Optimizing Monotherapy Selection, Aspirin Versus P2Y12 Inhibitors, Following Percutaneous Coronary Intervention

Charan Yerasi, MD, Brian C. Case, MD, Brian J. Forrestal, MBBS, Rebecca Torguson, MPH, William S. Weintraub, MD, Hector M. Garcia-Garcia, MD, PhD, and Ron Waksman, MD*

Dual antiplatelet therapy (DAPT) reduces ischemic and thrombotic events after percutaneous coronary intervention (PCI). Initial reports of higher myocardial infarction and mortality rates prompted guideline committees to choose 12-month duration of DAPT after PCI. However, higher bleeding rates with DAPT remain a major concern. Since these guidelines were published, there have been improvements in stent design, deployment techniques, and antiplatelet therapies, which have reduced ischemic events. To address bleeding concerns, trials were performed to evaluate the effectiveness of short-duration DAPT. Two main strategies were employed: (1) aspirin monotherapy after a short-duration DAPT, and (2) P2Y12 inhibitor monotherapy after a short-duration DAPT. In this review, we outline all the major trials on short-duration DAPT that have examined the previously mentioned strategies and propose a new individualized treatment algorithm for which monotherapy to choose or remove after PCI. In conclusion, while removing the P2Y12 inhibitor after a short DAPT appears to be safe in the low-risk population, removing aspirin and continuing the P2Y12 inhibitor as monotherapy would be the preferred strategy in intermediate- to high-risk patients to mitigate the bleeding risk. **(Am J Cardiol 2020;135:154−165)**

Adding aspirin as an antiplatelet therapy after percutaneous coronary intervention (PCI) began 3 decades ago. In the PCI era, the CURE[1] and CREDO studies[2] showed the benefits of adding clopidogrel to aspirin versus aspirin alone after PCI or myocardial infarction (MI), forming the basis for dual antiplatelet therapy (DAPT). Later studies showed[3,4] higher rates of ischemic events after interruption of antiplatelet therapy, which favored prolonged DAPT for at least 12 months. The previously mentioned findings, along with the recommendation of 12 months of DAPT, are reflected in major society guidelines.[5,6] To address the ischemic complications after PCI, improvements in stent design/biocompatibility were made. These changes included thinner struts, compatible polymers, and procedural techniques, all resulting in a dramatic decrease in the incidence of stent thrombosis.[7] However bleeding events remained same. In this review, we present an overview of the major short-duration antiplatelet therapy trials and propose a new management algorithm for antiplatelet therapy after PCI based on the available evidence. Extended DAPT regimens of more than 12 months and DAPT in patients who are on oral anticoagulation are other challenging areas and are not discussed in this review.

Short-duration DAPT trials

To date, there have been many single-arm prospective studies, numerous meta-analyses, and many randomized clinical trials evaluating short-duration DAPT. Table 1 provides an overview of all the major short-duration DAPT randomized clinical trials. Two strategies were tested in all of these trials: (1) short duration of DAPT followed by aspirin monotherapy, and (2) short duration of DAPT followed by P2Y12 inhibitor (P2Y12i) monotherapy. The baseline, clinical presentation, and procedural characteristics of these studies are displayed in Tables 2, 3, and 4, respectively. Major ischemic and bleeding event rates of all the short-duration DAPT trials are summarized in Figures 1 and 2.

Six-month DAPT followed by aspirin monotherapy

Initial trials evaluated the safety and efficacy of 6-month DAPT followed by aspirin monotherapy in patients with stable ischemic heart disease (SIHD). The comparator for these studies was 12-month DAPT or prolonged DAPT (18 to 24 months). Studies testing this particular strategy are EXCELLENT,[8] PRODIGY,[9] SECURITY,[10] ITALIC,[11] ISAR-SAFE,[12] IVUS-XPL,[13] NIPPON,[14] I-LOVE-IT 2,[15] and OPTIMA-C.[16]

Important features of these trials are listed as follows:

1. Most patients in these studies underwent PCI for SIHD.
2. Most studies randomized patients at the index procedure or at 30 days, except for ISAR SAFE and ITALIC, which randomized patients at 6 months.
3. Except for PRODIGY, all the studies used second- and latest-generation DES.
4. All the trials met noninferiority for different composite end points except for the PRODIGY study. PRODIGY was a superiority trial (composite end point of all-cause

Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, District of Columbia. Manuscript received June 2, 2020; revised manuscript received and accepted July 27, 2020.

See page 163 for disclosure information.

*Corresponding author: Tel: (202) 877-2812; fax: (202) 877-2715.
E-mail address: ron.waksman@medstar.net (R. Waksman).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.07.061

