Optimal duration and combination of antiplatelet therapies following percutaneous coronary intervention: a meta-analysis

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ABSTRACT

Introduction: The ideal duration of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) is still unknown. In this meta-analysis, we aimed to compare very short-term (1–3 months), short-term (6 months), standard-term (12 months) and long-term (>12 months) DAPT durations for efficacy and safety.
Methods: Overall DAPT comparisons were classified as "any shorter-term"/"any longer-term" DAPT. The primary outcome was a composite of major adverse cardiovascular events (MACE: non-fatal myocardial infarction, non-fatal stroke and cardiovascular death). The primary safety outcome was major bleeding.
Results: Twenty-six studies comprising 103.394 patients were included. Compared with standard-term DAPT duration, very short-term DAPT duration with subsequent drop of aspirin (RR 1.06, 95% CI, 0.95–1.18, p = 0.26) or drop of the P2Y$_{12}$ inhibitor (RR 0.92, 95% CI, 0.72-1.16, p = 0.47) was not associated with a higher risk of MACE. Any longer-term compared with any shorter-term DAPT durations led to a significantly lower risk of MACE (RR 0.88, 95% CI, 0.81–0.96, p = 0.002), but a significantly higher risk of BARC 3-5 major bleeding events (RR 1.63, 95% CI, 1.22–2.17, p = 0.001). In the ACS subgroup receiving prasugrel or ticagrelor but not clopidogrel, any longer-term DAPT duration was associated with a significantly lower risk of MACE compared to any shorter-term DAPT duration (RR 0.84, 95% CI, 0.77–0.92, p = 0.0001).
Conclusion: DAPT may be shortened to 1-3 months in patients with low ischemic but high bleeding risk followed by aspirin or P2Y$_{12}$ monotherapy. Prasugrel or ticagrelor based DAPT may be extended to >12 months in case of high ischemic and low bleeding risk.
PROSPERO registration no: CRD42020163719.

1. Introduction

Dual antiplatelet therapy (DAPT), defined as a combination of aspirin plus a P2Y$_{12}$ inhibitor, has become a cornerstone treatment in patients with acute coronary syndrome (ACS) or undergoing planned percutaneous coronary intervention (PCI) [1,2]. For patients with stable coronary artery disease (CAD) and no high bleeding risk undergoing PCI, current guidelines, from both the European Society of Cardiology (ESC)

and the American College of Cardiology (ACC)/American Heart Association (AHA), recommend DAPT with clopidogrel for the duration of 6 months [1,2]. For ACS patients that are being treated with primary PCI, both guidelines suggest DAPT for a period of 12 months, with a class IIb recommendation to continue DAPT for an extended period over 1 year.

Importantly, the balance between ischemic and bleeding risks determines the overall benefit of antithrombotic treatments. Accordingly, it is well recognized that prolonged DAPT increases the bleeding risk

[3]. Bleeding, especially spontaneous major bleeding in the first month after an ACS in patients on DAPT, is associated with increased mortality [4]. Therefore, optimal DAPT duration remains a subject of debate. Several meta-analyses performed to clarify this issue have reported contradictory findings, but also did not focus on the type of $P2Y_{12}$ antagonists administered [5]. Currently, a novel treatment strategy for DAPT after PCI involving $P2Y_{12}$ monotherapy has emerged, the role of which remains to be elucidated. In the light of these findings, we aimed at a better understanding of benefits and risks of different DAPT durations also stratified according to the type of $P2Y_{12}$ antagonists used in comparative trials for DAPT duration.

2. Methods

2.1. Data sources, trial eligibility and data extraction

Our review was registered with PROSPERO under the registration number CRD42020163719. This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and performed according to established methods [6]. A systematic search of online databases was performed until December 2019 for RCTs (Supplementary Fig. S1). Randomized controlled trials that (1) compared any different DAPT durations and (2) reported on at least one of the outcomes of interest were included. Details of data extraction are provided in the online appendix.

2.2. Outcomes

The primary efficacy outcome was MACE (the composite of myocardial infarction, stroke and cardiovascular death). The secondary efficacy outcomes included myocardial infarction, stroke, all-cause death, cardiovascular death and stent thrombosis (definite and probable). Major bleeding was defined as the primary safety outcome. All outcomes were analyzed by an intention-to-treat analysis. The online appendix provides more details regarding study outcomes and definitions.

2.3. Data synthesis and statistical analysis

Variables were reported as number or percentages, as appropriate. Risk ratios (RR) were computed from individual studies and pooled according to the inverse variance random effect method with 95% confidence intervals (CI) using Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Unadjusted p values were reported throughout, with hypothesis testing set at the two-tailed significance level of 0.05. We assessed studies for clinical and statistical heterogeneity. To assess statistical heterogeneity, we calculated the I^2 index and a p value. Percentages lower than 25% ($I^2 = 25$), 50% ($I^2 = 50$), and 75% ($I^2 = 75$) correlate to low, medium, and high heterogeneities, respectively [7]. Due to the high clinical heterogeneity, we used the random-effect model.

Different durations of DAPT were categorized into very short-term (1-3 months), short-term (6 months), standard-term (12 months) and long-term (> 12 months) to account for better structure and comparability.

Due to the large heterogeneity of compared DAPT durations in the studies included, DAPT comparisons in the overall analysis (including all trials) were termed "any longer-term" DAPT and "any shorter-term" DAPT.

2.4. Secondary analyses

We performed sensitivity analyses and multiple subgroup analyses for the primary outcome and the primary safety outcome. Subgroup analyses included ACS patients, the type of $P2Y_{12}$ receptor inhibitor and the drop strategy (aspirin vs $P2Y_{12}$ inhibitor). (Online appendix).

3. Results

3.1. Description of studies

Our search yielded 5.556 references. Twenty-six studies [8–33], including a total of 103.394 patients, met our inclusion criteria and were eligible for our meta-analysis (Supplementary Fig. S1).

All except for one study exclusively included patients who had undergone placement of a drug-eluting stent (DES). Thirteen studies only included patients receiving DAPT with clopidogrel, ten studies included patients with both clopidogrel and new-generation $P2Y_{12}$ inhibitors and three studies only included patients receiving ticagrelor. Five trials studied a novel concept of $P2Y_{12}$ inhibitor monotherapy instead of aspirin. Detailed information on the studies included can be found in Supplementary Tables 1 and 2.

3.2. Overall analysis

3.2.1. Primary outcome: MACE

3.2.1.1. Early aspirin drop followed by $P2Y_{12}$ inhibitor monotherapy. Very short-term DAPT with aspirin drop in the investigational arm was associated with a similar risk of MACE when compared with standard-term DAPT as reported in four trials (RR 1.06, 95% CI, 0.95–1.18, p = 0.26, $I^2 = 0\%$, Fig. 1).

3.2.1.2. Early $P2Y_{12}$ inhibitor drop followed by aspirin monotherapy. Any longer-term DAPT duration significantly reduced the RR of MACE by 12% (RR 0.88, 95% CI, 0.81–0.96, p = 0.002, $I^2 = 12\%$, Fig. 1) when compared with any shorter-term DAPT duration in studies where the $P2Y_{12}$ inhibitor was dropped at any time point in the control arm in the overall analysis including 21 studies.

3.2.1.3. MACE according to diverse treatment durations. There was no statistical difference between the groups when analyzed for specific treatment durations. Very short-term DAPT and subsequent drop of the $P2Y_{12}$ inhibitor was not associated with a higher risk of MACE (RR 0.92, 95% CI, 0.72-1.16, $I^2 = 0\%$, p = 0.47) when compared with standard-term DAPT (Supplementary Fig. S2).

