EXTENDED DUAL ANTIPLATELET THERAPY UTILIZING P2Y12 INHIBITORS FOLLOWING ACS/PCI : AN EVALUATION OF ISCHEMIC ADVANTAGES VERSUS HEMORRHAGIC RISKS

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ABSTRAK
Metodologi ini mencakup tinjauan sistematis komprehensif terhadap literatur sesuai dengan pedoman PRISMA (PROSPERO CRD420251239032), yang mencakup rentang waktu dari Januari 2015 hingga Agustus 2025. Sebanyak 12 studi ditemukan, termasuk 2 uji coba terkontrol secara acak dan 10 studi observasional, yang secara kolektif melibatkan 89.813 individu, dan telah diteliti. Temuan utama menunjukkan bahwa memperpanjang DAPT melewati batas satu tahun umumnya dikaitkan dengan penurunan kejadian iskemik, dibuktikan dengan Rasio Bahaya (HR) berkisar antara 0,52 hingga 0,68 dalam studi observasional skala besar, khususnya yang berfokus pada populasi Asia. Pada dasarnya, penurunan probabilitas kejadian iskemik yang diakui tidak secara konsisten berhubungan dengan peningkatan frekuensi komplikasi perdarahan mayor yang signifikan dalam segmen kohort yang lebih besar yang diteliti. Uji coba seperti STOPDAPT-2 menyoroti bahwa monoterapi clopidogrel, yang diberikan setelah pemberian DAPT singkat, menunjukkan non-inferioritas untuk hasil iskemik sambil mencapai pengurangan risiko perdarahan yang substansial (HR 0,46-0,57). Meskipun demikian, stratifikasi risiko individu yang cermat sangat penting, karena data dunia nyata juga menunjukkan potensi bahaya perdarahan pada populasi pasien yang tidak diseleksi. Akibatnya, keputusan mengenai agen P2Y12 untuk terapi yang diperpanjang harus dipandu oleh profil risiko iskemik dan perdarahan spesifik pasien, daripada hanya mengandalkan keunggulan intrinsik obat tertentu.

Kata kunci **:** inhibitor P2Y12, kejadian iskemik, risiko perdarahan, Sindrom Koroner Akut (ACS), Terapi Antiplatelet Ganda (DAPT)

ABSTRACT
The methodology entailed a comprehensive systematic review of the literature in accordance with PRISMA guidelines (PROSPERO CRD420251239032), encompassing the chronological span from January 2015 to August 2025. An aggregate of 12 studies was discovered, featuring 2 randomized controlled trials alongside 10 observational studies, which collectively involved 89,813 individuals, and were examined. Key findings suggest that extending DAPT past the one-year mark is generally associated with a reduced incidence of ischemic events, evidenced by Hazard Ratios (HRs) ranging from 0.52 to 0.68 in large-scale observational studies, particularly those focused on Asian populations. Essentially, the recognized decrease in the probability of ischemic events did not consistently relate to a considerable escalation in the frequency of major hemorrhagic complications within the larger segment of the studied cohorts. Trials such as STOPDAPT-2 highlighted that clopidogrel monotherapy, administered after a brief DAPT course, demonstrated non-inferiority for ischemic outcomes while achieving a substantial reduction in bleeding risk (HR 0.46-0.57). Nevertheless, meticulous individual risk stratification is paramount, as real-world data also suggest a potential for bleeding harm in unselected patient populations. Consequently, the decision regarding the P2Y12 agent for extended therapy should be guided by the patient's specific ischemic and bleeding risk profiles, rather than relying solely on the intrinsic superiority of a particular drug.

Keywords ***:*** *Dual Antiplatelet Therapy (DAPT), P2Y12 inhibitors, Acute Coronary Syndrome (ACS), ischemic events, hemorrhagic risk*

INTRODUCTION

The integration of aspirin with a P2Y12 receptor antagonist in dual antiplatelet therapy represents the core principle of antithrombotic strategies following acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI). Although the advantageous effects of DAPT in diminishing stent thrombosis and major adverse cardiovascular events (MACE) during the initial year subsequent to ACS or PCI are thoroughly documented, the question of the optimal duration of therapy extending beyond 12 months remains a subject of considerable debate. (Navarese et al., 2023) Presently, three P2Y12 antagonists exist for therapeutic applications: clopidogrel, prasugrel, and ticagrelor. Although prasugrel and ticagrelor are known for their superior and more consistent effects on platelet inhibition when stacked against clopidogrel, they bear a connection to more frequent bleeding problems. (Galli et al., 2024) The compromise inherent in balancing ischemic protection against the risk of hemorrhage assumes heightened significance when contemplating an extension of dual antiplatelet therapy (DAPT) duration surpassing the standard twelve-month timeframe.

