br>24097439 | **Aim:** To compare 12 mo DAPT to >12 mo DAPT after DES<br><br>**Study type:** RCT, open label<br><br>**Size:** 5,045 pts | **Inclusion criteria:** Pts treated with DES event-free after 12-18 mo of DAPT<br><br>**Exclusion criteria:** Recent ACS, ischemic or bleeding event on DAPT before enrollment | **Intervention:** Continued DAPT after 12 mo of Rx (n=2514)<br><br>**Comparator:** ASA monotherapy (n=2531) | **1° endpoint:** CV death, MI, CVA 24 mo after randomization<br>• 2.4% in ASA alone vs 2.6% in continued DAPT (HR: 0.94; 95% CI: 0.66–1.35; p=0.75) | • Publications includes pts from ZEST-LATE and REAL-LATE (the results of which were first published by Park SJ in 2010) and an additional 2,344 pts TIMI major bleeding at 24 mo follow-up occurred in 1.1% of ASA alone vs. 1.4 of continued DAPT (HR: 0.71; 95% CI: 0.42–1.20; p=0.20); difference was statistically significant by the end of all follow-up<br>• No significant difference in stent thrombosis |

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| **PRODIGY**<br>Valgimigli M, et al.,<br>2012<br>(7)<br>22438530 | **Aim:** To evaluate the impact of up 6 or 24 mo DAPT after BMS or DES<br><br>**Study type:** RCT<br><br>**Size:** 2,013 pts (1,970 eligible for randomization at 30 d) | **Inclusion criteria:** SIHD or ACS pts undergoing PCI<br><br>**Exclusion criteria:** Bleeding diathesis, bleeding or stroke within 6 mo, oral anticoagulant therapy | **Intervention:** 24 mo DAPT (n-987)<br><br>**Comparator:** 6 mo DAPT (n=983) | **1° endpoint:** Death, MI or CVA at 2 y<br>• 10.1% with 24 mo DAPT vs. 10.0% with 6 mo DAPT (HR: 0.98; 95% CI: 0.74–1.29; p=0.91)<br><br>**1° Safety endpoint:** BARC type 2, 3 or 5 bleeding<br>• 7.4% with 24 mo DAPT vs. 3.5% with 6 mo DAPT (HR: 0.46; 95% CI: 0.31–0.69; p=0.00018) | • Stent thrombosis rates low and not significantly different between treatment groups |
| Park SJ, et al.,<br>2010<br>(12)<br>20231231 | **Aim:** Compare ASA + clopidogrel to ASA alone in pts treated with DES who were event free for 12 mo<br><br>**Study type:** RCT, open label<br><br>**Size:** 2,701 pts | **Inclusion criteria:** Pts treated with DES who were event free for 12 mo<br><br>**Exclusion criteria:** Ischemic or bleeding event during first 12 mo of DAPT after DES implantation | **Intervention:** ASA + clopiodogrel<br><br>**Comparator:** ASA alone | **1° endpoint:** MI or cardiac death at 2 y<br>•1.8% with DAPT vs. 1.2% with ASA (HR: 1.65; 95% CI: 0.80–3.36; p=0.17) | • Study combined pts from ZEST-LATE and REAL-LATE |

ACS indicates acute coronary syndrome; ASA, aspirin; BMS, bare metal stent; CI, confidence interval; CV, cardiovascular; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; f/u, follow up; HR, hazard ratio; ITT, intent to treat; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; Rx, prescription;  SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; and TVR, target-vessel revascularization.

## Data Supplement 3. Meta-Analyses of Duration of DAPT

| Author;<br>Year Published | Aim of Study;<br>Study Type;<br>Study Size (N) | Patient Population | Study Intervention<br>(# patients) /<br>Study Comparator<br>(# patients) | Endpoint Results<br>(Absolute Event Rates,<br>P values; OR or RR; &<br>95% CI) | Relevant  2° Endpoint (if any);<br>Study Limitations;<br>Adverse Events |
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| Udell JA, et al.,<br>2015<br>(13)<br>26324537 | **Aim:** Compare benefits and risks of more than one y of DAPT with ASA alone in high-risk pts with Hx of prior MI<br><br>**Study type:** Meta-analysis<br><br>**Size:** 33,435 pts | **Inclusion criteria:** RCTs of secondary prevention in pts with MI randomized to extended duration (>12 mo) DAPT compared with ASA alone<br><br>**Exclusion criteria:** ≤12 mo of follow-up, trials of oral anticoagulant therapies, trials of pts with | **Intervention:** >12 mo DAPT<br><br>**Comparator:** ASA therapy alone | **1° endpoint:**  MACE (CV death, nonfatal MI, and nonfatal stroke)<br>• 6.4% with DAPT vs. 7.5% with ASA alone (RR: 0.78; 95% CI: 0.67–0.90; p=0.001) | • Studies included in analysis: CHARISMA, PRODIGY, ARCTIC-Interruption, DAPT, DES-LATE, and PEGASUS-TIMI 54<br>• For all studies except PEGASUS-TIMI 54, a subgroup of the study population was used for the meta-analysis<br>• CV death 2.3% with DAPT vs. 2.6% with ASA alone (RR: 0.85; 95% CI: 0.74–0.98; p= 0.03), |

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| | | SIHD alone undergoing PCI | | | • No increase in non–CV death (RR: 1.03; CI: 0.86–1.23; p= 0.76). <br> • Major bleeding 1.85% with DAPT vs. 1.09% with ASA (RR: 1.73; 95% CI: 1.19–2.50; p=0.004) |
| Elmariah S, et al., 2015 (14) 25467565 | **Aim:** Assess the effect of extended duration DAPT on mortality <br><br> **Study type:** Hierarchical Bayesian random effects model meta-analysis, trial level data <br><br> **Size:** 14 RCT; total n=69,644 pts | **Patients:** Pts enrolled in RCTs of extended vs. short duration DAPT or DAPT vs. ASA alone. Clinical settings of studies included post-PCI, post-ACS, atrial fibrillation, lacunar stroke, and documented or high-risk of CV disease | **Intervention:** Longer duration DAPT <br><br> **Comparators:** Shorter duration DAPT or ASA alone | **CV Mortality:** 4.2% with longer DAPT vs. 4.1% with shorter DAPT/ASA alone (HR:1.01; 95% credible interval: 0.93–1.12; p=0.81) <br><br> **Non–CV Mortality:** 1.7% with longer DAPT vs. 1.7% with shorter DAPT/ASA alone (HR: 1.04; 95% credible interval: I: 0.90–1.26; p=0.66) <br><br> **All-cause mortality:** 5.8% with longer DAPT vs. 5.7% with shorter DAPT/ASA alone (HR: 1.04; 95% credible interval: I: 0.96–1.18; p=0.17) | • Trial level data used <br> • Authors concluded extended-duration APT not associated with differences in all-cause, CV, or non–CV death compared with ASA alone or short duration DAPT |
| Palmerini T, et al., 2015 (15) 25790880 | **Aim:** To compare clinical outcomes between short- (≤6 mo) and long-term (1 y) DAPT in pts treated with DES <br><br> **Study type:** Individual pts data pairwise and network meta-analysis of RCTs <br><br> **Size:** 4 RCT; total n=8,180 pts | **Inclusion criteria:** RCTs comparing short-duration (3 or 6 mo) with longer-duration DAPT (≥1 y). | **Intervention:** Short-term (≤6 mo) DAPT <br><br> **Comparator:** Long-term (1 y) DAPT | **1° endpoint:** MACE (cardiac death, MI, stent thrombosis) <br> • For short-term DAPT, HR: 1.11 (95% CI: 0.86–1.42; p=0.44) <br><br> **Safety endpoint:** Bleeding <br> • For short-term DAPT, HR: 0.66 (95% CI: 0.46–0.94; p=0.03) | • No significant differences in 1 y rates of MACE among 3 mo vs. 1 y DAPT, 6-mo vs. 1 y DAPT, or 3 mo vs. 6 mo DAPT |
| Giustino G, et al., 2015 (16) 25681754 | **Aim:** Evaluate the efficacy and safety of DAPT after DES <br><br> **Study type:** Meta-analysis of RCT, trial level data <br><br> **Size:** 10 RCT; total | **Patients:** Pts treated with DES enrolled in RCTs of shorter vs. longer duration DAPT | **Comparators:** Shorter duration vs. Longer duration DAPT | **Stent thrombosis:** 0.9% with shorter vs. 0.5% with longer (OR: 1.71; 95% CI:1.26–2.32, p=0.001) <br><br> **Clinically significant bleeding:** 1.2% with shorter vs. 1.9% with longer (OR: 0.63, 95% CI: 0.52–0.75; p<0.001) | • Trial level data used <br> • The effect of shorter DAPT on stent thrombosis was attenuated with the use of second-generation DES (OR: 1.54; 95% CI: 0.96–2.47) compared with the use of first-generation DES (OR: 3.94; 95% CI: 2.20–7.05); p for interaction=0.008. <br> • All-cause mortality 2.0% with shorter |