3.2.1.4. MACE according to $P2Y_{12}$ inhibitor type. In prasugrel- or ticagrelor-treated patients, long-term DAPT duration was associated with a 24% RRR of MACE (RR 0.76, 95% CI, 0.63–0.93, p = 0.007, $I^2 = 76\%$, Fig. 2A) compared with standard-term DAPT duration. For prasugrel, the RRR was 48% (95% CI, 0.38–0.71), for ticagrelor 16% (95% CI, 0.77–0.92).

In clopidogrel-treated patients, the risk of MACE was similar for standard-term vs. long-term DAPT durations (RR 0.91, 95% CI, 0.71–1.17, p = 0.47, $I^2 = 53\%$, Fig. 2A).

3.2.1.5. MACE in the setting of ACS

3.2.1.5.1. Treatment with prasugrel or ticagrelor. In ACS patients under DAPT with prasugrel or ticagrelor, longer-term DAPT duration was associated with a significant RRR of MACE of 16% (RR 0.84, 95% CI, 0.77–0.92, p = 0.0001, $I^2 = 0\%$, Fig. 2B) compared with shorter-term DAPT duration.

3.2.1.5.2. Treatment with clopidogrel. There was no statistically significant difference between different DAPT durations in clopidogrel-treated ACS patients with regard to MACE (RR 1.04, 95% CI, 0.89–1.20, p = 0.64, $I^2 = 0\%$, Fig. 2B).

3.2.1.6. MACE in the setting without ACS. In patients presenting without ACS, any longer-term DAPT duration did not reduce the risk of MACE (RR 0.90, 95% CI, 0.72–1.12, p = 0.34, $I^2 = 16\%$, Supplementary Fig. S3) as compared with any shorter-term DAPT duration.
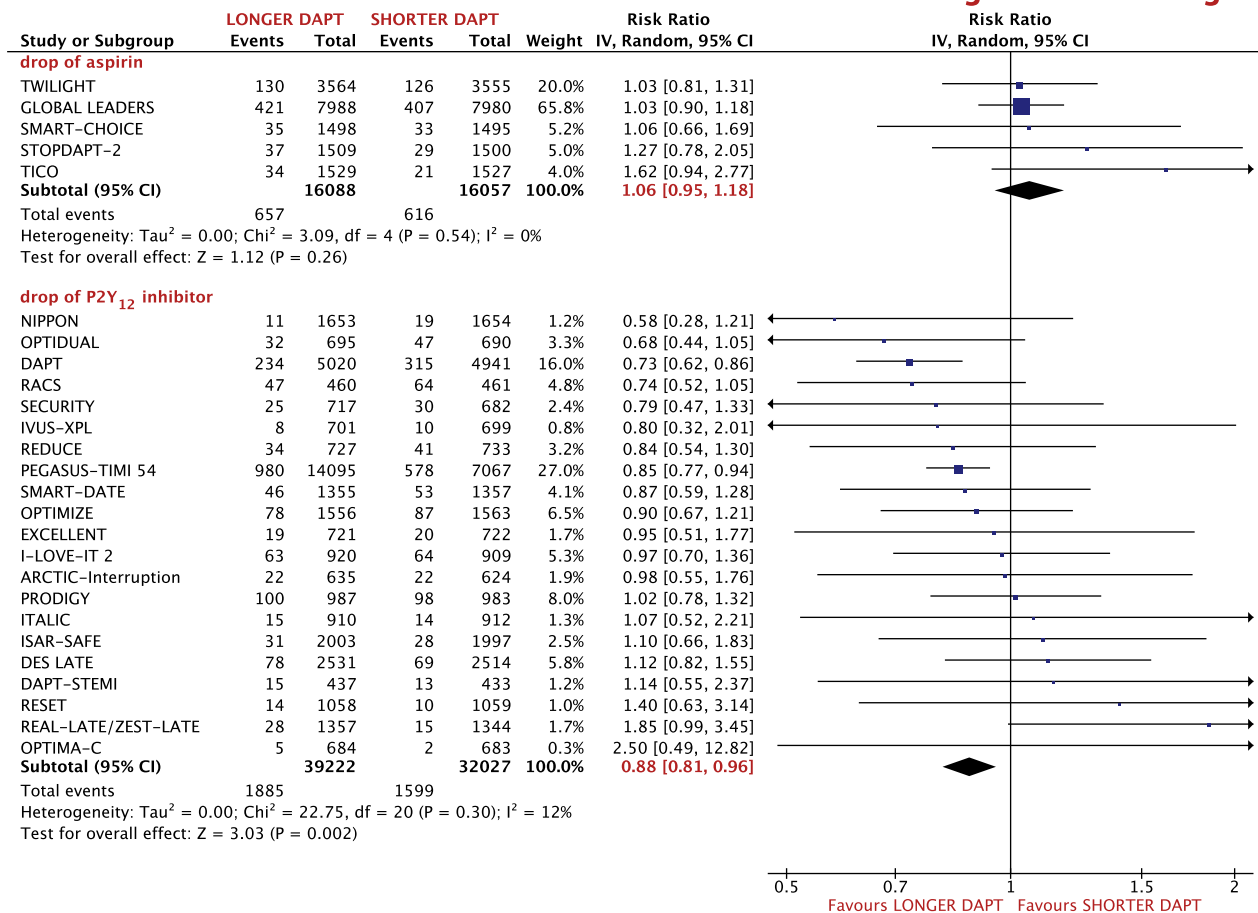
MACE according to treatment regimen

Study or Subgroup	LONGER DAPT Events	Total	SHORTER DAPT Events	Total	Weight	Risk Ratio IV, Random, 95% CI
drop of aspirin						
TWILIGHT	130	3564	126	3555	20.0%	1.03 [0.81, 1.31]
GLOBAL LEADERS	421	7988	407	7980	65.8%	1.03 [0.90, 1.18]
SMART–CHOICE	35	1498	33	1495	5.2%	1.06 [0.66, 1.69]
STOPDAPT–2	37	1509	29	1500	5.0%	1.27 [0.78, 2.05]
TICO	34	1529	21	1527	4.0%	1.62 [0.94, 2.77]
Subtotal (95% CI)		**16088**		**16057**	**100.0%**	**1.06 [0.95, 1.18]**
Total events	657		616			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.09, df = 4 (P = 0.54); I^2 = 0%
Test for overall effect: Z = 1.12 (P = 0.26)