Table 1
Major randomized trials on short-duration antiplatelet therapy

STUDY	Year	First author	n (overall)	n (study)	Design	Follow-up	DAPT duration	Dropped	Results of primary end point	Randomization	Results of primary end point.
6 month DAPT followed by aspirin monotherapy											
EXCELLENT (15)	2012	Gwon	1,443	722	Noninferiority	12 months	6 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index procedure	4.8% vs 4.3%, p = 0.001 for noninferiority
PRODIGY (16)	2012	Valgimigli	1,970	983	Superiority	24 months	6 vs 24	P2Y12 inhibitor	Superiority not achieved	30 days	10% vs 10.1%, p = 0.91
SECURITY (17)	2014	Colombo	1,399	682	Noninferiority	12 months	6 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index procedure	4.5% vs 3.7%, p <0.05 for noninferiority
ITALIC (18)	2015	Glard	1,822	910	Noninferiority	12 months	6 vs 24	P2Y12 inhibitor	Noninferiority achieved	6 months	1.6% vs 1.5%, p = 0.0002 for noninferiority
ISAR-SAFE (19)	2015	Schulz-schuzpke	4,000	1,997	Noninferiority	15 months	6 vs 12	P2Y12 inhibitor	Noninferiority achieved	6 months	1.5% vs 1.6%, p <0.001 for noninferiority
IVUS-XPL (20)	2016	Hong	1,400	699	Substudy	12 months	6 vs 12	P2Y12 inhibitor	No difference	Index procedure	2.2 vs 2.1% p = 0.85
NIPPON (21)	2017	Nakamura	3,773	1,886	Noninferiority	18 months	6 vs 18	P2Y12 inhibitor	Noninferiority achieved	Index admission	2.1% vs 1.5%, p met noninferiority
I-LOVE-IT 2 (22)	2017	Han	1,829	909	Noninferiority	12 months	6 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index procedure	6.5% vs 5.8%, p = 0.0065 for noninferiority
OPTIMA-C (23)	2018	Kwon-Lee	1,368	684	Noninferiority	12 months	6 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index procedure	1.2% vs 0.6%, p <0.005 for noninferiority
3-month DAPT followed by aspirin monotherapy											
RESET (26)	2012	Kim	2,117	1,059	Noninferiority	12 months	3 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index procedure	4.7 % vs 4.7%, p <0.001 for noninferiority
OPTIMIZE (27)	2013	Feres	3,119	1,563	Noninferiority	12 months	3 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index admission	6% vs 5.8%, p = 0.002 for noninferiority
1-month DAPT followed by aspirin monotherapy in high-bleeding risk patients.											
LEADERSFREE (28)	2015	Urban	2,466	1,239	Both noninferiority and superiority	12 months	1 month	P2Y12 inhibitor	Superiority achieved	Index procedure	9.4% vs 12.9%, p = 0.005 for superiority
ZEUS (29)	2015	Valgimigli	1,606	802	Superiority	12 months	1 month	P2Y12 inhibitor	Superiority achieved	Index procedure	17.5% vs 22%, p = 0.01 for superiority
SENIOR (30)	2018	Varenne	1200	596	Superiority	12 months	1 month/6 months	P2Y12 inhibitor	Superiority achieved	Index procedure	12% vs 16%, p = 0.02 for superiority
ONYX ONE (32)	2020	Windecker	1996	1,003	Noninferiority	12 months	1 month	P2Y12 inhibitor	Noninferiority achieved	Index procedure	17.1% vs 16.9%, p = 0.01 for noninferiority
3-month DAPT of 1-month DAPT followed by P2Y12 inhibitor monotherapy											
GLOBAL LEADERS (34)	2018	Vranckx	15,968	7,980	Superiority	24 months	1 vs 12	Aspirin	Superiority not achieved	Index procedure	3.8% vs 4.37%, p = 0.07
SMART- CHOICE (36)	2019	Hahn	2,993	1,495	Noninferiority	12 months	3 vs 12	Aspirin	Noninferiority and superiority achieved	Index procedure or within 3 months	2.9% vs 2.5%, p = 0.007 for noninferiority
STOPDAPT-2 (37)	2019	Watanabe	3,045	1,500	Noninferiority	12 months	1 vs 12	Aspirin	Noninferiority and superiority achieved	Index procedure before hospital discharge	2.36% vs 3.7%, p = 0.04, p <0.001 for noninferiority
TWILIGHT (38)	2019	Mehran	7,119	3,555	Superiority	12 months	3 vs 12	Aspirin	Superiority achieved	3 months	4% vs 7.1%, p <0.001
Antiplatelet drug studies in Acute coronary syndrome											
DAPTSTEMI (39)	2018	Kedhi	870	432	Noninferiority	18 months	6 vs 12	P2Y12 inhibitor	Noninferiority achieved	6 months	4.8% vs 6.6% (p = 0.26, p = 0.004 for noninferiority)
SMART-DATE (40)	2018	Hahn	2,712	1,357	Noninferiority	18 months	6 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index procedure	4.7% vs 4.2%, p = 0.51, p = 0.03 for noninferiority
REDUCE (41)	2019	De Luca	1,496	751	Noninferiority	12 months	3 vs 12	P2Y12 inhibitor	Noninferiority achieved	Index procedure	8.2% vs 8.4%, p <0.001 for noninferiority
TICO (44)	2020	Kim	3,056	1,527	Superiority	12 months	3 vs 12	Aspirin	Superiority Achieved	Index procedure	3.9% vs 5.9%, p = 0.01

DAPT = dual antiplatelet therapy.

Table 2
Baseline characteristics of the study population in short-duration antiplatelet therapy trials

STUDY	Age (St)	Age (Co)	Males (St)	Males (Co)	HTN (St)	HTN (Co)	DM (St)	DM (Co)	HLD (St)	HLD (Co)	Tobacco use (St)	Tobacco use (Co)	Previous PCI (St)	Previous PCI (Co)	Previous CABG (St)	Previous CABG (Co)	Previous stroke (St)	Previous stroke (Co)
EXCELLENT (15)	63 ± 10	62 ± 10	65%	64%	73%	74%	38%	39%	75%	76%	27%	26%	9%	9%	2%	1%	7%	7%
PRODIGY (16)	68 ± 11	68 ± 11	76%	77%	70%	73%	24%	25%	53%	56%	25%	23%	18%	19%	11%	11%	4%	4%
SECURITY (17)	65 ± 10	66 ± 10	78%	77%	75%	71%	30%	31%	65%	61%	21%	24%	19%	16%	6%	5%	-	-
ITALIC (18)	62 ± 11	62 ± 11	81%	79%	65%	65%	36%	38%	67%	67%	51%	53%	24%	23%	7%	5%	3%	3%
ISAR-SAFE (19)	67 (59,73)	67 (59−74)	81%	80%	90%	91%	25%	24%	88%	87%	15%	15%	-	-	8%	8%	-	-
IVUS-XPL (20)	63 ± 9	64 ± 9	67%	70%	63%	65%	36%	37%	68%	65%	25%	24%	10%	10%	3%	2%	-	-
NIPPON (21)	67 ± 10	67 ± 10	79%	79%	71%	73%	37%	38%	68%	69%	58%	60%	25%	26%	1%	2%	3%	3%
I-LOVE-IT 2 (22)	60 ± 10	60 ± 10	67%	69%	61%	65%	23%	22%	25%	23%	37%	38%	9%	7%	0%	0%	9%	10%
OPTIMA-C (23)	63 ± 11	64 ± 10	70%	68%	62%	63%	29%	30%	30%	29%	27%	27%	9%	10%	-	-	-	-
RESET (26)	62 ± 9	62 ± 10	64%	63%	62%	61%	30%	29%	58%	60%	25%	23%	4%	3%	0%	1%	-	-
OPTIMIZE (27)	61 ± 10	62 ± 11	64%	63%	86%	88%	35%	35%	63%	64%	19%	17%	21%	19%	7%	8%	3%	3%
LEADERSFREE (28)	76 ± 9	76 ± 9	70%	69%	78%	80%	34%	32%	62%	63%	-	-	22%	22%	9%	10%	11%	9%
ZEUS (29)	72 ± 12	72 ± 11	70%	71%	76%	75%	27%	26%	48%	50%	21%	21%	19%	19%	7%	7%	6%	7%
SENIOR (30)	81.4 ± 4.3	81.4 ± 4.2	62%	63%	72%	81%	27%	26%	52%	53%	7%	6%	23%	24%	6%	7%	7%	8%
ONYX ONE (32)	74 ± 9.5	74 ± 9.8	68%	66%	79%	84%	39%	39%	64%	62%	9%	11%	24%	23%	8%	7%	14%	13%
GLOBAL LEADERS (34)	64 ± 10	65 ± 10	77%	77%	74%	73%	26%	25%	69%	70%	26%	26%	33%	33%	6%	6%	3%	3%
SMART- CHOICE (36)	65 ± 11	64 ± 11	73%	74%	62%	61%	38%	37%	45%	46%	28%	25%	12%	12%	-	-	7%	7%
STOPDAPT-2 (37)	68 ± 11	69 ± 10	79%	77%	74%	74%	39%	38%	74%	75%	27%	21%	34%	35%	1%	3%	5%	7%
TWILIGHT (38)	65 ± 10	65 ± 10	76%	76%	73%	72%	37%	37%	61%	60%	20%	23%	42%	42%	10%	10%	-	-
DAPTSTEMI (39)	60 ± 11	60 ± 10	78%	76%	45%	45%	13%	14%	28%	29%	51%	47%	7%	4%	2%	1%	3%	2%
SMART-DATE (40)	62 ± 11	62 ± 12	75%	76%	50%	49%	27%	28%	24%	25%	38%	40%	-	-	-	-	4%	4%
REDUCE (41)	61 (53,69)	60 (52,68)	83%	77%	51%	51%	22%	20%	46%	45%	42%	43%	12%	10%	3%	3%	2%	2%
TICO (44)	61 ± 11	61 ± 11	79%	80%	50%	51%	27%	27%	61%	60%	36%	38%	9%	8%	1%	1%	4%	4%