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| | n=32,135 pts | | | | vs. 2.2% with longer (OR: 0.87; 95% CI: 0.74–1.01; p=0.073) |
| Navarese, et al., 2015 (17) 25883067 | **Aim:** To assess the benefits and risks of short term (<12 mo) or extended (>12 mo) DAPT vs. 12 mo DAPT after DES.<br><br>**Study type:** Meta-analysis of RCT, trial level data<br><br>**Size:** 10 RCT; total n=32,287 | **Patients:** Pts treated with DES enrolled in RCT of shorter vs. longer duration DAPT | **Comparator:** Shorter or longer duration DAPT compared to 12 mo DAPT | **MI:**<br>• Short vs. 12 mo: 1.65% vs. 1.50% (OR: 1.11; 95% CI: 087–1.43; p=0.40)<br>• Extended vs. 12 mo: 1.55% vs. 2.89% (OR: 0.53; 95% CI: 0.42–0.66; p<0.001)<br><br>**Stent thrombosis:**<br>• Short vs. 12 mo: 0.53% vs. 0.40% (OR: 1.32; 95% CI: 0.83–2.08; p=0.24)<br>• Extended vs. 12 mo: 0.32% vs. 0.98% (OR: 0.33; 95% CI: 0.21–0.51; p<0.001)<br><br>**Major bleeding:**<br>• Short vs. 12 mo: 0.35% vs. 0.61% (OR:0.58; 95% CI: 0.36–0.92, p=0.02)<br>• Extended vs. 12 mo: 1.95% vs. 1.21% (OR:1.62; 95% CI: 1.26–2.09; p<0.001)<br><br>**CV mortality:**<br>• Short vs. 12 mo: 1.13% vs. 1.20% (OR: 0.95; 95% CI: 0.68–1.33; p=0.76)<br>• Extended vs. 12 mo: 1.03% vs. 0.95% (OR:1.09; 95% CI: 0.79–1.50; p=0.62)<br><br>**All-cause mortality:**<br>• Short vs. 12 mo: 1.43% vs. 1.56% (OR: 0.91; 95% CI: 0.781–1.18; p=0.49)<br>• Extended vs. 12 mo: 1.84% vs. 1.42% (OR: 1.30; 95% CI: 1.02–1.66; p=0.03) | • Trial level data used<br>• Authors concluded that compared with standard 12 mo DAPT, shorter duration reduced bleeding with no apparent increase in ischemic complications and could be considered for most pts. In selected pts with low bleeding risk and very high ischemic risk, extended DAPT could be considered |
| Palmerini T, et al., 2015 (18) 26065988 | **Aim:** Investigate mortality and other clinical outcomes with different DAPT strategies<br><br>**Study type:** Pair wise and Bayesian network meta-analysis of RCT, trial level data | **Patients:** Pts treated with DES enrolled in RCT of shorter vs. longer duration DAPT | **Comparators:** Shorter duration vs. longer duration DAPT | **All-cause mortality:** Shorter vs. longer DAPT: HR: 0.82; 95% CI: 0.69–0.98; p=0.02; NNT=325 | • Trial level data used<br>• Reduced mortality with shorter compared to longer DAPT attributable to lower non–cardiac mortality (HR: 0.67; 95% CI: 0.51–0.89; p=0.006; NNT=347) with similar cardiac mortality (HR: 0.93; 95% CI: 0.73–1.17; p=0.52)<br>• Shorter DAPT associated with lower risk of major bleeding, but a higher risk of MI and stent thrombosis |

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| | Size: 10 RCT; total n=31,666 pts | | | | |
| Spencer FA, et al., 2015 (19) 26005909 | Aim: To summarize data on clinical outcome with longer vs. shorter duration DAPT after DES<br><br>Study type: Meta-analysis of RCT, trial level data<br><br>Size: 9 RCT; total n=28,808 | Patients: Pts treated with DES enrolled in RCT of shorter vs. longer duration DAPT | Comparators: Shorter duration vs. longer duration DAPT | MI: 1.7% with longer vs. 2.6% with shorter (RR: 0.73; CI: 0.58–0.92)<br><br>Major Bleeding: 1.4% with longer vs. 0.8% with shorter (RR: 1.66; 95% CI: 1.34–1.99)<br><br>Total Mortality: 2.0% with longer vs. 1.7% with shorter (RR–1.19; 95% CI: 1.04–1.36) | • Trial level data used<br>• Authors concluded moderate-quality evidence showed that longer-duration DAPT decreased risk for MI and increased mortality, and that high-quality evidence showed that DAPT increased risk for major bleeding<br>• Authors calculated that extended DAPT associated with 8 fewer MI per 1000 treated per year but 6 more major bleeding events per year than shorter-duration DAPT |

ACS indicates acute coronary syndrome; ASA, aspirin; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HR, hazard ratio; Hx, history; MACE, major adverse cardiac events; MI, myocardial infarction; NNT, number need to treat; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SIHD, stable ischemic heart disease; and TIMI, Thrombolysis In Myocardial Infarction.

## Data Supplement 4. RCTs, RCT Subgroup Analyses, and Meta-Analyses of RCTs of DAPT Post–MI or Post–ACS

| Study Acronym Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
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| Udell JA, et al., 2015 (13) 26324537 | Aim: Compare benefits and risks of more than one y of DAPT with ASA alone in high-risk pts with Hx of prior MI<br><br>Study type: Meta-analysis<br><br>Size: 33,435 pts | Inclusion criteria: RCTs of secondary prevention in pts with MI randomized to extended duration (>12 mo) DAPT compared with ASA alone<br><br>Exclusion criteria: ≤12 mo of follow-up, trials of oral anticoagulant therapies, trials of pts with SIHD alone undergoing PCI | Intervention: >12 mo DAPT<br><br>Comparator: ASA therapy alone | 1° endpoint: MACE (CV death, nonfatal MI, and nonfatal stroke)<br>• 6.4% with DAPT vs. 7.5% with ASA alone (RR: 0.78; 95% CI: 0.67–0.90; p=0.001) | • Studies included in analysis: CHARISMA, PRODIGY, ARCTIC-Interruption, DAPT,-LATE, and PEGASUS-TIMI 54<br>• For all studies except PEGASUS-TIMI 54, a subgroup of the study population was used for the meta-analysis<br>• CV death 2.3% with DAPT vs. 2.6% with ASA alone (RR: 0.85; 95% CI: 0.74–0.98; p=0.03),<br>• No increase in non–CV death (RR: 1.03; 95% CI: 0.86–1.23; p=0.76).<br>• Major bleeding 1.85% with DAPT vs 1.09% with ASA (RR: 1.73; 95% CI:1.19–2.50; p=0.004) |

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| DAPT (MI subgroup analysis)<br>Yeh RW, et al., 2015<br>(20)<br>25787199 | **Aim:** Assess benefits and risks of extended DAPT in subgroups of pts in the DAPT study with MI and stable presentations<br><br>**Study type:** Post-hoc analysis of the DAPT trial<br><br>**Size:** 11,648 pts | **Inclusion criteria:** Pts enrolled in DAPT trial treated with either BMS or DES<br><br>**Exclusion criteria:** N/A | **Intervention:** Additional 18 mo DAPT after initial 12 mo<br><br>**Comparator:** Placebo thienopyridine after initial 12 mo DAPT<br><br>**Subgroup analysis:** Pts with MI (n=3,576) and without MI (n=8,072) | **Co-1° endpoints (after additional 18 mo Rx):**<br>• Stent thrombosis in MI group: 0.5% with extended DAPT vs. 1.9% with placebo thienopyridine (HR: 0.27; CI: 0.13–0.57, p<0.001)<br>• MACCE (death, MI, CVA) in MI group: 3.9% with continued DAPT vs. 6.8% with placebo thienopyridine (HR: 0.56; CI: 0.42–0.76; p<0.001)<br><br>**1° Safety endpoint:** GUSTO moderate or severe bleeding<br>• In pts with MI: 1.9% with continued DAPT vs. 0.8% with placebo thienopyridine (HR: 2.38; CI: 1.28–4.43, p=0.005) | • All cause death 1.4% with extended DAPT vs. 1.6% with placebo thienopyridine (HR: 0.87; CI: 0.50–1.50, p=0.61) |
| PEGASUS-TIMI 54<br>Bonaca MP, et al., 2015<br>(21)<br>25773268 | **Aim:** To investigate the efficacy and safety of ticagrelor beyond 1 y after a MI<br><br>**Study type:** RCT, placebo controlled<br><br>**Size:** 21,162 pts | **Inclusion criteria:** MI 1-3 y prior, age ≥50, and an additional high-risk feature<br><br>**Exclusion criteria:** Bleeding disorder, Hx of ischemic stroke of ICH, CNS tumor, GI bleeding within 6 mo, major surgery within 30 d, oral anticoagulant use | **Intervention:** Ticagrelor 90 mg (n=7050) or ticagrelor 60 mg (n=7045)<br><br>**Comparator:** Placebo (n=7067) | **1° endpoint:** CV death, MI or stroke at median 33 mo follow-up<br>• 7.85% with 90 mg ticagrelor, 7.77% with 60 mg ticagrelor, and 9.04% with placebo •HR for 90 mg vs. placebo: 0.85; 95% CI: 0.75–0.96; p=0.008<br>• HR for 60 mg vs. placebo: 0.84; 95% CI: 0.74–0.95; p=0.004<br><br>**1° Safety endpoint:** TIMI major bleeding<br>• 2.60 with 90 mg ticagrelor, 2.30 with 60 mg ticagrelor, and 1.06% with placebo (p<0.001 for each dose vs. placebo) | • All pts treated with ASA<br>• No differences in death between the either dose of ticagrelor and placebo |

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| **TRILOGY**<br>Row MT, et al., 2012<br>(22)<br>22920930 | **Aim:** To compare prasugrel with clopidogrel in pts with NSTE-ACS not undergoing revascularization<br><br>**Study type:** RCT<br><br>**Size:** 7,243 pts | **Inclusion criteria:** Pts with NSTE-ACS selected for medical management without revascularization<br><br>**Exclusion criteria:** Hx CVA or TIA, PCI or CABG within prior 30 d, renal failure requiring dialysis, concomitant oral anticoagulation treatment | **Intervention:**<br>Prasugrel<br><br>**Comparator:**<br>Clopidogrel | **1° endpoint:** MACE (CV death, MI or CVA) in pts <75 y at 30 mo<br>• 13.9% with prasugrel vs. 16.0% with clopidogrel (HR: 0.91; 95% CI: 0.79–1.05; p=0.21)<br><br>**Safety endpoint):** GUSTO severe or life-threatening bleeding<br>• 0.9% with prasugrel vs. 0.6% with clopidogrel (HR: 0.94; 95% CI: 0.44–1.99; p=0.87) | • All pts treated with ASA |
| **PLATO**<br>James SK, et al., 2011<br>(23)<br>21685437 | **Aim:** To evaluate efficacy and safety outcomes in pts in PLATO who at randomization were planned for a noninvasive treatment strategy.<br><br>**Study type:** Pre-specified subgroup analysis of the PLATO RCT<br><br>**Size:** 5,216 pts | **Inclusion criteria:** Pts with ACS admitted to hospital with planned noninvasive management<br><br>**Exclusion criteria:** Pts in PLATO with planned invasive management | **Intervention:**<br>Ticagrelor (90 mg bid)<br><br>**Comparator:**<br>Clopidogrel (75 mg qD) | **1° endpoint:** Vascular death, MI or CVA<br>• 12.0% with ticagrelor compared to 14.3% with clopidogrel (HR: 0.85; 95% CI: 0.73–1.00; p=0.04)<br><br>**Safety endpoint:**<br>• Total major bleeding: (11.9% with ticagrelor vs. 10.3% with clopidogrel (HR: 1.17; 95% CI: 0.98–1.39; p=0.08)<br>• Non–CABG major bleeding: 4.0% with ticagrelor vs. 3.1% with clopidogrel (HR: 1.30, 95% CI:0.95–1.77; p=0.10) | • N/A |
| **PLATO**<br>Steg PG, et al., 2010<br>(24)<br>21060072 | **Aim:** To examine the efficacy and safety of ticagrelor compared with clopidogrel in pts with STE-ACS intended for reperfusion with primary PCI.<br><br>**Study type:** Pre specified subgroup analysis of PLATO; RCT<br><br>**Size:** 7,544 pts | **Inclusion criteria:** Pts enrolled in PLATO with STEMI<br><br>**Exclusion criteria:** Same as PLATO study | **Intervention:**<br>Ticagrelor<br><br>**Comparator:**<br>Clopidogrel | **1° endpoint:** MACE (CV death, MI, CVA)<br>• 9.4% with ticagrelor vs. 10.8% with clopdiogrel; (HR: 0.87; 95% CI: 0.75–1.01; p=0.07)<br><br>**Safety endpoint:** major bleeding<br>• No difference in major bleeding (HR: 0.98; p=0.76). | • 72% of pts with STEMI underwent primary PCI<br>• Definite stent thrombosis lower with ticagrelor (HR: 0.66; p=0.03).<br>• Risk of stroke higher with ticagrelor (1.7% vs. 1.0%; HR: 1.63; 95% CI: 1.07–2.48; p=0.02). |