Study or Subgroup	LONGER DAPT Events	Total	SHORTER DAPT Events	Total	Weight	Risk Ratio IV, Random, 95% CI
drop of P2Y$_{12}$ inhibitor						
NIPPON	11	1653	19	1654	1.2%	0.58 [0.28, 1.21]
OPTIDUAL	32	695	47	690	3.3%	0.68 [0.44, 1.05]
DAPT	234	5020	315	4941	16.0%	0.73 [0.62, 0.86]
RACS	47	460	64	461	4.8%	0.74 [0.52, 1.05]
SECURITY	25	717	30	682	2.4%	0.79 [0.47, 1.33]
IVUS–XPL	8	701	10	699	0.8%	0.80 [0.32, 2.01]
REDUCE	34	727	41	733	3.2%	0.84 [0.54, 1.30]
PEGASUS–TIMI 54	980	14095	578	7067	27.0%	0.85 [0.77, 0.94]
SMART–DATE	46	1355	53	1357	4.1%	0.87 [0.59, 1.28]
OPTIMIZE	78	1556	87	1563	6.5%	0.90 [0.67, 1.21]
EXCELLENT	19	721	20	722	1.7%	0.95 [0.51, 1.76]
I–LOVE–IT 2	63	920	64	909	5.3%	0.97 [0.70, 1.36]
ARCTIC–Interruption	22	635	22	624	1.9%	0.98 [0.55, 1.76]
PRODIGY	100	987	98	983	8.0%	1.02 [0.78, 1.32]
ITALIC	15	910	14	912	1.3%	1.07 [0.52, 2.21]
ISAR–SAFE	31	2003	28	1997	2.5%	1.10 [0.66, 1.83]
DES LATE	78	2531	69	2514	5.8%	1.12 [0.82, 1.55]
DAPT–STEMI	15	437	13	433	1.2%	1.14 [0.55, 2.37]
RESET	14	1058	10	1059	1.0%	1.40 [0.63, 3.14]
REAL–LATE/ZEST–LATE	28	1357	15	1344	1.7%	1.85 [0.99, 3.45]
OPTIMA–C	5	684	2	683	0.3%	2.50 [0.49, 12.82]
Subtotal (95% CI)		**39222**		**32027**	**100.0%**	**0.88 [0.81, 0.96]**
Total events	1885		1599			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 22.75, df = 20 (P = 0.30); I^2 = 12%
Test for overall effect: Z = 3.03 (P = 0.002)

Risk Ratio IV, Random, 95% CI
0.5   0.7   1   1.5   2
Favours LONGER DAPT   Favours SHORTER DAPT

Fig. 1. Forest plot depicting the risk ratio of MACE of the two treatment regimens: drop of aspirin vs. drop of P2Y$_{12}$ inhibitor.

3.2.1.7. MACE according to diabetes status. In both diabetic and non-diabetic patients, any longer-term DAPT duration was not associated with a statistically significant reduction of MACE (RR 0.90, 95% CI, 0.71–1.13, p = 0.35, I^2 = 53%, Supplementary Fig. S4; and RR 0.84, 95% CI, 0.65–1.10, p = 0.21, I^2 = 74%, Supplementary Fig. S4; respectively) compared with any shorter-term DAPT duration.

3.2.2. Secondary outcome: myocardial infarction (MI)

3.2.2.1. Overall analysis. Any longer-term DAPT duration was associated with a significant 16% RRR of MI (RR 0.84, 95% CI, 0.73–0.95, p = 0.008, I^2 = 37%, Supplementary Fig. S5) compared with any shorter-term DAPT duration. A forest plot depicting the outcome myocardial infarction according to different treatment regimens is shown in the Supplementary Fig. S6.

3.2.2.2. Early aspirin drop followed by P2Y$_{12}$ inhibitor monotherapy. There was no difference in the relative risk of MI between very short-term vs. standard-term DAPT duration in 5 studies where aspirin was dropped (RR 1.03, 95% CI, 0.89–1.18, p = 0.72, I^2 = 0%, Fig. 3A).

3.2.2.3. Early P2Y$_{12}$ inhibitor drop followed by aspirin monotherapy. Any longer-term DAPT duration was associated with a significant 24% RRR of MI (RR 0.76, 95% CI, 0.66–0.87, p = 0.0001, I^2 = 22%, Fig. 3A) vs. any shorter-term DAPT duration with P2Y$_{12}$ inhibitor drop.

3.2.2.4. Subgroup analysis of different DAPT durations on the risk of MI. Long-term DAPT duration showed the greatest RRR of MI of 27% (RR

0.73, 95% CI, 0.53–0.99, p = 0.05, I^2 = 70%, Supplementary Fig. S6) when compared with standard DAPT duration and a subsequent drop of P2Y$_{12}$ inhibitor. Very short-term DAPT with subsequent drop of aspirin as well as very short-term DAPT with subsequent drop of P2Y$_{12}$ inhibitor were associated with a similar risk of MACE as in the standard DAPT duration group (Supplementary Fig. S6)

3.2.3. Secondary outcome: Stent thrombosis (ST)

3.2.3.1. Overall analysis. Any longer-term DAPT duration resulted in a 27% RRR of ST (RR 0.73, 95% CI, 0.57–0.94, p = 0.02, I^2 = 27%, Supplementary Fig. S7) compared with any shorter-term DAPT duration.

3.2.3.2. Early aspirin drop followed by P2Y$_{12}$ inhibitor monotherapy. There was no difference in the risk of ST between very short-term and standard-term DAPT durations in studies with early aspirin drop (RR 1.00, 95% CI, 0.74–1.34, p = 0.98, I^2 = 0%, Fig. 3B).

3.2.3.3. Early P2Y$_{12}$ inhibitor drop followed by aspirin monotherapy. Any longer-term DAPT duration reduced the relative risk of ST by 36% (RR 0.64, 95% CI, 0.47–0.88, p = 0.0006, I^2 = 23%, Fig. 3B) vs. any shorter-term DAPT duration with drop of P2Y$_{12}$ inhibitor.

3.2.4. Secondary outcome: stroke

3.2.4.1. Overall analysis. Any longer-term DAPT duration did not significantly decrease the RR of stroke (RR 0.93, 95% CI, 0.81–1.06, p = 0.25, I^2 = 0%, Supplementary Fig. S8) compared with any shorter-term
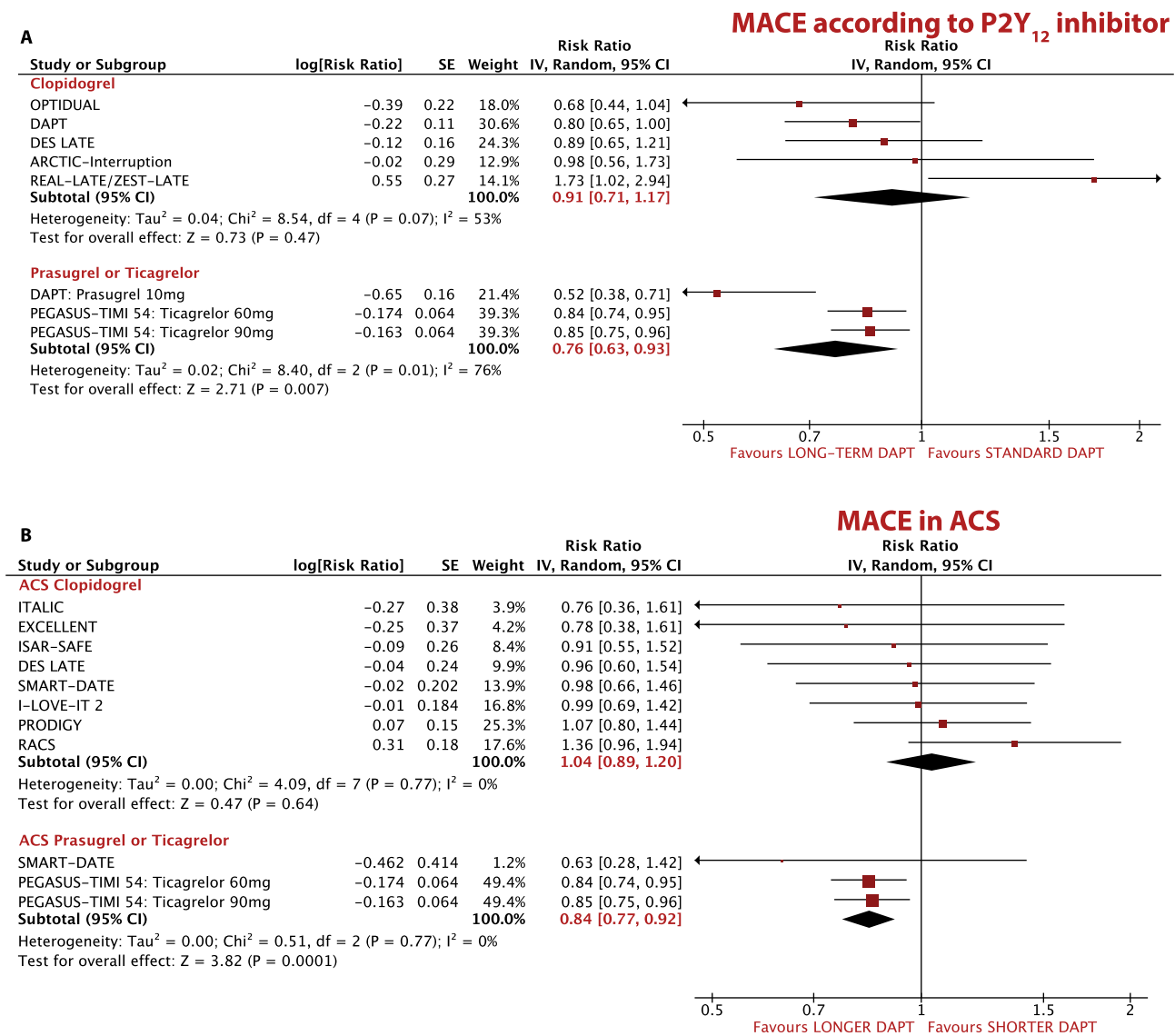
Fig. 2. Forest plots depicting the risk ratio of MACE according to (A) P2Y$_{12}$ inhibitor and (B) in patients presenting with ACS according to P2Y$_{12}$ inhibitor.