CABG = Coronary artery bypass surgery; Co = control group; DM = Diabetes mellitus; HLD = Hyperlipidemia; HTN = Hypertension; PCI = Percutaneous coronary intervention; St = study (short DAPT group).

Age expressed in years.

Table 3
Clinical presentation of the study population in short-duration antiplatelet therapy trials

STUDY	Silent (St)	Silent (Co)	Stable Angina (St)	Stable angina (Co)	Unstable angina (St)	Unstable (Co)	NSTEMI (St)	NSTEMI (Co)	STEMI (St)	STEMI (Co)
EXCELLENT (15)			49%	48%	Reported as combined Unstable/ NSTEMI	Reported as combined Unstable/ NSTEMI	49%	48%	3%	4%
PRODIGY (16)	-	-	25%	26%	19%	19%	41%	42%	33%	33%
SECURITY (17)	-	-	62%	62%	38%	38%	Excluded	Excluded	Excluded	Excluded
ITALIC (18)	20%	20%	41%	42%	16%	16%	7%	7%	0%	0%
ISAR-SAFE (19)	11%	11%	49%	48%	21%	22%	10%	10%	8%	8%
IVUS-XPL (20)	-	-	51%	51%	34%	33%	15%	16%	Included in NSTEMI	Included in NSTEMI
NIPPON (21)	17%	16%	44%	49%	20%	18%	2%	2%	11%	12%
I-LOVE-IT 2 (22)	-	-	14%	15%	58%	57%	11%	11%	13%	14%
OPTIMA-C (23)	-	-	50%	49%	37%	37%	13%	14%	-	-
RESET (26)	-	-	45%	46%	41%	40%	15%	14%	Excluded	Excluded
OPTIMIZE (27)	9%	9%	60%	59%	26%	27%	55%	50%	Excluded	Excluded
LEADERSFREE (28)	-	-	59%	57%	15%	16%	22%	23%	5%	4%
ZEUS (29)	-	-	37%	37%	17%	16%	27%	28%	19%	19%
SENIOR (30)	20%	20%	34%	36%	10%	9%	26%	26%	11%	10%
ONYX ONE (32)	9%	11%	38%	39%	20%	19%	27%	27%	6%	5%
GLOBAL LEADERS (34)	-	-	53%	53%	13%	13%	21%	21%	13%	13%
SMART- CHOICE (36)	-	-	42%	42%	31%	33%	16%	15%	11%	10%
STOPDAPT-2 (37)	-	-	62%	61%	13%	14%	5%	7%	19%	48%
TWILIGHT (38)	7%	6%	30%	28%	35%	35%	29%	31%	0%	0%
DAPTSTEMI (39)	-	-	-	-	-	-	-	-	100%	100%
SMART-DATE (40)	Excluded	Excluded	Excluded	Excluded	31%	31%	31%	31%	38%	38%
REDUCE (41)	-	-	-	-	15%	14%	36%	41%	49%	45%
TICO (44)	-	-	-	-	29%	32%	35%	32%	36%	36%

Co = control group; NSTEMI = non-ST elevation myocardial infarction; St = study (short DAPT group); STEMI = ST elevation myocardial infarction.

Table 4
Procedural characteristics of the study population in short-duration antiplatelet therapy trials

STUDY	Left main (St)	Left main (Co)	LAD (St)	LAD (Co)	LCx (St)	LCx (Co)	RCA (St)	RCA (Co)	Bifurcation (St)	Bifurcation (Co)	CTO (St)	CTO (Co)	Vein grafts (St)	Vein grafts (Co)	MVD (St)	MVD (Co)	Total stent length in mm (St)	Total stent length in mm (Co)
EXCELLENT (15)	Excluded	Excluded	63%	62%	-	-	-	-	-	-	-	-	-	-	52%	40%	27.8 ± 13	28.3 ± 13.7
PRODIGY (16)	6%	6%	52%	52%	32%	33%	37%	35%	-	-			2%	2%	38%	37%	30 (20,48)	30 (20,48)
SECURITY (17)	-	-	43%	44%	14%	14%	22%	22%	14%	14%	-	-	Excluded	Excluded	44%	49%	19.1 ± 7.2	19 ± 7.2
ITALIC (18)	2%	1%	73%	72%	50%	48%	54%	52%	-	-	-	-	7%	4%	50%	46%	38.6 ± 25.6	37.8 ± 26.1
ISAR-SAFE (19)	1%	0.20%	40%	41%	26%	24%	32%	34%	19%	19%	8%	7%	2%	1%	38%	38%	28(18,43)	28 (18,43)
IVUS-XPL (20)	-	-	55%	56%	20%	18%	25%	26%	-	-	-	-	-	-	67%	70%	46.5 ± 19.7	48.2 ± 20.2
NIPPON (21)	0%	1%	52%	52%	20%	20%	27%	27%	-	-	-	-	-	-	18%	19%	20.3 ± 5	20.1 ± 5
I-LOVE-IT 2 (22)	2%	2%	46%	45%	22%	22%	29%	31%	30%	33%	12%	13%	-	-	-	-	41 ± 25	41 ± 25
OPTIMA-C (23)	-	-	58%	52%	20%	24%	23%	24%	-	-	-	-	-	-	34%	37%	21 ± 4.9	20.1 ± 4.8
RESET (26)	-	-	53%	54%	21%	19%	26%	27%	-	-	-	-	-	-	43%	43%	22.7 ± 10.1	22.9 ± 10.7
OPTIMIZE (27)	1%	2%	48%	47%	23%	24%	28%	28%	15%	15%	4%	4%	-	-	25%	26%	32.7 ± 20	32.7 ± 20
LEADERSFREE (28)	3%	4%	52%	52%	29%	29%	37%	35%	15%	16%	5%	4%	1%	2%	22%	21%	34.5 ± 23.1	33.4 ± 23.4
ZEUS (29)	5%	5%	53%	51%	33%	35%	42%	39%	-	-	-	-	1%	2%	28%	26%	26 (18,45)	30 (18,47)
SENIOR (30)	4%	1%	54%	52%	30%	27%	36%	38%	16%	14%	7%	7%	1%	1%	34%	31%	32.6 ± 20.8	30.3 ± 20.3
ONYX ONE (32)	1%	2%	55%	59%	26%	26%	35%	32%	15%	17%	3%	2%	2%	2%	18%	19%	37.9 ± 25.2	37.3 ± 25
GLOBAL LEADERS (34)	2%	2%	41%	42%	24%	25%	32%	31%	12%	12%	-	-	1%	1%	26%	25%	24.8 ± 13.9	24.8 ± 14
SMART- CHOICE (36)	1%	2%	49%	50%	22%	20%	28%	28%	13%	12%	-	-	-	-	23%	25%	38 ± 22.5	37.8 ± 22.9
STOPDAPT-2 (37)	3%	3%	55%	57%	18%	20%	29%	27%	25%	26%	4%	4%	0.20%	0.20%	7%	8%	30.3 ± 16.7	30.5 ± 16.8
TWILIGHT (38)	5%	5%	56%	56%	32%	32%	35%	35%	12%	12%	6%	6%	2%	2%	64%	62%	40 ± 24	39.7 ± 24.3
DAPTSTEMI (39)	Excluded	Excluded	39%	43%	21%	16%	41%	41%	-	-	-	-	-	-	13%	14%	28.5 ± 16	29.8 ± 16
SMART-DATE (40)	2%	1%	57%	61%	24%	25%	37%	36%	9%	9%	-	-	-	-	44%	47%	26.1 ± 10	26.3 ± 10.3
REDUCE (41)	-	-	48%	44%	20%	22%	31%	33%							36%	34%	23(18,28)	23 (18,28)
TICO (44)	3%	2%	48%	48%	19%	19%	30%	31%	14%	15%	-	-	-	-	55%	56%	35 ± 20	35 ± 21