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| **TRITON-TIMI 38** Montalescot, et al., 2009 (25) 19249633 | **Aim:** To asses prasugrel vs. clopidogrel in pts undergoing PCI for STEMI enrolled in TRITON-TIMI 38 **Study type:** Double-blind RCT **Size:** 3,534 pts | **Inclusion criteria:** Pts undergoing PCI for STEMI **Exclusion criteria:** Increased risk of bleeding, anemia, recent fibrinolytic administration, need from chronic oral anticoagulants, cardiogenic shock, or thienopyridine treatment within 5 d of randomization. | **Intervention:** Prasugrel (n=1,769) **Comparator:** Clopidogrel (n=1,765) | **1° endpoint:** CV death, nonfatal MI, nonfatal stroke at 15 mo. • 10.0% with prasugrel vs. 12.4% with clopidogrel (HR: 0.79; 95% CI: 0.65-0.97; p=0.0221) **Safety endpoint:** • No significant different in non–CABG related TIMI major bleeding at 30 d or 15 mo | • Secondary endpoint of CV death, nonfatal MI or target vessel revascularization at 30 d 6.5% with prasugrel vs. 9.5% with clopidogrel (HR: 0.75; 95% CI: 0.59–0.96; p=0.0205) |
| **TRITON** Wiviott SD, et al., 2007 (26) 17982182 | **Aim:** To compare prasugrel with clopidogrel in pts with ACS scheduled for PCI **Study type:** RCT, double-blind, double-dummy design **Size:** 13,608 pts | **Inclusion criteria:** ACS (NSTE-ACS or STEMI) pts undergoing planned PCI **Exclusion criteria:** Increased risk of bleeding, anemia, thrombocytopenia | **Intervention:** Prasugrel (10 mg qD) (n=6,813) **Comparator:** Clopidogrel (75 mg qD) (n=6,795) | **1° endpoint:** CV death, MI, CVA • 9.9% with prasugrel vs. 12.1% with clopidogrel (HR: 0.81; CI: 0.73–0.90; p<0.001) **1° Safety endpoint:** Non–CABG related TIMI major bleeding • 2.4% with prasugrel vs. 1.8% with clopidogrel (HR: 1.32; 95% CI: 1.03–1.68, p=0.03) | • Stent thrombosis rate lower with prasugrel (1.1% vs. 2.4%, p=0.001) • Life-threatening bleeding higher with prasugrel (1.4% vs. 0.9%, p=0.01) • Fatal bleeding higher with prasugrel (0.4% vs. 0.1%, p=0.002) • Increased rate of ICH in those treated with prasugrel with Hx of CVA or TIA • Increased risk of bleeding in those with Hx CVA or TIA, elderly (≥75 y) and body weight <60 kg |
| **CHARISMA** Bhatt DL, et al., 2006, 2007 (27,28) 7498584 16531616 | **Aim:** Assess effect of DAPT in a broad population of pts at high risk for atherothrombotic events **Study type:** RCT, placebo controlled **Size:** 15,603 pts | **Inclusion criteria:** Age ≥45 with multiple atherothrombotic risk factors and/or documented CAD, cerebrovascular disease, or PAD **Exclusion criteria:** Long-term use of oral antithrombotic medications of NSAID, recent ACS | **Intervention:** ASA + clopidogrel (n=7,802) **Comparator:** ASA + placebo (n=7,801) | **1° endpoint:** CV death, MI or CVA (median follow-up 28 mo) • 6.8% with ASA+clopidogrel vs. 7.4% with ASA+placebo (RR: 0.93; 95% CI: 0.83–1.05; p=0.22) **1° Safety endpoint:** GUSTO severe bleeding • 1.7% with ASA+clopidogrel vs. 1.3% with ASA+placebo (RR: 1.25; 95% CI: 0.97–1.61; p=0.09) | • In a post hoc subgroup analysis of those with Hx of prior MI, composite endpoint of CV death, MI and CVA occurred in 8.3% of placebo-treated pts and 6.6% of clopidogrel-treated pts (HR: 0.774; 95% CI: 0.613–0.978; p=0.031) |

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| COMMIT-CCS 2<br>Chen ZM, et al.,<br>2005<br>(29)<br>16271642 | Aim: To compare ASA alone to ASA + clopidogrel in pts with STEMI<br><br>Study type: RCT<br><br>Size: 45,852 pts | Inclusion criteria: Pts with suspected MI within 24 H<br><br>Exclusion criteria: Pts undergoing primary PCI, high-risk of adverse event with study treatments | Intervention: ASA + clopidogrel<br><br>Comparator: ASA alone | Co-1° endpoints (during scheduled treatment – discharge or d 28):<br>● MACE (death, reinfarction, CVA): 9.2% with DAPT vs. 10.1% with ASA (RRR: 9%; 95% CI: 3%–14%; p=0.002)<br>● Death: 7.5% with DAPT vs. 8.1% with ASA (RRR: 7%; 95% CI: 1%–13%; p=0.03)<br><br>Safety endpoint: Life-threatening bleeding<br>● 0.58% with DAPT vs. 0.55% with ASA (p=0.59) | ● 87% with ST elevation; 6% with bundle branch block; and 7% with ST depression |
| PCI-CLARITY<br>Sabatine MS, et al.,<br>2005<br>(30)<br>16143698 | Aim: Determine if clopidogrel pretreatment before PCI in pts with recent STEMI is superior to clopidogrel treatment initiated at the time of PCI in preventing MACE<br><br>Study type: RCT; prespecified subgroup analysis of pts in CLARITY-TIMI 28 who underwent PCI<br><br>Size: 1,863 pts | Inclusion criteria: Pts receiving fibrinolytics for STEMI undergoing subsequent angiography and PCI enrolled in CLARITY<br><br>Exclusion criteria: Planned treatment with clopidogrel or a GPI before angiography, cardiogenic shock, prior CABG | Intervention: Clopidogrel pretreament<br><br>Comparator: Standard therapy (clopidogrel at the time of PCI) | 1° endpoint: MACE at 30 d<br>● 3.6% with pretreatment vs. 6.2% with standard Rx; (adjusted OR=0.54; 95% CI: 0.35–0.85; p=0.008)<br><br>Safety endpoint: TIMI major or minor bleeding<br>● 2.0% with pretreatment vs. 1.9% with standard Rx (p>0.99) | ● Pretreatment with clopidogrel also reduced the incidence of MI or stroke prior to PCI (4.0% vs. 6.2%; OR: 0.62; 95% CI: 0.40–0.95; p=0.03) |
| Sabatine MS, et al.,<br>2005<br>(31)<br>15758000 | Aim: To assess benefit of addition of clopidogrel to ASA in pts with STEMI treated with fibrinolytic therapy<br><br>Study type: RCT<br><br>Size: 3,491 pts | Inclusion criteria: Pts with STEMI being treated with fibrinolytic therapy and ASA<br><br>Exclusion criteria: recent clopidogrel treatment or GPI, planned performance of angiography within 48 h, prior CABG, cardiogenic shock | Intervention: Clopidogrel + ASA<br><br>Comparator: Placebo + ASA | 1° endpoint: Composite of occluded infarct-related artery (TIMI flow grade 0 or1) at angiography, or death or recurrent MI before angiography<br>● 15.0% with DAPT vs. 21.7% with ASA (absolute reduction 6.7%; RRR: 36%; 95% CI: 24%–47%; p<0.001)<br><br>Safety endpoint: TIMI major bleeding<br>● 1.3% with DAPT vs. 1.1% with ASA (p=0.64) | ● At 30 d, DAPT reduced composite endpoint of CV death, recurrent MI or recurrent ischemia leading to urgent TVR by 20% (from 14.1% – 11.6%; p=0.03)<br>● Angiography performed 48-192 h after the start of the study |