DAPT duration.

3.2.4.2. Early aspirin drop followed by P2Y$_{12}$ inhibitor monotherapy. In studies investigating drop of aspirin, there was no difference in the incidence of stroke between very short-term and standard-term DAPT durations (RR 0.96, 95% CI, 0.61–1.51, p = 0.85, I^2 = 49%, Supplementary Fig. S9).

3.2.4.3. Early P2Y$_{12}$ inhibitor drop followed by aspirin monotherapy. In studies, in which the P2Y$_{12}$ receptor inhibitor was dropped, there was no significant difference in the incidence of stroke between any longer-term and any shorter-term DAPT duration (RR 0.90, 95% CI, 0.77–1.05, p = 0.19, I^2 = 0%, Supplementary Fig. S9).

3.2.5. Secondary outcome: all-cause mortality

3.2.5.1. Overall analysis. There was no difference between different DAPT durations with respect to all-cause mortality (RR 1.04, 95% CI, 0.97–1.13, p = 0.28, I^2 = 0%, Supplementary Fig. S10A).

3.2.5.2. Early aspirin drop followed by P2Y$_{12}$ inhibitor monotherapy. In studies investigating the drop of aspirin, there was no significant

difference in the incidence of all-cause mortality between very short-term and standard-term DAPT durations (RR 1.13, 95% CI, 0.97–1.31, p = 0.12, I^2 = 0%, Supplementary Fig. S10B).

3.2.5.3. Early P2Y$_{12}$ inhibitor drop followed by aspirin monotherapy. In those studies, in which the P2Y$_{12}$ receptor inhibitor was dropped, there was no significant difference in the incidence of all-cause mortality between different DAPT durations (RR 1.02, 95% CI, 0.92–1.14, p = 0.64, I^2 = 3%, Supplementary Fig. S10B).

3.2.6. Secondary outcome: cardiovascular mortality

3.2.6.1. Overall analysis. There was no difference between different DAPT durations with respect to cardiovascular mortality (RR 0.97, 95% CI, 0.86–1.10, p = 0.65, I^2 = 0%, Supplementary Fig. S11A).

3.2.6.2. Early aspirin drop followed by P2Y$_{12}$ inhibitor monotherapy. In studies investigating the drop of aspirin, there was no significant difference in the incidence of cardiovascular mortality between very short-term and standard-term DAPT durations (RR 1.37, 95% CI, 0.96–1.95, p = 0.08, I^2 = 0%, Supplementary Fig. S11B).
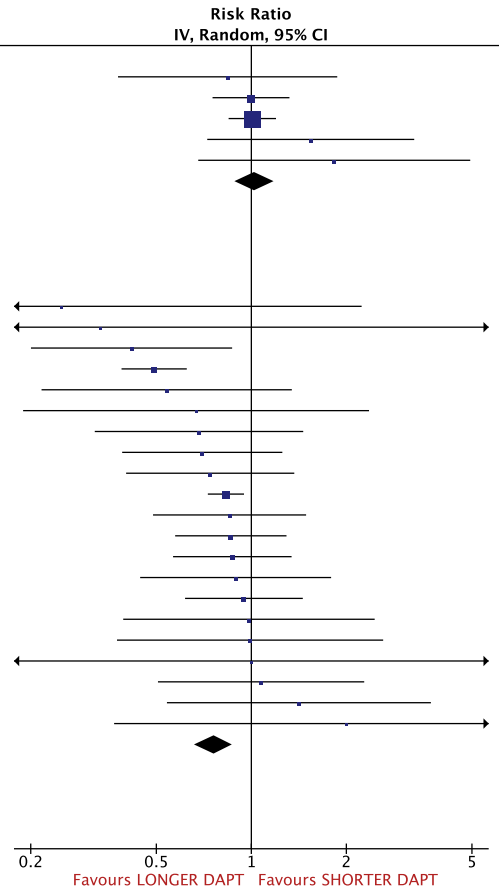
A   **MYOCARDIAL INFARCTION**

Study or Subgroup	LONGER DAPT Events	Total	SHORTER DAPT Events	Total	Weight	Risk Ratio IV, Random, 95% CI
drop of aspirin						
STOPDAPT-2	11	1509	13	1500	3.1%	0.84 [0.38, 1.87]
TWILIGHT	95	3564	95	3555	25.2%	1.00 [0.75, 1.32]
GLOBAL LEADERS	250	7988	248	7980	66.3%	1.01 [0.85, 1.20]
SMART-CHOICE	17	1498	11	1495	3.5%	1.54 [0.72, 3.28]
TICO	11	1529	6	1527	2.0%	1.83 [0.68, 4.94]
Subtotal (95% CI)		16088		16057	100.0%	**1.03 [0.89, 1.18]**
Total events	384		373			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.75, df = 4 (P = 0.60); I^2 = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

Study or Subgroup	LONGER DAPT Events	Total	SHORTER DAPT Events	Total	Weight	Risk Ratio IV, Random, 95% CI
drop of P2Y$_{12}$ inhibitor						
NIPPON	1	1653	4	1654	0.4%	0.25 [0.03, 2.24]
IVUS-XPL	0	701	1	699	0.2%	0.33 [0.01, 8.15]
SMART-DATE	10	1355	24	1357	3.2%	0.42 [0.20, 0.87]
DAPT	99	5020	198	4941	15.6%	0.49 [0.39, 0.62]
EXCELLENT	7	721	13	722	2.2%	0.54 [0.22, 1.34]
ITALIC	4	910	6	912	1.2%	0.67 [0.19, 2.36]
OPTIDUAL	11	695	16	690	3.0%	0.68 [0.32, 1.46]
DES LATE	19	2531	27	2514	4.7%	0.70 [0.39, 1.25]
RACS	17	460	23	461	4.4%	0.74 [0.40, 1.37]
PEGASUS-TIMI 54	560	14095	338	7067	22.8%	0.83 [0.73, 0.95]
REDUCE	22	727	26	733	5.1%	0.85 [0.49, 1.49]
OPTIMIZE	42	1556	49	1563	8.4%	0.86 [0.57, 1.29]
I-LOVE-IT 2	37	920	42	909	7.6%	0.87 [0.56, 1.34]
SECURITY	15	717	16	682	3.5%	0.89 [0.44, 1.79]
PRODIGY	39	987	41	983	7.7%	0.95 [0.62, 1.46]
ARCTIC-Interruption	9	635	9	624	2.1%	0.98 [0.39, 2.46]
DAPT-STEMI	8	437	8	433	1.9%	0.99 [0.38, 2.62]
OPTIMA-C	1	684	1	683	0.3%	1.00 [0.06, 15.93]
ISAR-SAFE	14	2003	13	1997	3.1%	1.07 [0.51, 2.28]
REAL-LATE/ZEST-LATE	10	1357	7	1344	2.0%	1.41 [0.54, 3.71]
RESET	4	1058	2	1059	0.7%	2.00 [0.37, 10.91]
Subtotal (95% CI)		39222		32027	100.0%	**0.76 [0.66, 0.87]**
Total events	929		864			