Co = Control group; CTO = chronic total occlusion; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MVD = Multivessel disease; RCA = right coronary artery; St = Study group.

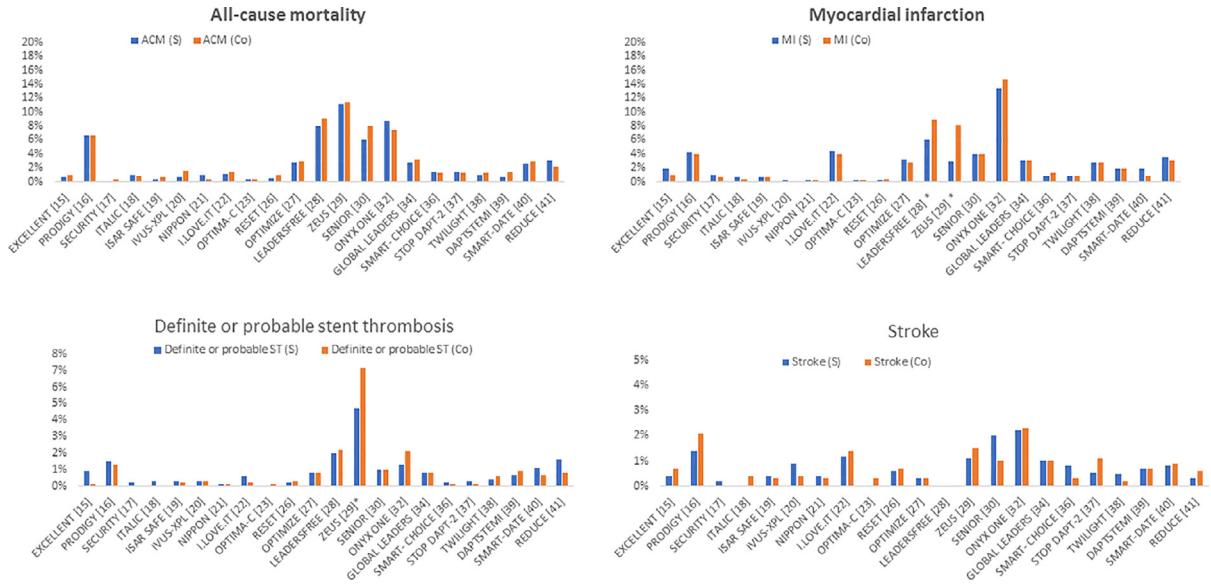

Figure 1. Ischemic events in all the major studies. *Outcome is statistically significant between the groups ($p < 0.05$). S = study (short DAPT); Co = control group; ACM = All-cause mortality; MI = Myocardial infarction; ST = Stent thrombosis.

mortality, MI, and stroke) and did not differ between 6-month versus 24-month DAPT groups (10% vs 10.1%, $p = 0.91$). Also, a meta-analysis with adequate power showed no significant differences in ischemic events with short-duration DAPT.[17]

5. Patients with left main disease, chronic total occlusions, vein graft disease, and cardiogenic shock were underrepresented in these studies.
6. Event rates were low in all the studies, which reflect improved outcomes with PCI and new-generation DES (Figure 1). This could also be due to early termination of a few studies and incomplete follow-up.
7. All the studies showed either numerically lower bleeding rates or significantly lower bleeding rates (PRODIGY and ISAR-SAFE) with 6-month DAPT (Figure 1).

Based on the available evidence, in SIHD, major societies' guidelines[18,19] recommend a 6-month DAPT after PCI, followed by aspirin monotherapy.

Three-month DAPT followed by aspirin monotherapy

Very-short-duration DAPT (3 months) followed by aspirin monotherapy was also tested in 2 trials that predominantly