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| **CURE**<br>Fox KA, et al., 2004<br>(32)<br>15313956 | **Aim:** To assess benefits and risks of ASA plus clopidogrel in pts undergoing CABG for NSTE-ACS<br><br>**Study type:** Post hoc subgroup analysis of CURE; RCT<br><br>**Size:** 12,562 pts entire study population; 1,061 pts underwent CABG | **Inclusion criteria:**<br>NSTE-ACS within <24 h<br><br>**Exclusion criteria:**<br>NYHA class IV HF, PCI or CABG <3 mo, contraindication to antiplatelets and antithrombotics, hemorrhagic or IC stroke, severe thrombocytopenia | **Intervention:**<br>Clopidogrel + ASA<br><br>**Comparator:**<br>Placebo + ASA | **1° endpoint:** MACE (CV death, MI or stroke)<br>● 14.5% with DAPT vs. 16.2% with ASA (RR: 0.89; 95% CI: 0.71–1.11) | ● Benefits of DAPT with CABG were deemed "consistent" (test for interaction among strata 0.53) with the benefits in pts undergoing PCI (9.6% with DAPT vs. 13.2% with ASA; RR: 0.72; 95% CI: 0.47–0.90) and in those treated with medical therapy alone (8.1% with DAPT vs. 10.0% with ASA; RR: 0.80; 95% CI: 0.69–0.92) |
| **CURE**<br>CURE Investigators, 2001<br>(33)<br>11519503 | **Aim:** Compare efficacy and safety of DAPT in pts with NSTE-ACS treated 3-12 mo<br><br>**Study type:** Randomized, double-blind, placebo controlled trial<br><br>**Size:** 12,562 pts | **Inclusion criteria:** Pts with NSTE-ACS hospitalized within 24 h of symptom onset<br><br>**Exclusion criteria:** STEMI, high bleeding risk, oral anticoagulant use | **Intervention:** ASA + clopidogrel (DAPT) (n=6,259)<br><br>**Comparator:** ASA + placebo (n=6,303) | **1° endpoint:** CV death, MI or CVA<br>● 9.3% with DAPT vs. 11.4% with ASA alone (RR: 0.80; 95% CI: 0.72–0.90; p<0.01)<br><br>**1° Safety endpoint:** Major bleeding<br>● 3.7% with DAPT vs. 2.7% with ASA alone (RR: 1.38; p=0.001) | ● Mean duration of treatment was 9 mo<br>● Results comparable in those with and without a Dx of "MI" |
| **PCI-CURE**<br>Mehta SR, et al., 2001<br>(34)<br>11520521 | **Aim:** To assess whether pretreatment with clopidogrel followed by long-term Rx after PCI is superior to no pretreatment and 4 wk Rx<br><br>**Study type:** Analysis of those pts in CURE who were treated with PCI<br><br>**Size:** 2,658 pts | **Inclusion criteria:** Pts enrolled in CURE undergoing PCI<br><br>**Exclusion criteria:** N/A | **Intervention:** ASA + clopidogrel (DAPT) (n=1,313)<br><br>**Comparator:** ASA + placebo (n=1,345) | **1° endpoint:** CV death, MI or urgent TVR within 30 d of PCI<br>● 4.5% with ASA+clopidogrel vs. 6.4% with ASA+placebo (RR: 0.70; 95% CI: 0.50–0.97; p=0.03) | ● CV death or MI rate between PCI and end of follow-up: 6.0% with ASA+clopidogrel vs. 8.0% with ASA+placebo (RR: 0.75; 95% CI: 0.56–1.00; p=0.047) |

ACS indicates acute coronary syndrome; ASA, aspirin; bid, two times per day; BMS, bare metal stent; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CNS, central nervous system; CVA, cerebrovascular accident; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Dx, diagnosis; GI; gastrointestinal; GPI, glycoprotein inhibitor; HR, hazard ratio; Hx, history; ICH, intracerebral hemorrhage; MACE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCT, randomized

controlled trial; RR, relative risk; Rx, prescription;  TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction; SIHD, stable ischemic heart disease; STE-ACS, ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction; and TVR, target-vessel revascularization.

## Data Supplement 5. RCTs and RCT Subgroup Analyses Comparing Clopidogel With Prasugrel or Ticagrelor In Patients With ACS

| Study Acronym Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant  2° Endpoint (if any); Study Limitations; Adverse Events |
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| TRILOGY Row MT, et al., 2012 (22) 22920930 | **Aim:** To compare prasugrel with clopidogrel in pts with NSTE-ACS not undergoing revascularization<br><br>**Study type:** RCT<br><br>**Size:** 7,243 pts | **Inclusion criteria:** Pts with NSTE-ACS selected for medical management without revascularization<br><br>**Exclusion criteria:** Hx CVA or TIA, PCI or CABG within prior 30 d, renal failure requiring dialysis, concomitant oral anticoagulation treatment | **Intervention:** Prasugrel<br><br>**Comparator:** Clopidogrel | **1° endpoint:** MACE (CV death, MI or CVA) in pts <75 y at 30 mo<br>●13.9% with prasugrel vs. 16.0% with clopidogrel (HR: 0.91; 95% CI: 0.79–1.05; p=0.21)<br><br>**Safety endpoint):** GUSTO severe or life-threatening bleeding<br>● 0.9% with prasugrel vs. 0.6% with clopidogrel (HR: 0.94; 95% CI: 0.44–1.99; p=0.87) | ● All pts treated with ASA |
| PLATO James SK, et al., 2011 (23) 21685437 | **Aim:** To evaluate efficacy and safety outcomes in pts in PLATO who at randomization were planned for a noninvasive treatment strategy.<br><br>**Study type:** Prespecified subgroup analysis of the PLATO RCT<br><br>**Size:** 5,216 pts | **Inclusion criteria:** Pts with ACS admitted to hospital with planned noninvasive management<br><br>**Exclusion criteria:** Pts in PLATO with planned invasive management | **Intervention:** Ticagrelor (90 mg bid)<br><br>**Comparator:** Clopidogrel (75 mg qD) | **1° endpoint:** Vascular death, MI or CVA<br>● 12.0% with ticagrelor compared to 14.3% with clopidogrel  (HR: 0.85; 95% CI: 0.73–1.00; p=0.04)<br><br>**Safety endpoint:**<br>● Total major bleeding: (11.9% with ticagrelor vs. 10.3% with clopidogrel (HR: 1.17; 95% CI: 0.98–1.39; p=0.08)<br>● Non–CABG major bleeding: 4.0% with ticagrelor vs. 3.1% with clopidogrel (HR: 1.30, 95% CI: 0.95–1.77; p=0.10) | ● N/A |

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| **PLATO**<br>Steg PG, et al., 2010<br>(24)<br>21060072 | **Aim:** To examine the efficacy and safety of ticagrelor compared with clopidogrel in pts with STE-ACS intended for reperfusion with primary PCI.<br><br>**Study type:** Prespecified subgroup analysis of PLATO; RCT<br><br>**Size:** 7,544 pts | **Inclusion criteria:** Pts enrolled in PLATO with STEMI<br><br>**Exclusion criteria:** Same as PLATO study | **Intervention:** Ticagrelor<br><br>**Comparator:** Clopidogrel | **1° endpoint:** MACE (CV death, MI, CVA)<br>• 9.4% with ticagrelor vs. 10.8% with clopdiogrel; HR: 0.87; 95% CI: 0.75–1.01; p=0.07<br><br>**Safety endpoint: major bleeding**<br>• No difference in major bleeding (HR: 0.98; p=0.76). | • 72% of pts with STEMI underwent primary PCI<br>• Definite stent thrombosis lower with ticagrelor (HR: 0.66; p=0.03).<br>• Risk of stroke higher with ticagrelor (1.7% vs. 1.0%; HR: 1.63; 95% CI: 1.07–2.48; p=0.02). |
| **PLATO**<br>Wallentin L, et al., 2009<br>(35)<br>19717846 | **Aim:** To compare ticagrelor and clopidogrel in pts with ACS<br><br>**Study type:** RCT, double-blind, double-dummy design<br><br>**Size:** 18,624 pts | **Inclusion criteria:** ACS with symptom onset within 24 h<br><br>**Exclusion criteria:** Fibrinolytic therapy within 24 h, oral anticoagulant therapy, increased risk of bradycardia, concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer | **Intervention:** Ticagrelor (90 mg bid) (n=9,333)<br><br>**Comparator:** Clopidogrel (75 mg qD) (n=9,291) | **1° endpoint:** Vascular death, MI or CVA<br>• 9.8% with ticagrelor vs. 11.7% with clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p<0.001<br><br>**1° Safety endpoint:** Trial-defined major bleeding<br> • 11.6% with ticagrelor vs. 11.2% with clopidogrel (p=0.43) | • All pts treated with ASA<br>• Study included both NSTE-ACS and STEMI pts, with treatment either med Rx alone or med Rx plus revascularization<br>• Ticagrelor associated with higher rate of non–CABG related bleeding (4.5% vs. 3.8%, p=0.03<br>• Stent thrombosis rate lower with ticagrelor (1.3% vs. 1.9%, HR: 0.67; 95% CI: 0.50–0.91; p=0.009) |
| **TRITON-TIMI 38**<br>Montalescot, et al., 2009<br>(25)<br>19249633 | **Aim:** To asses prasugrel vs. clopidogrel in pts undergoing PCI for STEMI enrolled in TRITON-TIMI 38<br><br>**Study type:** Double-blind RCT<br><br>**Size:** 3,534 pts | **Inclusion criteria:** Pts undergoing PCI for STEMI<br><br>**Exclusion criteria:** Increased risk of bleeding, anemia, recent fibrinolytic administration, need from chronic oral anticoagulants, cardiogenic shock, or thienopyridine treatment within 5 d of randomization. | **Intervention:** Prasugrel (n=1,769)<br><br>**Comparator:** Clopidogrel (n=1,765) | **1° endpoint:** CV death, nonfatal MI, nonfatal stroke at 15 mo.<br>• 10.0% with prasugrel vs. 12.4% with clopidogrel (HR: 0.79; 95% CI: 0.65–0.97; p=0.0221)<br><br>**Safety endpoint:**<br>• No significant different in non–CABG related TIMI major bleeding at 30 d or 15 mo | • Secondary endpoint of CV death, nonfatal MI or TVR at 30 d 6.5% with prasugrel vs. 9.5% with clopidogrel (HR: 0.75; 95% CI: 0.59–0.96; p=0.0205) |

| TRITON<br>Wiviott SD, et al.,<br>2007<br>(26)<br>17982182 | **Aim:** To compare prasugrel with clopidogrel in pts with ACS scheduled for PCI<br><br>**Study type:** RCT, double-blind, double-dummy design<br><br>**Size:** 13,608 pts | **Inclusion criteria:** ACS (NSTE-ACS or STEMI) pts undergoing planned PCI<br><br>**Exclusion criteria:** Increased risk of bleeding, anemia, thrombocytopenia | **Intervention:** Prasugrel (10 mg qD) (n=6,813)<br><br>**Comparator:** Clopidogrel (75 mg qD) (n=6,795) | **1° endpoint:** CV death, MI, CVA<br>• 9.9% with prasugrel vs. 12.1% with clopidogrel (HR: 0.81; 95% CI: 0.73–0.90; p<0.001)<br><br>**1° Safety endpoint:** Non–CABG related TIMI major bleeding<br>• 2.4% with prasugrel vs. 1.8% with clopidogrel (HR: 1.32; CI: 1.03–1.68; p=0.03) | • Stent thrombosis rate lower with prasugrel (1.1% vs. 2.4%, p=0.001)<br>• Life-threatening bleeding higher with prasugrel (1.4% vs. 0.9%, p=0.01)<br>• Fatal bleeding higher with prasugrel (0.4% vs. 0.1%, p=0.002)<br>• Increased rate of ICH in those treated with prasugrel with Hx of CVA or TIA<br>• Increased risk of bleeding in those with Hx CVA or TIA, elderly (≥75 y) and body weight <60 kg |

ACS indicates acute coronary syndrome; ASA, aspirin; bid, two times per day; CABG, coronary artery bypass graft; CI, confidence interval; CVA, cerebrovascular accident; CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard ratio; Hx, history; MACE; major adverse cardiac events; MI, myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; Rx, prescription; TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; and TVR, target-vessel revascularization.