Heterogeneity: Tau^2 = 0.02; Chi^2 = 25.50, df = 20 (P = 0.18); I^2 = 22%
Test for overall effect: Z = 3.86 (P = 0.0001)

0.2   0.5   1   2   5
Favours LONGER DAPT   Favours SHORTER DAPT

B   **STENT THROMBOSIS**

Study or Subgroup	LONGER DAPT Events	Total	SHORTER DAPT Events	Total	Weight	Risk Ratio IV, Random, 95% CI
drop of aspirin						
STOPDAPT-2	1	1509	4	1500	1.8%	0.25 [0.03, 2.22]
SMART-CHOICE	2	1498	3	1495	2.7%	0.67 [0.11, 3.98]
TICO	4	1529	6	1527	5.4%	0.67 [0.19, 2.35]
GLOBAL LEADERS	64	7988	64	7980	72.1%	1.00 [0.71, 1.41]
TWILIGHT	19	3564	14	3555	18.1%	1.35 [0.68, 2.70]
Subtotal (95% CI)		16088		16057	100.0%	**1.00 [0.74, 1.34]**
Total events	90		91			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.89, df = 4 (P = 0.58); I^2 = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

Study or Subgroup	LONGER DAPT Events	Total	SHORTER DAPT Events	Total	Weight	Risk Ratio IV, Random, 95% CI
drop of P2Y$_{12}$ inhibitor						
ARCTIC-Interruption	0	635	3	624	1.1%	0.14 [0.01, 2.71]
ITALIC	0	910	3	912	1.1%	0.14 [0.01, 2.77]
DAPT	19	5020	65	4941	18.1%	0.29 [0.17, 0.48]
NIPPON	1	1653	2	1654	1.7%	0.50 [0.05, 5.51]
REDUCE	6	727	12	733	8.1%	0.50 [0.19, 1.34]
SECURITY	2	717	3	682	2.9%	0.63 [0.11, 3.78]
I-LOVE-IT 2	8	920	12	909	9.2%	0.66 [0.27, 1.60]
SMART-DATE	10	1355	15	1357	10.8%	0.67 [0.30, 1.48]
ISAR-SAFE	4	2003	5	1997	5.0%	0.80 [0.21, 2.97]
PRODIGY	76	987	92	983	26.5%	0.82 [0.62, 1.10]
IVUS-XPL	2	701	2	699	2.4%	1.00 [0.14, 7.06]
OPTIMIZE	3	1556	3	1563	3.5%	1.00 [0.20, 4.97]
DAPT-STEMI	4	437	3	433	4.0%	1.32 [0.30, 5.87]
RESET	3	1058	2	1059	2.9%	1.50 [0.25, 8.97]
OPTIDUAL	3	695	1	690	1.9%	2.98 [0.31, 28.56]
OPTIMA-C	1	684	0	683	1.0%	3.00 [0.12, 73.41]
Subtotal (95% CI)		20058		19919	100.0%	**0.64 [0.47, 0.88]**
Total events	142		223			

Heterogeneity: Tau^2 = 0.08; Chi^2 = 19.55, df = 15 (P = 0.19); I^2 = 23%
Test for overall effect: Z = 2.72 (P = 0.006)

0.2   0.5   1   2   5
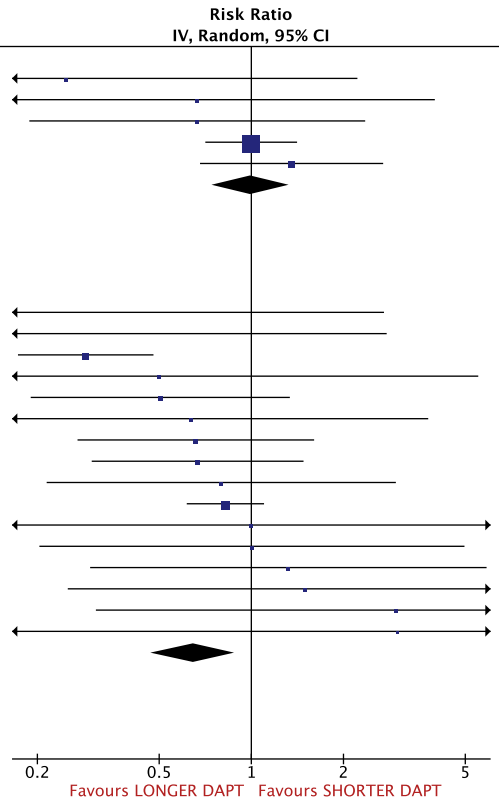Favours LONGER DAPT   Favours SHORTER DAPT

Fig. 3. Forest plots depicting the risk ratio of (A) myocardial infarction and (B) stent thrombosis according to the two treatment regimens: drop of aspirin vs. drop of P2Y$_{12}$ inhibitor.

3.2.6.3. Early P2Y$_{12}$ inhibitor drop followed by aspirin monotherapy. In those studies, in which the P2Y$_{12}$ receptor inhibitor was dropped, there was no significant difference in the incidence of cardiovascular mortality between different DAPT durations (RR 0.93, 95% CI, 0.82–1.06, p = 0.27, I^2 = 0%, Supplementary Fig. S11B).

3.2.7. Primary safety outcome: major bleeding

3.2.7.1. Overall analysis

3.2.7.1.1. TIMI bleeding score. TIMI bleeding score: Any longer-term DAPT duration was associated with a 1.86-fold RRI of TIMI major bleeding (RR 1.85, 95% CI, 1.54–2.22, p < 0.00001, I^2 = 0%, Fig. 4A) compared with any shorter-term DAPT duration.

3.2.7.1.2. BARC bleeding score. Any longer-term DAPT duration resulted in a 1.54-fold RRI of BARC 3–5 major bleeding (RR 1.54, 95% CI, 1.21–1.97, p = 0.0005, I^2 = 60%, Fig. 4B) compared with any shorter-term DAPT duration.

3.2.7.2. Early aspirin drop followed by P2Y$_{12}$ inhibitor monotherapy. Standard-term DAPT duration was associated with a numerical increase in the risk of BARC 3–5 major bleeding events (RR 1.61, 95% CI, 0.96–2.71, p = 0.07, I^2 = 79%, Fig. 5) compared with very short-term DAPT with aspirin drop.