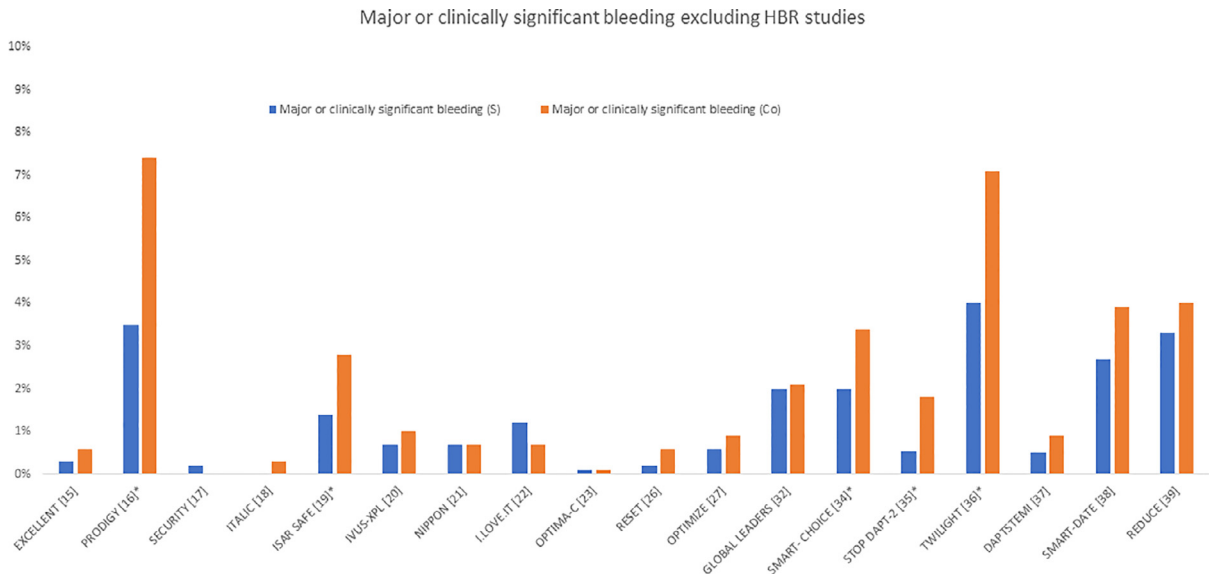

Figure 2. Major or clinically significant bleeding in all the studies excluding high-bleeding-risk studies. *Outcome is statistically significant between the groups ($p < 0.05$). S = study (short DAPT); Co = control group; HBR = high bleeding risk.

enrolled SIHD patients. The RESET[20] and OPTIMIZE[21] trials enrolled low- and intermediate-ischemic-risk patients (excluding ST-elevation myocardial infarction [STEMI]) and showed noninferior results in terms of ischemic end points. Major or clinically significant bleeding rates were numerically lower in the shorter-DAPT group.

One-month DAPT followed by aspirin monotherapy in high-bleeding-risk patients

Short-duration antiplatelet therapy is an attractive option for the high-bleeding-risk population. Traditionally, to shorten antiplatelet therapy, PCI is usually performed with a bare metal stent (BMS). The LEADERS FREE[22] and ZEUS[23] studies showed that both the polymer-free BioFreedom umirolimus-coated stent and Endeavor Sprint zotarolimus-eluting stent were superior to a BMS in significantly reducing major adverse cardiovascular (CV) events, primarily driven by lower MI and target vessel revascularization rates. In the SENIOR study,[24] elderly patients at high risk of bleeding had a lower event rate with a bioabsorbable-polymer Synergy everolimus-eluting stent than with a BMS. Improvements in new-generation DES have led to a better safety and efficacy profile. Furthermore, DES is more cost-effective in the long term than BMS.[25]The recently published ONYX ONE study[26] confirmed that in the high-bleeding-risk population, a 1-month DAPT can be safely practiced without increasing ischemic events. However, in the majority of 1-month DAPT studies, ischemic events were numerically higher than in other longer-duration antiplatelet therapy studies (Figure 1) indicating that these patients are still at high ischemic risk. Currently, guidelines[18,19] recommend a 1- or 3-month DAPT followed by aspirin monotherapy in patients with SIHD and high bleeding risk.

Three-month or 1-month DAPT followed by P2Y12 inhibitor monotherapy

Although aspirin was considered the default for antiplatelet therapy, its role in secondary prevention has been questioned.[27] Thus, the strategy of continuing only P2Y12i after stopping aspirin has been considered. With this strategy, it was presumed that bleeding complications, especially gastrointestinal toxicity related to aspirin, would be decreased without increasing the incidence of ischemic events.[27]

This strategy was first tested in GLOBAL LEADERS, the largest antiplatelet therapy study to date.[28] In GLOBAL LEADERS, patients received 1 month of DAPT followed by ticagrelor monotherapy for 23 months, which was compared with a traditional 12-month DAPT followed by aspirin monotherapy. At 2 years, the ticagrelor monotherapy arm (n = 7,980) was not superior to DAPT (n = 7,988) for the primary end point, all-cause mortality or new Q-wave MI (Table 1). Bleeding rates also did not differ between the groups at 1 year. One of the major limitations of the study was adjudication. In a recently published GLOBAL LEADERS substudy, GLASSY,[29] at 1 year, there was no increased ischemic risk.

Two other trials, SMART-CHOICE[30] and STOPDAPT-2[31] have also shown similar results. In SMART-CHOICE,[30] 2,993 patients were randomized to receive either aspirin plus a P2Y12i for 3 months and then P2Y12i alone (n = 1,495) or DAPT for 12 months (n = 1,498). Unlike GLOBAL LEADERS, any P2Y12i (clopidogrel 77%, prasugrel or ticagrelor 23%) was used. At 1 year, the primary end point of major adverse cardiac and cerebrovascular events, which was a composite of all-cause death, MI, or stroke at 12 months after the index procedure, achieved noninferiority in the study arm. The incidence of major or clinically significant bleeding was lower in the P2Y12i monotherapy group than in the DAPT group (2% vs 3.4%, hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.36 to 0.92, p = 0.02). In the STOPDAPT-2 study,[31] 3,045 patients were randomized to either 1-month DAPT followed by clopidogrel monotherapy (n = 1,523) or 12-month DAPT (n = 1,522). At 1 year, clopidogrel monotherapy was both noninferior and superior for its primary end point, which was a composite of CV death, MI, ischemic or hemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months (2.36% vs 3.7%, p < 0.001 for noninferiority and p = 0.04 for superiority). Another important feature of this study was the high use of intravascular ultrasound or optical coherence tomography to guide PCI (99%).

Major criticisms of the previously mentioned trials are that they enrolled low-ischemic-risk and low-bleeding-risk populations and the timing of randomization. The more recently published TWILIGHT[32] study enrolled baseline high-ischemic-risk and high-bleeding-risk patients and performed randomization in event-free patients at 3 months instead of at the time of the index procedure. All study patients received DAPT for 3 months and then received either ticagrelor monotherapy or conventional DAPT. Patients also needed to have 1 high-risk clinical or angiographic feature to be enrolled in the study. A total of 9,006 patients were enrolled, and only 7,119 were randomized after 3 months; 3,555 received ticagrelor monotherapy and 3,564 received DAPT. At 1 year, the primary end point, which was Bleeding Academic Research Consortium 2, 3, or 5 bleeding, was significantly lower in the ticagrelor monotherapy group (4% vs 7.1%, HR 0.56, 95% CI 0.45 to 0.68, p < 0.001). Secondary ischemic end points did not differ between both groups.

In conclusion, important features of these studies are:

1. Most enrolled low-risk patients, with higher percentages of SIHD, except for TWILIGHT.
2. Randomization was done at the time of the index procedure or within 3 months in all the studies except for TWILIGHT.
3. Ischemic end points did not differ between the 2 groups in all the studies. Studies involving imaging-guided PCI showed better ischemic outcomes.
4. Major or clinically significant bleeding rates were significantly lower with P2Y12i monotherapy than with traditional DAPT in all the studies, except for GLOBAL LEADERS, where the bleeding rates did not differ between both strategies.