## Data Supplement 6. Studies and Comparisons of Short-Term or Chronic Aspirin Dose in Patients With Coronary Artery Disease

| Study Acronym; Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
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| TRANSLATE-ACS<br>Xian Y, et al., 2015<br>(36)<br>25995313 | **Aim:** Compare outcome of pts in TRANSLATE-ACS treated with high-dose (325 mg) or low-dose (81 mg) ASA<br><br>**Study type:** Analysis of data in the TRANSLATE-ACS observational study<br><br>**Size:** 10,213 pts | **Inclusion criteria:** Pts enrolled in TRANSLATE-ACS<br><br>**Exclusion criteria:** Pts died in-hospital, were not discharged on ASA or were missing ASA dosing information, did not undergo stent implantation, or did not complete follow-up | **Intervention:** ASA dose (nonrandomized)<br><br>**Comparator:** Higher or lower ASA dose | **1° endpoint:** MACE<br>• MACE not statistically significantly different between treatment groups<br>• 8.2% with high dose vs. 9.2% with low-dose (adjusted HR: 0.99; 95% CI: 0.85–1.17).<br><br>**Safety endpoint:** bleeding (BARC)<br>• BARC (1-5) bleeding higher with high-dose ASA (unadjusted 24.2% with high-dose vs. 22.7% with low-dose; adjusted HR: 1.19; 95% CI:1.06–1.33) | • High-dose ASA was 325 mg; low-dose ASA was 81 mg |
| CURRENT-OASIS 7<br>Mehta SR, et al., 2010<br>(37)<br>20817281 | **Aim:** To assess the efficacy and safety of standard vs. double-dose clopidogrel and of high- vs. low-dose ASA in pts with ACS undergoing PCI | **Inclusion criteria:** Pts with ACS (STEMI or non–STEMI) undergoing PCI<br><br>**Exclusion criteria:** | **Intervention 1:** High-dose ASA (300-325 mg)<br><br>**Intervention 1:** Low-dose ASA (75-100 mg) | **1° endpoint:** CV death, MI, or stroke at 30 d<br>• 4.1% with high-dose ASA vs. 4.2% with low-dose ASA (HR: 0.98; 95% CI: 0.84–1.13; p=0.76)<br><br>**Safety endpoint:** Major bleeding | |

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| | **Study type:** Randomized factorial trial. Analysis of pts in CURRENT-OASIS 7 undergoing PCI<br><br>**Size:** 17,260 pts | Increased risk of bleeding or active bleeding | | • 1.5% with high-dose ASA vs. 1.3% with low-dose ASA (HR: 1.18; 95% CI: 0.92–1.53; p=0.20) | |
| **PCI-CURE**<br>Jolly SS, et al., 2009<br>(38)<br>18819961 | **Aim:** Evaluate the safety of different doses of ASA after PCI in PCI-CURE<br><br>**Study type:** Post hoc analysis of PCI-CURE<br><br>**Size:** 2,658 pts | **Inclusion criteria:** NSTE-ACS pts in CURE who underwent PCI (PCI-CURE cohort)<br><br>**Exclusion criteria:** N/A | **Intervention:** ASA dose (nonrandomized)<br><br>**Comparator:** Higher or lower ASA dose | **1° endpoint:** N/A<br><br>**Safety endpoint:** Major bleeding at 30 d and long term (mean 8 mo)<br>• Major bleeding increased with high-dose ASA<br>• 1.9% with low-dose, 1.5% with moderate dose, and 3.9% with high-dose<br>• For high vs. low-dose HR: 2.05 (95% CI: 1.20–3.50; p=0.009) | • ASA doses were categorized as low-dose (≤100 mg), moderate dose (101–199 mg), and high-dose (≥200 mg<br>• Net adverse clinical events (death, MI, stroke, major bleeding) favored Low-dose over high-dose ASA (8.4% vs. 11.0%; HR: 1.31; 95% CI: 1.00–1.73; p=0.056). |
| **CHARISMA**<br>Steinhubl, et al., 2009<br>(39)<br>19293071 | **Aim:** Assess MACE based on ASA dose in CHARISMA<br><br>**Study type:** Post hoc observational analyses<br><br>**Size:** 15,595 pts | **Inclusion criteria:** Pts enrolled in CHARISMA<br><br>**Exclusion criteria:** N/A | **Intervention:** ASA dose (nonrandomized)<br><br>**Comparator:** Higher or lower ASA dose | **1° endpoint:** MACE MI, CVA or CV death)<br>• The hazard the same regardless of dose<br>• Adjusted HR: 0.95, 95% CI: 0.80–1.13, for 100 mg vs. <100 mg<br>• Adjusted HR: 1.0; 95% CI: 0.85–1.18; for >100 mg vs. <100 mg.<br><br>**Safety endpoint:** Severe or life-threatening bleeding<br>• Hazard similar regardless of dose<br>• Adjusted HR: 0.85; 95% CI: 0.57–1.26, for 100 mg vs. <100 mg<br>• Adjusted HR: 1.05; 95% CI: 0.74–1.48, for > 100 mg vs. <100 mg. | • ASA doses were categorized as <100 mg (75 mg or 81 mg), 100 mg or>100 mg (150 mg or 162 mg)<br>• In pts also receiving clopidogrel, daily ASA doses >100 mg seemed to be nonstatistically significantly associated with reduced efficacy (adjusted HR: 1.16; CI: 0.93–1.44]) and increased harm (adjusted HR: 1.30; CI: 0.83–2.04]). |
| Patrono C, et al., 2008<br>(40)<br>18574266 | **Aim:** Comparison of OR in vascular events with different ASA doses<br><br>**Study type:** Indirect comparison of ASA doses reducing vascular events in high-risk pts; data from prior studies and publications | **Inclusion criteria:** Studies of ASA in high-risk pts<br><br>**Exclusion criteria:** N/A | **Intervention:** Different ASA dosing ranges | **1° endpoint:** Odds reduction in vascular events<br>• 500–1,500 mg/d: OR: 19±3%<br>• 160–325 mg/d: OR: 26±3%<br>• 75–150 mg/d: OR: 32±6%<br>• <75 mg/d: OR: 13±8% | • N/A |

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| | Size: 68 trials; >50,000 pts | | | | |
| Serebruany, et al., 2005 (41) 15877994 | Aim: To compare the risk of bleeding with low, moderate and high-doses of ASA<br><br>Study type: Systematic overview of 31 trials<br><br>Size: 192,036 pts | Inclusion criteria: Clinical trials with follow-up of ≥1 mo and contained a detailed description of hemorrhagic complications, pts characteristics, therapy duration and concomitant agents used.<br><br>Exclusion criteria: Studies not meeting above criteria | Intervention: ASA dose (nonrandomized)<br><br>Comparator: Higher or lower ASA dose | 1° endpoint: None specifically defined<br><br>Major bleeding event rates (most commonly TIMI bleeding):<br>• 1.56% with low-dose; 1.54% with moderate dose; 2.29% with high-dose; p=0.0001 for comparison of low-dose vs. high-dose<br><br>Total bleeding event rates:<br>• 3.72% with low-dose; 11.31% with moderate dose; 9.8% with high-dose; p=0.0001 for comparisons of low-dose with either moderate or high-dose | • Low-dose ASA defined as <100 mg; moderate-dose ASA 100–200 mg; high-dose ASA >200 mg |
| CURE Peters, et al., 2003 (42) 14504182 | Aim: To study the benefits and risks of adding clopidogrel to different doses of ASA in the treatment of pts with ACS<br><br>Study type: Post hoc analysis of the CURE study<br><br>Size: 12,562 pts | Inclusion criteria: Pts with NSTE-ACS enrolled in the CURE study | Intervention: ASA dose (nonrandomized)<br><br>Comparator: Higher or lower ASA dose | 1° endpoint: MACE<br>• Impact of clopidogrel in preventing MACE was not significantly heterogeneous by ASA dose<br>-high-dose group, 9.8% vs. 13.6%; RR: 0.71; 95% 95% CI: 0.59<br>-medium-dose group, 9.5% vs. 9.8%; RR: 0.97; 95% CI: 0.77–1.22<br>-low-dose group, 8.6% vs. 10.5%; RR: 0.81; 95% CI: 0.68–0.97<br><br>Safety endpoint: Major bleeding<br>• The incidence of major bleeding complications increased significantly with increasing ASA dose both in the placebo (1.9%, 2.8%, 3.7%; p=0.0001) and the clopidogrel (3.0%, 3.4%, 4.9%; p=0.0009) groups | • Incidence of MACE not heterogeneous in pts receiving ASA alone when examined by dose (highest and medium ASA dose groups compared with the low-dose group: adjusted OR, 1.0 (95% CI: 0.82–1.23) and 1.2 (95% CI: 1.08–1.51), respectively |
| Antithrombotic Trialists' Collaboration, 2002 (43) 11786451 | Aim: To determine the effects of antiplatelet therapy among pts at high-risk of occlusive vascular events.<br><br>Study type: Collaborative | Inclusion criteria: Randomized trials of an antiplatelet regimen vs. control or one regimen vs. another regimen | Intervention: ASA<br><br>Comparator: Control or placebo | 1° endpoint: Series vascular event (nonfatal MI, nonfatal stroke, vascular death)<br>• The proportional reduction in vascular events was 19% (3%) with 500–1500 mg daily, 26% (3%) with 160–325 mg daily, and 32% (6%) with 75–150 mg daily; parentheses denote standard error. | • N/A |

| | | meta-analyses | | | |
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| | | Size: 135,000 pts for comparisons of antiplatelet therapy vs. control and 77,000 pts for comparisons of different antiplatelet regimens | | | |
| Lorenz RL, et al., 1984 (44) 6144975 | Aim: To study the effect of ASA in the prevention of aortocoronary bypass occlusion<br><br>Study type: Prospective, double blind RCT<br><br>Size: 60 pts | Inclusion criteria: Pts undergoing aortocoronary bypass<br><br>Exclusion criteria: Peptic ulcer, anticoagulant therapy, acute MI | Intervention: 100 mg of ASA once daily (n=29)<br><br>Comparator: Placebo (n=31) | 1° endpoint: Grafts occluded at 4 mo angiographic follow-up<br>● 4/40 (10%) with ASA vs. 17/53 (32%) with placebo (2p=0.012)<br><br>Safety endpoint: N/A | ● 100 mg/d dose of ASA found to effectively block platelet thromboxane formation and thromboxane-supported aggregation on collagen |

ACS indicates acute coronary syndrome; ASA, aspirin; CI, confidence interval; CVA, cerebrovascular accident; CV, cardiovascular; HR, hazard ratio; MACE; major adverse cardiac events; MI, myocardial infarction; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; OR, odds ratio; RCT, randomized controlled trials; and RR, relative risk.