3.2.7.3. Early P2Y$_{12}$ inhibitor drop followed by aspirin monotherapy. Any

longer-term DAPT duration resulted in a significant RRI of major bleeding events assessed by both the TIMI and the BARC bleeding score (RR 1.81, 95% CI, 1.48–2.21, p < 0.00001, I^2 = 0%, Supplementary Fig. S12; and RR 1.63, 95% CI, 1.22–2.17, p = 0.0010, I^2 = 34%, Fig. 5; respectively) compared with any shorter-term DAPT duration with P2Y$_{12}$ inhibitor drop.

3.2.7.4. Major bleeding according to P2Y$_{12}$ inhibitor. In prasugrel- or ticagrelor-treated patients, long-term DAPT duration was associated with a significantly increased relative risk of major bleeding (RR 2.41, 95% CI, 1.28–4.56, p = 0.007, I^2 = 62%, Supplementary Fig. S13) compared with standard-term DAPT duration.
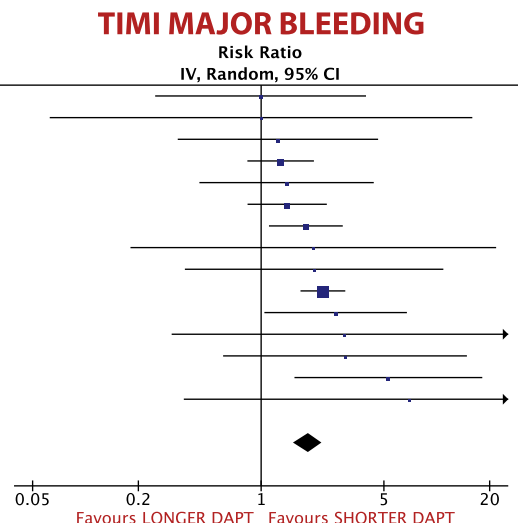
In clopidogrel-treated patients, the relative risk of major bleeding was also significantly increased for long-term DAPT when compared with standard-term DAPT duration, but the magnitude of the effect was less as compared to prasugrel or ticagrelor (RR 1.53, 95% CI, 1.16–2.03, p = 0.003, I^2 = 0%, Supplementary Fig. S13).

4. Discussion

In our meta-analysis, which included twenty-five studies and over 100.000 patients, we analyzed the efficacy and safety of DAPT durations in patients undergoing PCI and generated subgroups, involving ACS patients, the type of P2Y$_{12}$ receptor inhibitor and the drop strategy (aspirin vs P2Y$_{12}$ inhibitor).
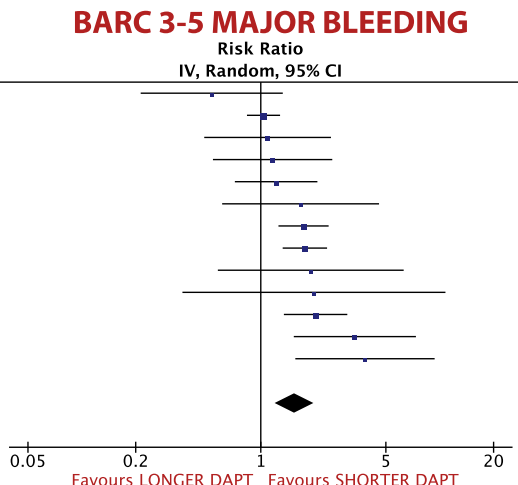

Fig. 4. Forest plots depicting the risk ratio of major bleeding according to the (A) TIMI and (B) BARC bleeding score in the overall population.

BARC 3-5 MAJOR BLEEDING according to treatment regimen

Study or Subgroup	LONGER DAPT Events	Total	SHORTER DAPT Events	Total	Weight	Risk Ratio IV, Random, 95% CI
drop of aspirin						
GLOBAL LEADERS	169	7988	163	7980	32.6%	1.04 [0.84, 1.28]
SMART–CHOICE	14	1498	12	1495	19.7%	1.16 [0.54, 2.51]
TWILIGHT	69	3564	34	3555	28.4%	2.02 [1.35, 3.04]
STOPDAPT–2	27	1509	8	1500	19.3%	3.35 [1.53, 7.36]
Subtotal (95% CI)		**14559**		**14530**	**100.0%**	**1.61 [0.96, 2.71]**
Total events	279		217			
Heterogeneity: Tau² = 0.20; Chi² = 14.45, df = 3 (P = 0.002); I² = 79%						
Test for overall effect: Z = 1.79 (P = 0.07)						
drop of P2Y₁₂ inhibitor						
I–LOVE–IT 2	7	920	13	909	8.1%	0.53 [0.21, 1.33]
NIPPON	12	1653	11	1654	9.8%	1.09 [0.48, 2.47]
SMART–DATE	10	1355	6	1357	6.9%	1.67 [0.61, 4.58]
PRODIGY	94	987	54	983	28.3%	1.73 [1.26, 2.39]
DAPT	129	5020	72	4941	30.6%	1.76 [1.33, 2.35]
SECURITY	8	717	4	682	5.2%	1.90 [0.58, 6.29]
DAPT–STEMI	4	437	2	433	2.7%	1.98 [0.36, 10.76]
ISAR–SAFE	23	2003	6	1997	8.4%	3.82 [1.56, 9.37]
Subtotal (95% CI)		**13092**		**12956**	**100.0%**	**1.63 [1.22, 2.17]**
Total events	287		168			
Heterogeneity: Tau² = 0.05; Chi² = 10.61, df = 7 (P = 0.16); I² = 34%						
Test for overall effect: Z = 3.30 (P = 0.0010)						

Risk Ratio IV, Random, 95% CI

0.1 0.2 0.5 1 2 5 10
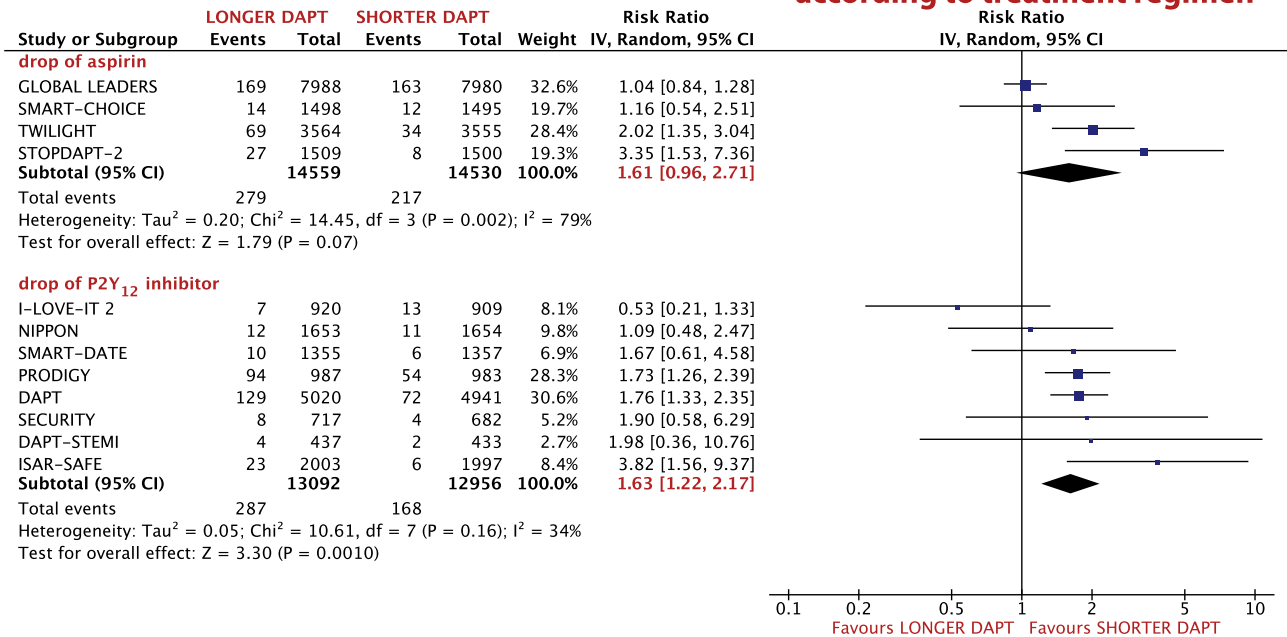Favours LONGER DAPT   Favours SHORTER DAPT

Fig. 5. Forest plot depicting the risk ratio of BARC 3–5 major bleeding according to the two treatment regimens: drop of aspirin vs. drop of P2Y₁₂ inhibitor.