5. Similar to aspirin monotherapy studies, patients with left main disease, chronic total occlusions, cardiogenic shock, and STEMI were under-represented. However, there were higher percentages of complex lesions (numerically higher total stent length, clinical presentation as NSTEMI/unstable angina, multivessel disease) in P2Y12i monotherapy studies.

Studies exclusively evaluating acute coronary syndromes

In acute coronary syndromes (ACS), current guidelines [18,19] recommend a 12-month DAPT. This recommendation was based primarily on 2 landmark trials that were performed 2 decades ago.[1,2]

Short-duration DAPT (3 or 6 months) followed by aspirin monotherapy in ACS

Patients who present with ACS are not only at high risk for future ischemic events but also for bleeding events.[33] Studies were undertaken to evaluate the utility of short-duration DAPT followed by aspirin monotherapy to reduce the bleeding risk in ACS patients. Notable studies are DAPT STEMI,[34] SMART-DATE,[35] and the REDUCE trial.[36]

In the SMART-DATE study,[35] 2,712 patients were randomly assigned to either 6-month duration DAPT (n = 1,357) or 12-month or longer duration DAPT (n = 1,355). Clopidogrel (80%) was the major P2Y12i. In the 6-month DAPT arm, 37.5% were STEMI patients, 31.5% were NSTEMI patients, and 31% had unstable angina. At 18 months, the primary end point, which was a composite of all-cause mortality, MI, or stroke, showed noninferior results in the short-duration DAPT group. However, in SMART-DATE, a significantly higher MI incidence was noted with short-duration DAPT (1.8% vs 0.8%, p = 0.02). Finally, the rate of Bleeding Academic Research Consortium 3-5 bleeding was lower with short DAPT.

In the DAPT-STEMI study,[34] 1,100 patients who were event-free at 6 months were randomized to a 6-month (n = 432) or 12-month (n = 438) DAPT. At 18 months, the primary end point, which is a composite of all-cause mortality, any MI, any revascularization, stroke, or major bleeding, was noninferior with short DAPT. MI incidence also did not differ between the groups. These results are discordant with the SMART-DATE trial, perhaps because of randomization only in event-free patients at 6 months. This difference in randomization in the DAPT-STEMI study represents a low-ischemic-risk subgroup in comparison with the SMART-DATE study population.

Recently, the REDUCE trial[36] evaluated a very-short-duration DAPT strategy in ACS patients. In this trial, 1,496 ACS patients were randomized to very short DAPT, 3 months duration, followed by aspirin (n = 751) or 12-month DAPT (n = 745). At 1-year follow-up, very-short-duration DAPT was noninferior, although with a wide CI, in comparison with 12-month DAPT for the primary end point. However, numerically higher rates of mortality and stent thrombosis were noted in very-short-duration DAPT. A meta-analysis done by Misumida et al.[37] did not show any differences in ischemic end points in the ACS population. However, these results should be interpreted with caution, as the population groups in these studies were different because of varied risk profiles, different composite end points, and different points of randomization, and the studies had wide noninferiority CIs. Future trials are needed before we can safely remove P2Y12i after a short-duration DAPT in PCI after ACS.

Short-duration DAPT (1 or 3 months) and then P2Y12 inhibitor monotherapy in ACS

In the recently published TICO trial,[38] 3056 patients with acute coronary syndrome were randomized to either ticagrelor monotherapy after 3 months (n = 1,527) or DAPT for 12 months (n = 1,529). At 12 months, the incidence of major CV or cerebrovascular events was not significantly different between the groups; however, the bleeding rate was significantly lower in the ticagrelor monotherapy group (1.7% vs 3%, p = 0.02). Arecently presented subgroup analysis of the TWILIGHT study (TWILIGHT-ACS-https://www.tctmd.com/news/aspirin-discontinuation-safe-effective-strategy-acs-subset-twilight), in 4,614 event-free patients at 3 months showed an absolute risk reduction of 4% in bleeding rates with ticagrelor monotherapy (3.6% vs 7.6%; HR 0.47; 95% CI: 0.36 to 0.61). Ischemic end points (all-cause mortality, MI, and stent thrombosis) did not differ between the 2 strategies. Subgroup analyses of GLOBAL LEADERS, SMART-CHOICE, and STOP-DAPT-2 showed similar benefits in reducing bleeding end points with no difference in ischemic end points in ACS patients. An approach of P2Y12i monotherapy after an initial short-duration DAPT appears to be appropriate in this subgroup of ACS patients with high ischemic and bleeding risk. A future study, STOPDAPT-2 ACS (NCT03462498) will provide more information in this high-ischemic-risk subgroup.

Individualizing DAPT on the basis of risk profiles

There is a growing body of evidence to individualize DAPT on the basis of the patient's ischemic and bleeding risk profile. European Society of Cardiology guidelines[19] give a Class II recommendation to use risk scores to evaluate the benefit of prolonged versus short DAPT. To assess ischemic risk, the DAPT score[39] is used, and for bleeding risk, the PRECISE-DAPT[40] and PARIS [41] risk scores are used. The DAPT score, which was primarily derived from the DAPT trial[39] and later validated in the PROTECT study,[42] identified patients who would benefit from long-term DAPT of more than 12 months. There have been no risk scores evaluated so far to identify the subset of patients with SIHD who would benefit from traditional DAPT within 12 months of PCI. In a DAPT substudy,[43] anatomic complexity of lesions (unprotected left main, >2 lesions per vessel, lesion length >30 mm, bifurcation lesion with a side branch ≥2.5 mm, vein grafts, or thrombus containing lesion) was identified as a predictor of ischemic events within 12 months of PCI. In the LEADERS FREE[22] and ZEUS[23] studies, patients needed to have at least 1

qualifying criterion (age >75 to 80 years, treatment with oral anticoagulation, a recent bleeding episode, coagulopathy, etc.) to be defined as high bleeding risk. The PRECISE-DAPT score, derived from PRECISE-DAPT,[40] is a simple 5-item risk measure, with a score ≥25 indicating a patient with high bleeding risk; it was later validated.[44,45] Although none of these risk scores has been prospectively validated in a clinical trial setting, a recent pooled analysis of 8 randomized trials by Costa et al.[46] showed that in patients with who underwent complex PCI with high-risk ischemic features and a PRECISE DAPT score ≥25, there was no benefit of long-term DAPT (12 or 24 months). Patients with a PRECISE DAPT score ≤25 benefited from long-term DAPT, particularly in the complex PCI group.