## Data Supplement 7. RCTs Comparing Antiplatelet Therapy With Anticoagulant Therapy in Patients Undergoing Coronary Stenting

| Study Acronym; Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
|---|---|---|---|---|---|
| STARS Leon MB, et al., 1998 (45) 9834303 | Aim: To compared the efficacy and safety of three antithrombotic-drug regimens — ASA alone, ASA and warfarin, and ASA and ticlopidine — after coronary stenting (BMS)<br><br>Study type: RCT<br><br>Size: 1,653 pts | Inclusion criteria: Pts undergoing successful coronary stent implantation<br><br>Exclusion criteria: Left main or bifurcation stenting, AMI, bleeding diathesis | Intervention 1: ASA alone<br><br>Intervention 2: ASA + warfarin<br><br>Intervention 3: ASA + ticlopidine | 1° endpoint: Death, TLR, Angiographically-evident thrombosis, or MI within 30 d<br>● 3.6% with ASA alone; 2.7% with ASA + warfarin; 0.5% with ASA + ticlopidine (p=0.001 for the comparison of all 3 groups).<br><br>Safety endpoint: bleeding complications<br>● 1.8% with ASA alone; 6.2% with ASA + warfarin; 5.5% with ASA + ticlopidine (p<0.001 for the comparison of all 3 groups) | ● Compared to ASA alone, ASA + ticlopidine reduced incidence of primary endpoint (RR: 0.15; CI: 0.05–0.43; p<0.001) |

| Schomig A, et al., 1996 (46) 8598866 | **Aim:** To compare antiplatelet therapy with conventional anticoagulant therapy with respect to clinical outcomes 30 d after coronary-artery stenting (BMS)<br><br>**Study type:** RCT<br><br>**Size:** 517 pts | **Inclusion criteria:** Pts undergoing coronary stent implantation (BMS)<br><br>**Exclusion criteria:** Stent placed as a bridge to CABG, cardiogenic shock, need for mechanical ventilation | **Intervention:** ASA + ticlopidine (antiplatelet therapy)<br><br>**Comparator:** anticoagulant therapy (intravenous heparin, phenprocoumon, and ASA) | **1° endpoint:** Primary cardiac endpoint a composite of CV death, MI, CABG or repeated angioplasty.<br>● 1.6% with antiplatelet therapy vs. 6.2% with anticoagulation therapy (RR: 0.25; 95% CI: 0.06–0.77)<br><br>**Safety endpoint:** Bleeding events<br>● 0% with antiplatelet therapy vs. 6.5% with anticoagulant therapy RR: 0.00; p<0.001) | ● N/A |

ASA indicates aspirin; BMS, bare metal stent; CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; and TLR, target-lesion revascularization.


## Data Supplement 8. Nonrandomized Studies of DAPT Duration After BMS or DES

| Study Acronym; Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
|---|---|---|---|---|---|
| Brar SS, et al., 2008 (47) 18534267 | **Aim:** To asses long term clinical outcomes with BMS or DES by duration of clopidogrel use in pts with DM<br><br>**Study type:** Retrospective, observational<br><br>**Size:** 749 pts | **Inclusion criteria:** Pts with DM who underwent stent implantation with either BMS or DES<br><br>**Exclusion criteria:** Pts with CABG, pts who received both a BMS and DES, pts with valvular disease, nonhealth plan members | **Intervention:** Clopidogrel >6 mo<br><br>**Comparator:** No clopidogrel >6 mo | **1° endpoint:** All-cause death and nonfatal MI<br>● 3.2% with >9 mo clopidogrel; 9.4% with 6–9 mo clopidogrel; and 16.5% with <6 mo clopidogrel (p<0.001) | ● For pts treated with DES adjusted HR: 0.48; 95% CI: 0.16–1.47; p=0.48) for >6 mo clopidogrel vs. no clopidogrel >6 mo |
| Eisenstein, et al., 2007 (48) 17148711 | **Aim:** Assess the association between clopidogrel use and long-term clinical outcomes of pts receiving DES and BMS<br><br>**Study type:** Observational study | **Inclusion criteria:** Consecutive pts treated at 1 institution undergoing BMS or DES | **Comparators:** Duration of self-reported clopidogrel use | <u>**1° endpoints in DES-treated pts at 24 mo follow-up:**</u><br>● <u>Death:</u> 2% with clopidogrel vs. 5.3% without clopidogrel (difference -3.3%; CI: -6.3% –- 0.3%; p=0.03)<br>● <u>Death or MI:</u> 3.1% with clopidogrel vs. 7.2% without clopidogrel (difference -4.1%; | ● Results based on landmark analysis of those event-free at 6 or 12 mo follow-up (6 mo results included in this table) |

| | Size: 4,666 pts; 3,165 BMS and 1,501 DES | | | 95% CI: -7.6% – -0.6%; p=0.02) | |

## Data Supplement 9. Randomized Studies of 1 Versus 12 Months of DAPT After BMS

| Study Acronym; Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
|---|---|---|---|---|---|
| Steinhubl SR, et al., 2002 (49) 12435254 | Aim: To evaluate the benefit of long-term (12 mo) treatment with clopidogrel (in addition to ASA) after PCI in pts treated with BMS Study type: RCT Size: 2,116 pts | Inclusion criteria: Pts referred for planned PCI Exclusion criteria: Contraindications to antiplatelet or antithrombotic therapy, recent STEMI, recent use of GPI, clopidogrel, or thrombolytic therapy | Intervention: ASA + clopidogrel Comparator: ASA + placebo | 1° endpoint: 1 y incidence of MACE (death, MI or stroke) ● RRR: 26.9% (CI: 3.9%–44.4%; p=0.02) Safety endpoint: Major bleeding ● 8.8% with DAPT vs. 6.7% with ASA (p=0.07) | ● All study pts treated with DAPT for the first 28 d ● Absolute risk reduction 3% with DAPT |

## Data Supplement 10. Studies and Meta-Analyses Comparing Graft Patency Post–CABG in Patients Treated With Either Antiplatelet Monotherapy or DAPT

| Study Acronym; Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
|---|---|---|---|---|---|
| Randomized Trials | | | | | |
| Mannacio VA, et al., 2012 (50) 22942294 | Aim: To determine the individual variability in the response to ASA and/or clopidogrel and its impact on graft patency after off-pump CABG | Inclusion criteria: Consecutive pts undergoing off-pump CABG Exclusion criteria: Additional surgical procedures, emergency | Intervention: ASA + clopidogrel Comparator: ASA | 1° endpoint: Platelet resistance and inhibition ● In the ASA group 32.6% were ASA resistant and, in the ASA-clopidogrel group, 12.6% were ASA and clopidogrel resistant. | ● Secondary endpoint of SVG graft occlusion at 12 mo as assessed by CTA: 7.4% with DAPT vs. 13.1% with ASA (p=0.04) |

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| | **Study type:** Single center RCT<br><br>**Size:** 300 pts | operations, active bleeding or bleeding diathesis | | **Safety endpoint:** Major bleeding<br>● 1.3% with DAPT vs. 1.3% with ASA (p=1.00) | |
| Sun JCJ, et al., 2010 (51) 21146675 | **Aim:** Assess graft patency 1 mo after CABG in pts treated with ASA alone or ASA+clopidogrel<br><br>**Study type:** RCT, pilot study<br><br>**Size:** 100 pts (79 of whom underwent follow-up CTA) | **Inclusion criteria:** Pts undergoing on-pump CABG treated with ≥1 free bypass graft<br><br>**Exclusion criteria:** Indication for anticoagulation, Hx of GI or intracranial bleeding | **Intervention:** ASA+clopidogrel<br><br>**Comparator:** ASA+ placebo | **1° endpoint:** Proportion of pts with ≥ occluded grafts at 1 mo as assessed by CTA<br>● 17.5% with ASA+clopidogrel vs. 23.1% with ASA+placebo (RR: 0.95; 95% CI: 0.80–1.14; p=0.54)<br><br>**Safety endpoint:** Major bleeding complication<br>● 6.1% with ASA+clopidogrel vs. 6.0% with ASA+placebo (p=1.00) | N/A |
| CASCADE Kulik A, et al., 2010 (52) 21135365 | **Aim:** Assess if addition of clopidogrel to ASA after CABG inhibits SVG disease at 1 y as assessed by IVUS<br><br>**Study type:** RCT<br><br>**Size:** 113 pts (92 underwent follow-up IVUS) | **Inclusion criteria:** Pts undergoing 1st time CABG treated with at least 2 SVG with or without the use of cardiopulmonary bypass<br><br>**Exclusion criteria:** Concomitant valve surgery, need for oral anticoagulation | **Intervention:** Clopidogrel (in addition to ASA)<br><br>**Comparator:** Placebo (in addition to ASA) | **1° endpoint:** Mean SVG intimal area per pts at 1 y follow-up<br>● 4.1 mm$^2$ with clopidogrel vs. 4.5 mm$^2$ with placebo (p=0.90)<br><br>**Safety endpoint:** Major bleeding<br>● 1.8% with clopidogrel vs. 0% with placebo (p=0.50) | ● Overall 1 y graft patency 95.2% with clopidogrel vs. 95.5% with placebo (p=0.90)<br>● 1 y SVG patency 94.3% with clopidogrel vs. 95.5% with placebo (p=0.90) |
| Gao G, et al., 2010 (53) 21050973 | **Aim:** Assess 3 mo graft patency after CABG in those treated with or without clopidogrel (in addition to baseline ASA)<br><br>**Study type:** Single center, RCT<br><br>**Size:** 249 pts (244 underwent CTA) | **Inclusion criteria:** Pts referred for isolated CABG, with or without cardiopulmonary bypass<br><br>**Exclusion criteria:** Thrombocytopenia, previous CABG, concomitant valve surgery or aneurysm resection | **Intervention:** Clopidogrel (n=113)<br><br>**Comparator:** No clopiodogrel (n=111) | **1° endpoint:** SVG graft patency at 3 mo (assessed by CTA)<br>● 91.6% with clopidogrel vs. 85.7% without clopidogrel (RR: 1.7; 95% CI: 1.0–2.9; p=0.043) | ● In the multivariate analysis, combined antiplatelet therapy independently<br>● Increased venous graft patency (RR: 1.996; CI: 1.015–3.922; p=0.045). |
| Gao C, et al 2009 (54) 19559191 | **Aim:** Assess 1 and 12 mo SVG patency after CABG with either clopidogrel alone or clopidogrel+ASA<br><br>**Study type:** RCT | **Inclusion criteria:** Elective CABG<br><br>**Exclusion criteria:** Thrombocytopenia, concomitant valve surgery | **Intervention:** Clopidogrel + ASA (n=95)<br><br>**Comparator:** Clopidogrel alone | **1° endpoint:** SVG patency rates (as assessed by CTA)<br>● 1 mo: 98.2% with clopdigrel+ASA vs. 98.1% with clopidogrel alone (p=0.73)<br>● 12 mo: 96.3% with clopiodgrel+ASA | ● All pts underwent CABG performed by one surgeon<br>● Treatment assignment was alternated every wk in consecutively treated pts<br>● Report states no obvious |