The main findings of this study are as follows (Fig. 6):

i) In trials with P2Y₁₂ inhibitor drop and continuation of aspirin monotherapy, any longer-term DAPT duration is associated with a significant reduction of MACE, MI and ST but a higher risk of major bleeding as compared with any shorter-term DAPT duration;

ii) High ischemic risk patients treated with potent P2Y₁₂ inhibitors such as prasugrel and ticagrelor showed a significantly lower risk of MACE with long-term DAPT of >18 months compared with standard-term DAPT of 12 months. Likewise, in the ACS population, the extent of reduction of ischemic events with longer-term DAPT duration group was significant only in patients treated with potent P2Y₁₂ inhibitors;

iii) Very short-term DAPT (1–3 months) with either aspirin or P2Y₁₂ inhibitor drop is associated with satisfactory efficacy and safety as compared with standard-term DAPT duration of 12 months.

4.1. P2Y₁₂ inhibitor drop and subsequent aspirin monotherapy

Any longer DAPT duration was associated with a reduced risk of MACE, MI and ST compared with any shorter DAPT duration and subsequent P2Y₁₂ inhibitor drop. However, the reduction of ischemic events is outweighed by a significant increase in major bleeding events. The benefit of long-term DAPT (>12 months) duration, compared with standard-term DAPT (12 months) duration, regarding ischemic events was mainly driven by two trials, DAPT and PEGASUS-TIMI 54 [9,18], while four other trials failed to show significant reductions of MACE [10,15,17,19]. However, in both aforementioned trials, a lower rate of

Antiplatelet Treatment Regimens following PCI

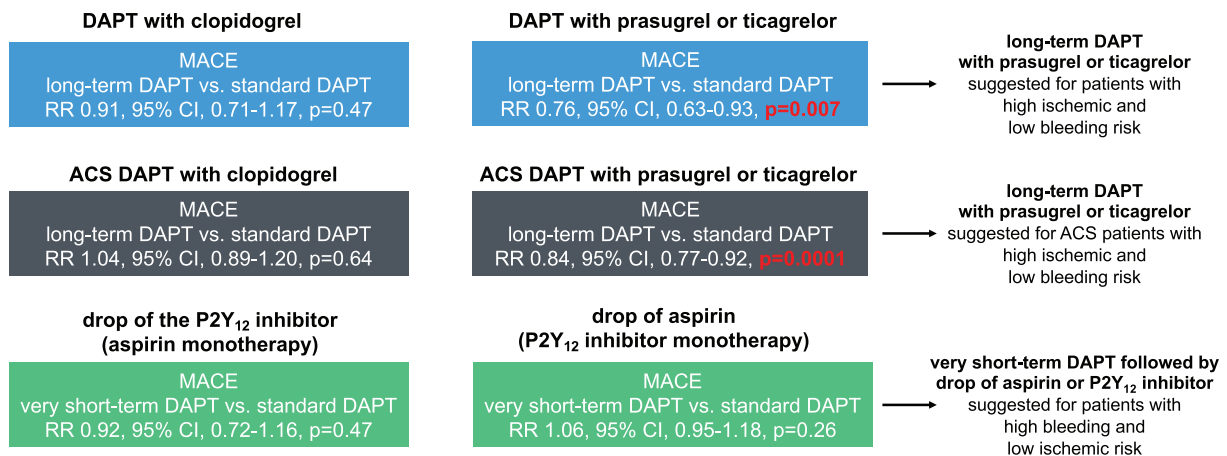| DAPT with clopidogrel	DAPT with prasugrel or ticagrelor	
MACE long-term DAPT vs. standard DAPT RR 0.91, 95% CI, 0.71-1.17, p=0.47	**MACE** long-term DAPT vs. standard DAPT RR 0.76, 95% CI, 0.63-0.93, **p=0.007**	**long-term DAPT with prasugrel or ticagrelor** suggested for patients with high ischemic and low bleeding risk
ACS DAPT with clopidogrel	**ACS DAPT with prasugrel or ticagrelor**	
MACE long-term DAPT vs. standard DAPT RR 1.04, 95% CI, 0.89-1.20, p=0.64	**MACE** long-term DAPT vs. standard DAPT RR 0.84, 95% CI, 0.77-0.92, **p=0.0001**	**long-term DAPT with prasugrel or ticagrelor** suggested for ACS patients with high ischemic and low bleeding risk
drop of the P2Y₁₂ inhibitor (aspirin monotherapy)	**drop of aspirin (P2Y₁₂ inhibitor monotherapy)**	
MACE very short-term DAPT vs. standard DAPT RR 0.92, 95% CI, 0.72-1.16, p=0.47	**MACE** very short-term DAPT vs. standard DAPT RR 1.06, 95% CI, 0.95-1.18, p=0.26	**very short-term DAPT followed by drop of aspirin or P2Y₁₂ inhibitor** suggested for patients with high bleeding and low ischemic risk

Fig. 6. Overview of key results and treatment recommendations.

ischemic events came at the cost of significantly more major bleeding events.

The long-term use of DAPT should be carefully considered. According to the results of our analysis, the extent of reduction of ischemic events for any longer-term DAPT after PCI was largest among (1) high ischemic risk patients treated with potent $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor, (2) patients presenting with ACS receiving a potent $P2Y_{12}$ inhibitor and (3) patients receiving long-term DAPT vs. standard-term DAPT. Nonetheless, a decreased ischemic risk naturally coincided with an increased risk of bleeding, which necessitates peculiar, individual patient selection for extended DAPT. Importantly, long-term DAPT with aspirin and clopidogrel is not associated with favorable outcome. This is important, as the current European NSTE-ACS guidelines recommend such a combination for high risk patients [34].

4.2. Novel approach: aspirin drop and subsequent $P2Y_{12}$ inhibitor monotherapy

Our analysis shows that, compared with standard-term DAPT, very short-term DAPT (1–3 months) followed by subsequent $P2Y_{12}$ inhibitor monotherapy or aspirin monotherapy results in an unchanged risk of MACE but a numerical decrease in major bleeding events. As most cases of ST, occur during the first 30 days after stent implantation [35], it would make sense to specifically cover this critical period of time with an intensified DAPT and only then switch to a $P2Y_{12}$ inhibitor-only (or an aspirin-only) regimen.

In comparison with standard-term DAPT duration, the emerging very short-term DAPT followed by $P2Y_{12}$ receptor inhibitor monotherapy allows for a shorter dual platelet inhibition exposure time, reducing the incidence of major bleeding, which is, at the same time, not associated with an increase in MACE. Importantly, head-to-head comparisons of aspirin vs $P2Y_{12}$ inhibitor monotherapy after a very short DAPT duration would be of interest.

The efficacy and safety of $P2Y_{12}$ inhibitor monotherapy has been established for clopidogrel and ticagrelor, with most data being available for ticagrelor monotherapy from the GLOBAL LEADERS, TWILIGHT and TICO trials.