DAPT treatment algorithm after PCI

With all the available literature, it can be a daunting prospect for physicians to select the antiplatelet therapy to remove or choose, as well as the optimal duration of DAPT or SAPT. Although a meta-analysis or a network meta-analysis can provide adequate statistical power to evaluate ischemic outcomes, it would be difficult to perform given different inclusion baseline criteria and timelines in the studies, leaving us with a heterogeneous population. Based on the available evidence, we propose a new treatment algorithm for DAPT after PCI for SIHD and ACS patients (Figure 3). The treatment strategy chosen should be based on the ischemic- and bleeding-risk profiles. We grouped NSTEMI and STEMI under acute coronary syndrome; adjusting antiplatelet therapy for these patients should be done on the basis of their risk profiles. Also, if P2Y12i monotherapy is chosen, ticagrelor must be preferred in the NSTEMI and STEMI populations, and clopidogrel or ticagrelor should be preferred for SIHD. Data on prasugrel monotherapy are limited, and this therapy was tested only in small subgroups in a few studies (GLOBAL LEADERS, SMART-DATE). Although there are few trials exclusively on the STEMI population at this point, we still recommend 12 months of DAPT in STEMI patients if the patients are not at high bleeding risk. This patient population is at higher risk of adverse events not only at culprit sites but also at nonculprit sites,[47] and prolonged DAPT may reduce the risk of future events. A strategy of P2Y12i monotherapy after a short-duration DAPT (3 months) in high-bleeding-risk patients can be considered. Also, caution should be employed in generalizing these results to venous bypass graft lesions, chronic total occlusions, and left main interventions, and in patients with stroke and cardiogenic shock. Finally, across all the trials, bleeding event rates are higher than those of ischemic events. If there is any concern regarding bleeding risk, short-duration DAPT is preferred and P2Y12i should be stopped.

Conclusion

Improvements in stent design, antiplatelet therapy, and procedural aspects have reduced ischemic complications after PCI. However, bleeding complication rates continue to remain high, mainly because of the duration and type of antiplatelet therapy. Although removing P2Y12i after a short DAPT appears to be safe in the low-risk population, removing aspirin and continuing P2Y12i as a monotherapy would be the preferred strategy in intermediate- to high-risk patients to mitigate the bleeding risk. Further studies are needed in very-high-risk NSTEMI and STEMI patients.

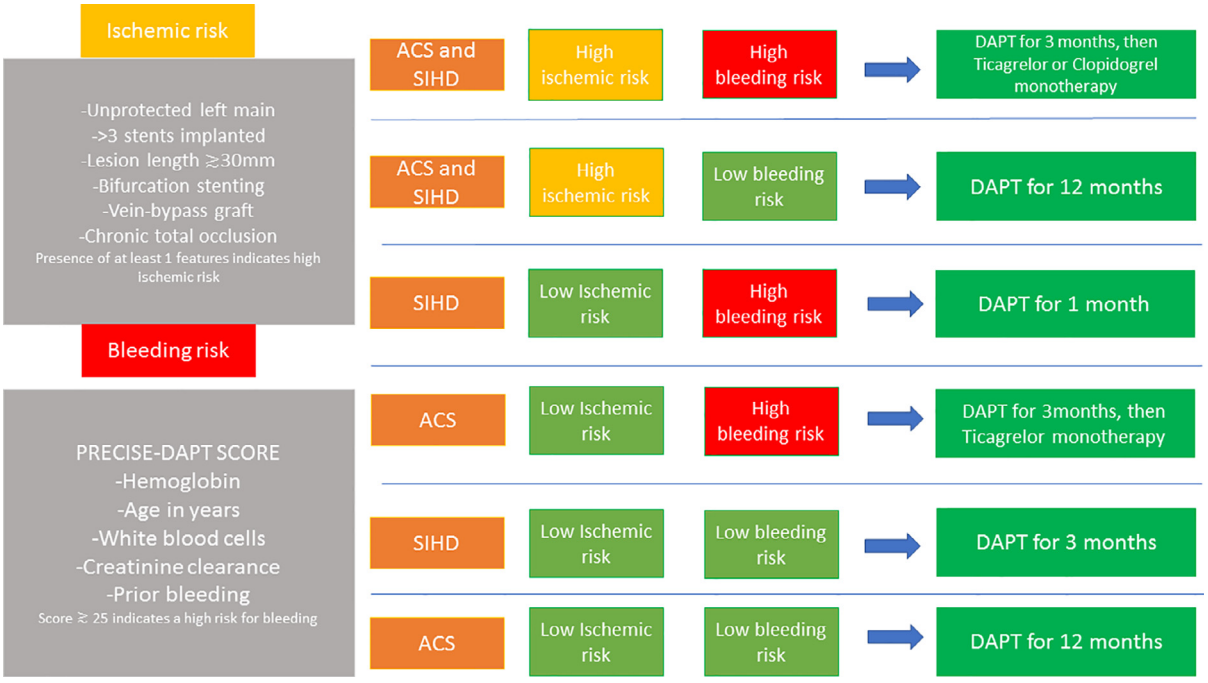

Figure 3. Proposed treatment algorithm of antiplatelet therapy after PC. ACS = Acute coronary syndrome; DAPT = Dual antiplatelet therapy; P2Y12i = P2Y12 inhibitors; SIHD = Stable ischemic heart disease. Based on a pooled analysis of 8 randomized trials by Costa et al and the DAPT substudy by Yeh et al.

Close follow-up and adjusting antiplatelet therapy on the basis of risk stratification tools after PCI should be the preferred strategy.

Declarations of Interest

Ron Waksman – Advisory Board: Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Consultant: Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

William S. Weintraub – Consultant and grants: Amarin. Advisory board: AstraZeneca, Consultant: scPharmaceuticals

All other authors – None.

Disclosures

The authors have no conflicts of interest to disclose.

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
2. Steinhubl SR, Berger PB, Mann JT, 3rd Fry ET, DeLago A, Wilmer C, Topol EJ, for the CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411–2420.
3. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519–1521.
4. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L, for the SCAAR Study Group. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;356:1009–1019.
5. Kolh P, Wijns W, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg* 2010;38(Suppl):S1–s52.
6. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2013;82:E266–E355.
7. Alazzoni A, Al-Saleh A, Jolly SS. Everolimus-eluting versus paclitaxel-eluting stents in percutaneous coronary intervention: meta-analysis of randomized trials. *Thrombosis* 2012;2012:126369.
8. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;125:505–513.
9. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fuca G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;125:2015–2026.
10. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, Oteo Dominguez JF, Steffanon L, Tarantini G, Presbitero P, Menozzi A, Pucci E, Mauri J, Cesana BM, Giustino G, Sardella G. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 2014;64:2086–2097.
11. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschat J, Morice MC. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol* 2015;65:777–786.
12. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tolg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wohrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PW, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz KL, Schomig A, Mehilli J, Kastrati A, on behalf of the Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) trial investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 2015;36:1252–1263.
13. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Her AY, Kim YH, Jang Y, Hong MK, IVUS-XPL Investigators. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JACC Cardiovasc Interv* 2016;9:1438–1446.
14. Nakamura M, Iijima R, Ako J, Shinke T, Okada H, Ito Y, Ando K, Anzai H, Tanaka H, Ueda Y, Takiuchi S, Nishida Y, Ohira H, Kawaguchi K, Kadotani M, Niinuma H, Omiya K, Morita T, Zen K, Yasaka Y, Inoue K, Ishiwata S, Ochiai M, Hamasaki T, Yokoi H, NIPPON Investigators. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. *JACC Cardiovasc Interv* 2017;10:1189–1198.
15. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, Li X, Zhao X, Wang H, Zhao X, Li X, Yu P, Zang H, Wang Z, Cao X, Zhang J, Pang W, Li J, Yang Y, Dangas GD. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv* 2016;9:e003145.
16. Lee BK, Kim JS, Lee OH, Min PK, Yoon YW, Hong BK, Shin DH, Kang TS, Kim BO, Cho DK, Jeon DW, Woo SI, Choi S, Kim YH, Kang WC, Kim S, Kim BK, Hong MK, Jang Y, Kwon HM. Safety of six-month dual antiplatelet therapy after second-generation drug-eluting stent implantation: OPTIMA-C randomised clinical trial and OCT substudy. *EuroIntervention* 2018;13:1923–1930.
17. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2015;65:1298–1310.
18. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr., Halperin JL, Levine GN, Al-Khatib SM, Birtcher KK, Bozkurt B, Brindis RG, Cigarroa JE, Curtis LH, Fleisher LA, Gentile F, Gidding S, Hlatky MA, Ikonomidis JS, Joglar JA, Pressler SJ, Wijeysundera DN. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg* 2016;152:1243–1275.
19. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. ESC Scientific Document Group. ESC Committee for Practice