| | | or aneurysm resection | (n=102) | vs. 93.5% with clopidogrel alone (p=0.25) | bleeding events in any pts |
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| | Size: 197 pts | | | | |

**Nonrandomized Studies**

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| ROOBY<br>Ebrahimi R, et al., 2014<br>(55)<br>24206971 | Aim: Evaluate the role of clopidogrel use post CABG to improve graft patency when added to ASA therapy.<br><br>Study type: Post hoc substudy analysis of the ROOBY trial<br><br>Size: 2,203 pts enrolled in trial; 953 pts included in analysis | Inclusion criteria: Pts who were enrolled in the ROOBY trial with complete data on clopidogrel use and with 1 y angiographic data<br><br>Exclusion criteria (for substudy): No data on clopidogrel use, no 1 y angiographic follow-up | Intervention: Clopidogrel use at discharge (nonrandomized) (n=345)<br><br>Comparator: No clopidogrel use at discharge (n=608) | 1° endpoint: 1 y graft patency rates at angiography<br>● 86.5% with clopiogrel vs. 85.3% without clopidogrel (p=0.43) | ● No significant difference in graft patency found in those who underwent on-pump CABG nor in those who underwent off-pump CABG |
| Ibrahim K, et al., 2006<br>(56)<br>17060036 | Aim: To evaluate the effect of clopidogrel on midterm graft patency following off-pump coronary revascularization surgery<br><br>Study type: Single center study in which the first 36 pts were treated with ASA alone then the next 58 pts were treated with ASA + clopidogrel<br><br>Size: 94 consecutively treated pts; 62 pts underwent angiographic follow-up | Inclusion criteria: Pts undergoing off-pump CABG | Intervention: ASA + clopidogrel<br><br>Comparator: Antiplatelet monotherapy | 1° endpoint: Overall graft patency at 6 mo angiographic follow-up<br>● 42/45 (93%) with ASA + clopidogrel vs. 31/37 (84%) with ASA alone (p=NS) | ● LIMA patency: 28/29 (96%) with DAPT vs. 23/35 (92%) with ASA (p=NS)<br>● SVG patency: 14/16 (87%) with DAPT vs. 7/11 (66%) with ASA (p=NS) |

**Meta-Analyses and Systematic Overviews**

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| Deo SV, et al., 2013<br>(57)<br>23488578 | Aim: Assess effects of clopidogrel (in addition to ASA) after CABG<br><br>Study type: Meta-analysis<br><br>Size: 5 RCT and 6 observations studies; 25,728 | Inclusion criteria: Studies of isolated CABG, on-pump or off-pump | Intervention: Clopidogrel (in addition to ASA)<br><br>Comparator: ASA alone | 1° endpoint: SVG patency as assessed by coronary angiography or CT angiography in the 5 RCT<br>● Early SVG occlusion rates reduced with DAPT (RR: 0.59; 95% CI: 0.43–0.82; p=0.02). | ● Trend towards a higher incidence of major bleeding episodes with DAPT (RR: 1.17; CI: 1.00–1.37; p=0.05) |

| | pts | | | | |
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| Nocerino AG, et al., 2013 (58) 24035160 | Aim: Assess whether DAPT is superior to antiplatelet monotherapy to improve graft patency early after CABG Study type: Meta-analysis of 5 RCT Size: 958 pts; 2,919 grafts | Inclusion criteria: RCT of single vs. dual antiplatelet therapy for ≥30 d Exclusion criteria: Nonrandomized studies | Intervention: DAPT Comparator: Antiplatelet monotherapy | 1° endpoint: Overall graft patency • Early graft occlusion 5.0% with DAPT vs. 7.7% with monotherapy (p=0.005) • OR=1.59 for graft occlusion with monotherapy (95% CI: 1.16–2.1) | • Follow-up in studies ranged from 3 d to 12 mo • For SVG only, monotherapy, when compared to DAPT, associated with increased graft loss rate (10.8% vs. 6.6%; OR: 1.70; p=0.03) • No significant reduction in arterial graft occlusion with DAPT found |
| de Leon N, et al., 2012 (59) 22570427 | Aim: Evaluate the evidence for DAPT post–CABG Study type: Systematic overview Size: 4 RCT evaluating surrogate endpoints and 9 studies evaluating clinical endpoints | Inclusion criteria: Peer-reviewed studies that evaluated DAPT after CABG | Intervention: DAPT after CABG Comparator: Antiplatelet monotherapy | Primary relevant finding: • 3 clinical trials assessing surrogate end points failed to demonstrate an improvement in graft patency with DAPT use, while 1 clinical trial found an increase in graft patency. | • N/A |

ASA indicates aspirin; CABG, coronary artery bypass graft; CI, confidence interval; CTA, computed tomography angiography; DAPT, dual antiplatelet therapy; GI, gastrointestinal; HR, hazard ratio; Hx, history; N/A, not available; LIMA, left internal mammary artery; OR, odds ratio; RCT, randomized controlled trials; RR, relative risk; and SVG, saphenous vein graft.


## Data Supplement 11.  Studies Comparing Outcome Post–CABG in Patients Treated With Either Aspirin or DAPT

| Study Acronym; Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
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| Sorenson, et al., 2001 (60) 21371637 | Aim: To study efficacy of post–op clopidogrel treatment in pts with MI undergoing CABG Study type: Registry study Size: 3,545 pts | Inclusion criteria: Pts surviving ≥ 30 d after CABG, pts observed 18 mo. after CABG Exclusion criteria: Those not meeting above inclusion criteria | Intervention: Clopidogrel (n=957) Comparator: No clopidogrel ( n=2,588) | 1° endpoint: Death or recurrent MI •4.1% with clopidogrel vs. 7.8% without clopidogrel (HR: 0.59; 95% CI: 0.42–0.85; p=0.0003) •By propensity score (total n=945) 4.0% with clopidogrel vs. 6.0% without clopidogrel (HR: 0.67; 95% CI: 0.44–1.00; p=0.05) | • N/A |

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| Kim DH, et al., 2009 (61) 19931667 | **Aim:** To determine benefit and risk of ASA + clopidogrel use (vs. ASA alone) postoperatively following on-pump or off-pump CABG. <br><br> **Study type:** Observational <br><br> **Size:** 15,067 pts | **Inclusion criteria:** Pts undergoing CABG treated in the early post–operative period with ASA or clopidogrel + ASA <br><br> **Exclusion criteria:** Pre-op and late post–op clopidogrel use, prolonged hospitalization >1wk before surgery, valvular procedure, warfarin use | **Intervention:** ASA + clopidogrel (n=3,268) <br><br> **Comparator:** ASA (n=11,799) | **1° endpoint:** In-hospital mortality <br> ● 0.95% with DAPT vs. 1.78% with ASA (adjusted OR: 0.50; 95% CI: 0.25–0.99) <br><br> **Safety endpoint:** in-hospital bleeding events <br> ● 4.19% with DAPT vs. 5.17% with ASA (adjusted OR: 0.70; 95% CI: 0.51–0.97) | ● Adjusted HR: 0.83 (CI: 0.61–1.12) for in-hospital mortality or 30 d readmission with DAPT compared to ASA |
| **CURE** Fox KA, et al., 2004 (32) 15313956 | **Aim:** To assess benefits and risks of ASA plus clopidogrel in pts undergoing CABG for NSTE-ACS <br><br> **Study type:** Post hoc subgroup analysis of CURE; RCT <br><br> **Size:** 12,562 pts entire study population; 1,061 pts underwent CABG | **Inclusion criteria:** NSTE-ACS within <24 h <br><br> **Exclusion criteria:** NYHA class IV HF, PCI or CABG <3 mo, contraindication to antiplatelets and antithrombotics, hemorrhagic or IC stroke, severe thrombocytopenia | **Intervention:** Clopidogrel + ASA <br><br> **Comparator:** Placebo + ASA | **1° endpoint:** MACE (CV death, MI or stroke) <br> ● 14.5% with DAPT % vs. 16.2% with ASA (RR: 0.89; 95% CI: 0.71–1.11) | ● Benefits of DAPT with CABG were deemed "consistent" (test for interaction among strata 0.53) with the benefits in pts undergoing PCI (9.6% with DAPT vs. 13.2% with ASA; RR: 0.72; CI: 0.47–0.90) and in those treated with medical therapy alone (8.1% with DAPT vs. 10.0% with ASA; RR: 0.80; CI: 0.69–0.92) |

ASA indicates aspirin; CABG, coronary artery bypass graft; CI, confidence interval; DAPT, dual antiplatelet therapy; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndrome; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention and RR, relative risk.