The recently published TICO trial showed that very-short term DAPT followed by $P2Y_{12}$ inhibitor monotherapy with ticagrelor may also be a suitable treatment regimen for patients presenting with ACS.

Two trials investigated the treatment concept of clopidogrel monotherapy. The STOPDAPT-2 trial investigated clopidogrel monotherapy only while in the SMART-CHOICE trial, 77% of patients included received clopidogrel monotherapy. Both trials showed $P2Y_{12}$ inhibitor monotherapy with clopidogrel, in comparison with standard-term DAPT, to effectively reduce major bleeding events with an unchanged ischemic risk.

Considering that clopidogrel is associated with rather high rates of high on-treatment platelet reactivity (HTPR) [36], monotherapy solely relying on clopidogrel may entail a potentially larger ischemic risk. The use of cardiovascular precision medicine (individualized antiplatelet approach), although not recommended in current clinical guidelines, may be of interest in this clinical setting, especially due to the potential ischemic risk brought on by the high interindividual response variability in clopidogrel-only treated patients [37].

Surprisingly, there is currently no specific study published investigating $P2Y_{12}$ inhibitor monotherapy with prasugrel after PCI given that prasugrel has recently shown a better efficacy combined with an equal safety profile as compared with ticagrelor in patients with ACS [38].

4.3. The challenges with $P2Y_{12}$ inhibitor monotherapy

All trials investigating the novel $P2Y_{12}$ inhibitor-only concept compared very short-term DAPT followed by $P2Y_{12}$ inhibitor monotherapy to standard-term DAPT duration. Conceivably, it is easier to demonstrate less bleeding with a single antiplatelet therapy than with

DAPT, but it is a lot more difficult to show non-inferiority in ischemic events. Each of these four clinical trials did not compare an additional arm of very-short term DAPT followed by aspirin monotherapy. These crucial head-to-head comparisons of shorter-term DAPT with either aspirin or $P2Y_{12}$ inhibitor drop are, however, missing to this day. Given the relatively inexpensive costs of aspirin compared to ticagrelor, the specific study design involving the omission of aspirin is most likely industry-driven. Interestingly, in comparison with studies investigating the drop-of-aspirin regimen, our pooled analysis of studies investigating very short-term DAPT and subsequent drop of the $P2Y_{12}$ inhibitor (REDUCE, OPTIMIZE, RESET) also found an unchanged ischemic risk, which may suggest a similar efficacy of both drop-strategies.

Results from a meta-analysis comparing monotherapies with a $P2Y_{12}$ inhibitor vs. aspirin for secondary prevention of cardiovascular disease show, that $P2Y_{12}$ inhibitor monotherapy was associated with a relative risk reduction of myocardial infarction but an unchanged risk of stroke, all-cause death, cardiovascular death and major bleeding [39]. Authors concluded therefore, that the benefit of $P2Y_{12}$ inhibitor monotherapy is therefore questionable due to the high number needed to treat to prevent myocardial infarction and the lack of effect on mortality, which casts reasonable doubt on the preferred use of $P2Y_{12}$ inhibitor over aspirin [39].

4.4. Implications for clinical guidelines

The challenge now will be how to integrate the data of our analysis supporting the very short-term 3-month DAPT and subsequent $P2Y_{12}$ inhibitor monotherapy (possibly also aspirin monotherapy) as non-inferior to standard-term 12-month; with opposite results showing that long-term DAPT duration with prasugrel or ticagrelor in ACS patients is better than the standard-term DAPT duration when ischemic outcomes are considered. In the light of these findings, our conclusion remains equivocal.

We conclude that long-term treatment with potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) might be the most appropriate choice in patients at low bleeding risk but high ischemic risk with underlying atherothrombosis in the coronary, cerebral, or peripheral vasculature. Contrary to the findings of our analysis, current ESC guidelines on chronic coronary syndromes and NSTE-ACS also suggest continued DAPT >12 months (long-term) with clopidogrel in patients who have a high or moderate risk of ischemic events, and do not have a high bleeding risk. This needs to be reconsidered, as clopidogrel has been associated with high rates of HTPR [36] resulting in an increased risk of ischemic events [40].

In contrast, patients with high bleeding risk might benefit in terms of the net outcome from very short DAPT duration with subsequent $P2Y_{12}$ inhibitor monotherapy, which is now additionally investigated in upcoming trials (A-CLOSE trial: NCT03947229 and SMART-CHOICEII trial: NCT03119012). For bleeding risk assessment, the PRECISE-DAPT score may be used [41]. The management of patients with both high ischemic and bleeding risk remains challenging.

5. Strengths and limitations

To our knowledge, this is the first meta-analysis that reports on outcomes according to the $P2Y_{12}$ inhibitor type and differentiating between aspirin or $P2Y_{12}$ inhibitor monotherapy. Further, this study includes a subgroup analysis of patients presenting with ACS and comprises a sufficiently great sample size of more than 100.000, making it the largest meta-analysis to report on DAPT outcomes to date.

However, this study has several limitations. Firstly, one study included BARC 2 major bleeding in their bleeding endpoint which, although expected to be only minimal, affected the result of our analysis [22]. Secondly, several studies did not report on outcomes of interest. Further, three different bleeding definitions were used in the trials included in this study, which made it impossible to unify the major

bleeding analysis. Thirdly, the study lacks a major bleeding analysis in the ACS subgroup as a counterpart to the ACS MACE analysis, which was not feasible due to lack of information provided in the original articles. Finally, our analysis may be underpowered for individual adverse cardiovascular events, especially in subgroup analyses on specific DAPT durations, types of antiplatelet agent and clinical presentations.

6. Conclusion

Overall, any longer-term DAPT duration is associated with a lower risk of ischemic events, which is counterbalanced by a significantly increased risk of major bleeding. ACS patients in particular appear to benefit from longer-term DAPT duration with prasugrel or ticagrelor. Very short-term DAPT and subsequent $P2Y_{12}$ inhibitor monotherapy or aspirin monotherapy is associated with a favourable risk to benefit profile when compared to the standard DAPT duration of 12 months. Very short-term DAPT followed by aspirin or $P2Y_{12}$ inhibitor monotherapy should be investigated in the future.

Conflicts of interest

Georg Gelbenegger: none.
Ummahan Erari-Canyurt: none.
Jürgen Grafeneder: none.
Bernd Jilma: no relevant COI.
Maciej Lesiak: AstraZeneca, Bayer, Boehringer Ingelheim, Pfizer - speaking
bureau.
Anna Komosa: none.
Raffaele De Caterina: R.D.C.: grants for congress organizations and personal fees and honoraria for lecturing and advisory board participations from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Portola, and Roche; Novartis, Sanofi, and Amgen, all outside the submitted work.
Marek Postula: none.
Jolanta M. Siller-Matula: lecture fees from Daiichi Sankyo, Chiesi, Astra Zeneca, Bayer, BMS; all unrelated to the present manuscript.

Author statement

Georg Gelbenegger: data curation, formal analysis, visualization, writing - original draft, writing - review & editing
Ummahan Erari-Canyurt: data curation, writing - review & editing
Jürgen Grafeneder: formal analysis, writing - review & editing
Bernd Jilma: funding acquisition, writing - review & editing
Maciej Lesiak: writing - review & editing
Anna Komosa: writing - review & editing
Raffaele De Caterina: formal analysis, writing - review & editing
Marek Postula: writing - review & editing
Jolanta M. Siller-Matula: conceptualization, formal analysis, methodology, supervision, validation, visualization, writing - original draft, writing - review & editing

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vph.2021.106858.

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