Guidelines (CPG). ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213–260.
20. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;60:1340–1348.
21. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB 3rd, Negoita M, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ Jr., Nicolela EL Jr., Perin MA, Devito FS, Labrunie A, Salvadori D Jr., Gusmao M, Staico R, Costa JR Jr., de Castro JP, Abizaid AS, Bhatt DL, for the OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013;310:2510–2522.
22. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C, Lipiecki J, Richardt G, Iniguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC, for the LEADERS FREE Investigators. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;373:2038–2047.
23. Valgimigli M, Patialiakas A, Thury A, McFadden E, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Airoldi F, Ferlini M, Liistro F, Dellavalle A, Vranckx P, Briguori C, ZEUS Investigators. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol* 2015;65:805–815.
24. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrie D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice MC, Sinnaeve PR, for the SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet* 2018;391:41–50.
25. Cheng HM, Chiou LJ, Chen TC, Sung SH, Chen CH, Lang HC. Real-world cost-effectiveness of drug-eluting stents vs. bare-metal stents for coronary heart disease-A five-year follow-up study. *Health Policy* 2019;123:229–234.
26. Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, Zaman A, Hudec M, Poliacikova P, Abdul Ghapar AKB, Selvaraj K, Petrov I, Mylotte D, Pinar E, Moreno R, Fabbiocchi F, Pasupati S, Kim HS, Aminian A, Tie C, Wlodarczak A, Hur SH, Marx SO, Jankovic I, Brar S, Bousquette L, Liu M, Stone GW, for the ONYX ONE Investigators. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med* 2020;382:1208–1218.
27. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, Dangas G, Rollini F, Kimura T, Collet JP, Gibson CM, Steg PG, Lopes RD, Gwon HC, Storey RF, Franchi F, Bhatt DL, Serruys PW, Angiolillo DJ. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;15:480–496.
28. Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Mollmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;392:940–949.
29. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopczuk J, Hamm C, Steg PG, Heg D, Juni P, Windecker S, Valgimigli M. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol* 2019;74:2223–2234.
30. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, Yun KH, Cho DK, Lee JY, Koh YY, Bae JW, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha SW, Lee JM, Park TK, Yang JH, Choi JH, Choi SH, Lee SH, Gwon HC, for the SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 2019;321:2428–2437.
31. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T, STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA* 2019;321:2414–2427.
32. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Dzavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019;381:2032–2042.
33. Palmerini T, Bacchi Reggiani L, Della Riva D, Romanello M, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Ahn JM, Park SJ, Schupke S, Kastrati A, Montalescot G, Steg PG, Diallo A, Vicaut E, Helft G, Biondi-Zoccai G, Xu B, Han Y, Genereux P, Bhatt DL, Stone GW. Bleeding-related deaths in relation to the duration of dual-antiplatelet Therapy after coronary stenting. *J Am Coll Cardiol* 2017;69:2011–2022.
34. Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, Zurakowski A, Schotborgh CE, Hoorntje JCA, Eek CH, Cook S, Togni M, Meuwissen M, van Royen N, van Vliet R, Wedel H, Delewi R, Zijlstra F. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ* 2018;363:k3793.
35. Hahn JY, Song YB, Oh JH, Cho DK, Lee JB, Doh JH, Kim SH, Jeong JO, Bae JH, Kim BO, Cho JH, Suh IW, Kim DI, Park HK, Park JS, Choi WG, Lee WS, Kim J, Choi KH, Park TK, Lee JM, Yang JH, Choi JH, Choi SH, Gwon HC, SMART-DATE investigators. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet* 2018;391:1274–1284.
36. De Luca G, Damen SA, Camaro C, Benit E, Verdoia M, Rasoul S, Liew HB, Polad J, Ahmad WA, Zambahari R, Postma S, Kedhi E, Suryapranata H, Collaborators. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention* 2019;15:e990–e998.
37. Misumida N, Abo-Aly M, Kim SM, Ogunbayo GO, Abdel-Latif A, Ziada KM. Efficacy and safety of short-term dual antiplatelet therapy (</=6 months) after percutaneous coronary intervention for acute coronary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Cardiol* 2018;41:1455–1462.
38. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, Yoo SY, Cho DK, Hong BK, Kwon H, Ahn CM, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y, for the TICO Investigators. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA* 2020;323:2407–2416.
39. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr., Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM, for the DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155–2166.

40. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M, PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025–1034.
41. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol* 2016;67:2224–2234.
42. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L, for the DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315:1735–1749.
43. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, Mauri L, DAPT Study Investigators. Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol* 2017;70:2213–2223.
44. Koskinas KC, Raber L, Zanchin T, Wenaweser P, Stortecky S, Moschovitis A, Khattab AA, Pilgrim T, Blochlinger S, Moro C, Juni P, Meier B, Heg D, Windecker S. Clinical impact of gastrointestinal bleeding in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv* 2015;8.
45. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–1057.
46. Costa F, Van Klaveren D, Feres F, James S, Raber L, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol* 2019;73:741–754.
47. Kubo T, Imanishi T, Kashiwagi M, Ikejima H, Tsujioka H, Kuroi A, Ishibashi K, Komukai K, Tanimoto T, Ino Y, Kitabata H, Takarada S, Tanaka A, Mizukoshi M, Akasaka T. Multiple coronary lesion instability in patients with acute myocardial infarction as determined by optical coherence tomography. *Am J Cardiol* 2010;105:318–322.