## Data Supplement 12. Studies of Timing of Noncardiac Surgery After PCI

| Study Acronym; Author; Year Published | Aim of Study; Study Type; Study Size (N) | Patient Population | Study Intervention (# patients) / Study Comparator (# patients) | Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI) | Relevant 2° Endpoint (if any); Study Limitations; Adverse Events |
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| Kaluza, et al., 2000 (62) 10758971 | **Aim:** To assess the clinical course of pts who have undergone coronary stent placement >6 wk before noncardiac surgery.<br><br>**Study type:** Retrospective cohort<br><br>**Size:** 40 pts | **Inclusion criteria:** Consecutive pts who underwent coronary stent placement >6 wk before noncardiac surgery requiring a general anesthesia were included in the study<br><br>**Exclusion criteria:** N/A | **Intervention:** N/A<br><br><br>**Comparator:** N/A | **1° endpoint:**<br>• MI: 7 pts<br>Major Bleeds: 11pts<br>Deaths: 8<br>• All deaths/MI and 8/11 bleeds occurred if surgery <14 d from stent placement | • DAPT not well described<br>• Single center |
| Wilson, et al., 2003 (63) 12875757 | **Aim:** To determine the frequency and timing of complications at our institution when surgery was performed within 2 mo of coronary stent placement.<br><br>**Study type:** Retrospective cohort<br><br>**Size:** 207 pts | **Inclusion criteria:** Analysis of the PCI database and the General Surgery database at Mayo Clinic for pts who underwent noncardiac surgery within 60 d of coronary stent placement. Surgical procedures included in this analysis were those that required a significant incision and had the potential for perioperative bleeding.<br><br>**Exclusion criteria:** Procedures such as joint aspirations, endoscopy, and skin biopsies, among others, were not included in this analysis | **Intervention:** N/A<br><br><br>**Comparator:** N/A | **1° endpoint:**<br>• MACE: 8/207<br><br>**1° Safety endpoint:**<br>• Excessive bleeding: 2/207 | • Single center |

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| Nuttal, et al., 2008 (64) 18813036 | **Aim:** To address the hypothesis that the risk of MACEs and bleeding events is related to the time interval between PCI with BMS and NCS **Study type:** Retrospective **Size:** 889 pts | **Inclusion criteria:** Analysis of pts who underwent NCS within 1 y after PCI with BMS at Mayo Clinic (Rochester, Minnesota) between January 1, 1990, and January 1, 2005. Pts were identified using the Mayo Clinic PCI registry and the Mayo Clinic Surgical database. **Exclusion criteria:** Pts on long-term warfarin therapy | **Intervention:** N/A **Comparator:** N/A | **1° endpoint:** • MACE- 47 (5.2%; 95% CI: 3.8–6.7%) • Frequency of MACEs was 10.5% (95% CI: 6.7–14.3%) when NCS was performed 30 or fewer d after PCI with BMS, 3.8% (95% CI: 1.5–6.2%) when NCS was 31–90 d after PCI with BMS, and 2.8% (95% CI: 1.2–4.5%) when NCS was 91 or more d after PCI with BMS | • DAPT not well described • Single center |
| Wijeysundera, et al., 2012 (65) 22893606 | **Aim:** To evaluate the outcomes of pts who underwent elective intermediate- to high-risk noncardiac surgery in Ontario, Canada after stent implantation. **Study type:** A population-based cohort study **Size:** 8,116 pts | **Inclusion criteria:** All Ontario residents who were ≥40 y, underwent any 1 of 16 prespecified elective noncardiac surgeries between April 1, 2003 and March 31, 2009, and underwent coronary stent implantation within 10 y before their index surgery. The included surgeries were abdominal aortic aneurysm repair, carotid endarterectomy, peripheral vascular bypass, total hip replacement, total knee replacement, large bowel resection, partial liver resection, Whipple procedure, pneumonectomy, pulmonary lobectomy, gastrectomy, esophagectomy, total abdominal hysterectomy, radical prostatectomy, nephrectomy, and cystectomy. **Exclusion criteria:** • Individuals who underwent CABG surgery between the preoperative PCI and subsequent index noncardiac surgery were excluded. • Low-risk ambulatory surgeries | **Intervention:** N/A **Comparator:** N/A | **1° endpoint:** • Overall risk of 30 d MACE was relatively low at 2.1% (n=170), whereas the risk of 1 y MACE was 9.8% (n=798). • The rate of postoperative mortality was 1.2% (n=100) at 30 d and 5.2% (n=419) at 1 y. • BMS: 1-45 d OR: 2.35 (95% CI: 0.98–5.64); 46–180 d OR: 1.06 (95% CI: 0.58–1.92); 181–365 d OR 1.89 (1.08–3.32) • DES: 1-45 d OR: 11.58 (95% CI: 4.08-32.80); 46-180 d OR: 1.71 (95% CI: 0.73–4.01); 181-365 d OR: 0.64 (95% CI: 0.20–2.04) | • Administrative database |
| EVENT Registry Berger, et al., 2010 (66) 20850090 | **Aim:** To determine the frequency of noncardiac surgery and adverse postoperative events among pts who recently | **Inclusion criteria:** The EVENT registry, consecutive pts who underwent attempted stent placement at 42 hospitals between July 2004 and September 2005 were enrolled | **Intervention:** Pts who underwent major surgery **Comparator:** | **1° endpoint:** • In the 7 d after surgery, 4 pts had a cardiac death, myocardial infarction, or stent thrombosis (1.9%; 95% | • DAPT status and bleeding endpoint not well described |

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| | | | | CI=0.5%–4.9%).<br>• The risk of the composite outcome was increased 27-fold in the wk following noncardiac surgery compared with any other wk after stent implantation (HR: 27.3; 95% CI: 10.0–74.2; p <0.001). | |
|---|---|---|---|---|---|
| received a DES following noncardiac surgery<br><br>**Study type:** Registry<br><br>**Size:** 206 pts | and followed for 1 y. Major noncardiac surgical procedures in which a significant surgical incision was required from which bleeding would result were included in this analysis.<br><br>**Exclusion criteria:** Pts who underwent CABG or valve surgery (n=67), pacemaker and defibrillator placement (n=46), and pts who underwent surgery whose nature could not be determined (n=50) were prospectively excluded from this analysis. Pts who underwent minor surgical procedures (n=27), such as minor dermatological procedures, endoscopic procedures, joint aspirations, and cataract surgery | Pts who did not undergo major surgery | | | |
| PARIS<br>Mehran, et al., 2013<br>(67)<br>24004642 | **Aim:** To determine the association between different modes of DAPT cessation and cardiovascular risk after PCI in the PARIS Registry<br><br>**Study type:** Retrospective analysis of a prospective registry<br><br>**Size:** 5,031 pts undergoing PCI | **Inclusion criteria:** Adult pts (≥18 y) undergoing successful stent implantation in ≥1native coronary artery and discharged on DAPT were eligible for enrolment.<br><br>**Exclusion criteria:** Pts participating in an investigational device or drug study or with evidence of stent thrombosis at the index procedure were excluded. | **DAPT Cessation 1:** physician recommended discontinuation<br><br>**DAPT Cessation 2:** brief interruption (for surgery)<br><br>**DAPT Cessation 3:** disruption (noncompliance or because of bleeding | **1° Findings:**<br>• Overall incidence DAPT cessation 57.3% (discontinuation 40.8%; interruption 10.5%; disruption 14.4%<br>• Compared with those on DAPT, the adjusted HR for MACE due to discontinuation was 0.63 (95% CI: 0.46–0.86); for interruption was 1·41 (95% CI: 0.94–2.12; p=0·10) and for disruption was 1·50 (95% CI: 1.14–1.97; p=0.004).<br>• Within 7 d, 8–30 d, and more than 30 d after disruption, adjusted HRs were 7·04 (95% CI: 3.31–14.95), 2.17 (95% CI: 0.97–4.88), and 1.3 (95% CI: 0.97–1.76), respectively. | • N/A |

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| Holcomb, et al., 2015 (68) 26720292 | **Aim:** To better understand the factors contributing to cardiac risk in pts who have undergone recent PCI and require noncardiac surgery, we comparatively examined the postoperative MACE associated with 3 distinct subgroups of stent indication: (1) MI; (2) unstable angina; and (3) non–ACS revascularization.<br><br>**Study type:** Retrospective cohort<br><br>**Size:** 26,661 pts | **Inclusion criteria:** All pts with coronary stents implanted in the VA between January 1, 2000, and December 31, 2010<br><br>**Exclusion criteria:** Minor operations such as endoscopic procedures and minor musculoskeletal procedures such as application of a cast and joint aspiration. Operations performed under local or monitored anesthesia were excluded from analyses. | **Intervention:** N/A<br><br>**Comparator:** N/A | **1° endpoint:**<br>• Postoperative MACE rates were significantly higher in the MI group (7.5%) compared with the unstable angina (2.7%) and non–ACS (2.6%) groups (p<0.001).<br>• When surgery was performed within 3 mo of PCI, adjusted odds of MACE were significantly higher in the MI group compared with the non–ACS group (OR: 5.25; 95% CI: 4.08–6.75). This risk decreased overtime, although it remained significantly higher at 12–24 mo from PCI (OR: 1.95; 95% CI: 1.58–2.40).<br>•The adjusted odds of MACE for the unstable angina group were similar to those for the non–ACS group when surgery was performed within 3 mo (OR: 1.11; CI: 0.80–1.53) or between 12 and 24 mo (OR: 1.08; CI: 0.86–1.37) from stent placement. | • Primarily older white males<br>• Unknown medication regimen<br>• Stent type was not significantly associated with MACE regardless of indication. |

ACS indicates acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; N/A, not available; NCS, noncardiac surgery; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trials; RR, relative risk; and VA, US Veterans Affairs Hospital.

ARCTIC indicates Assessment by a Double Randomisation of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation 1 Year AfterS; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DES-LATE, Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Events; EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE, Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC, Is There A Life for DES After Discontinuation of Clopidogrel; MACCE, major adverse cardiac and cerebrovascular events (death, MI, or stroke); MI, myocardial infarction; OPTIDUAL, Optimal Dual Antiplatelet Therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; NACCE, net adverse cardiac and cerebrovascular events (death, MI, stroke or major bleeding); PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; REAL-LATE, REAL-world patients treated with drug-eluting stent implantation and Late coronary Arterial Thrombotic Events; RESET, Real Safety and Efficacy of 3-month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; revasc, revascularization; SECURITY, Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; ST, stent thrombosis; TIMI, Thrombolysis In Myocardial Infarction; TVF, target-vessel failure; TVR, target-vessel revascularization; and ZEST-LATE, Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions-Late coronary Arterial Thrombotic Events.

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