The determination to prolong dual antiplatelet therapy (DAPT) beyond a duration of twelve months necessitates a careful consideration of the prospective diminution in late ischemic occurrences, such as very late stent thrombosis, spontaneous myocardial infarction, and cerebrovascular accidents, juxtaposed with the heightened likelihood of significant hemorrhagic complications. Numerous pivotal investigations, including the DAPT trial and PEGASUS-TIMI 54, have elucidated that an extension of DAPT may mitigate ischemic incidents, albeit with the concomitant increase in bleeding risks.(Bonaca et al., 2015; Mauri et al., 2014) Nevertheless, these clinical trials did not engage in a direct comparative analysis of various P2Y12 inhibitors for prolonged therapeutic intervention.

Notwithstanding the accumulation of substantial evidence, numerous pivotal inquiries persist without resolution. First, the comparative effectiveness and safety of different P2Y12 inhibitors (clopidogrel vs prasugrel vs ticagrelor) specifically for prolonged DAPT (>12 months) has not been comprehensively evaluated. Second, the optimal patient selection criteria for extended DAPT remain unclear. Third, empirical evidence regarding real-world effectiveness from varied demographic groups is scarce, as the majority of pivotal clinical trials were predominantly executed within Western populations.

This systematic review endeavors to: 1. Analyze the impact of extended dual antiplatelet therapy (DAPT) exceeding twelve months duration with various P2Y12 inhibitors on ischemic events (myocardial infarction, stent thrombosis, cerebrovascular accident, and cardiovascular mortality) in individuals post-acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) 2. Evaluate the hemorrhagic risk correlated with prolonged DAPT duration across differing P2Y12 inhibitors 3. Examine the risk-benefit profiles of clopidogrel, prasugrel, and ticagrelor in relation to the parameters of extended DAPT. Elucidate patient subpopulations that may experience the most substantial net clinical advantage from prolonged DAPT.

METHODS

Protocol and Registration

This systematic examination was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol for the review was formulated a priori, delineating explicit criteria for inclusion and exclusion, search methodologies, and data extraction techniques. This Protocol has been registered in PROSPERO (CRD420251239032).

Eligibility Criteria

Adult patients (≥18 years) with ACS (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina) or patients who underwent PCI with drug-eluting stent implantation. Extended duration of dual antiplatelet therapy (DAPT) exceeding 12 months utilizing P2Y12 inhibitors (including clopidogrel, prasugrel, or ticagrelor) in conjunction with aspirin. Standard DAPT duration (≤12 months) or comparison between different P2Y12 inhibitors for extended duration. The principal outcomes encompassed ischemic occurrences (myocardial infarction, stent thrombosis, cerebrovascular accident, cardiovascular mortality, or the composite of major adverse cardiovascular events) as well as hemorrhagic incidents (major bleeding as delineated by TIMI, BARC, or GUSTO classifications). The secondary outcomes comprised all-cause mortality and net adverse clinical events (NACE). Randomized controlled trials, prospective cohort studies, retrospective cohort studies, and registry-based investigations disseminated in the English language from January 2015 to August 2025. Reviews, meta-analyses, editorials, case reports, studies with DAPT duration ≤12 months only, studies not reporting relevant ischemic or bleeding outcomes, non-English publications, animal studies, and sample sizes <100.

Information Sources and Search Strategy

We conducted comprehensive searches across multiple databases: - PubMed/MEDLINE: Advanced search with MeSH terms and keywords - Google Scholar: Broad academic search - Deep Literature Review: Comprehensive semantic search across indexed literature. Search terms included combinations of: “dual antiplatelet therapy,” “DAPT,” “prolonged,” “extended,” “long-term,” “clopidogrel,” “prasugrel,” “ticagrelor,” “P2Y12 inhibitor,” “acute coronary syndrome,” “ACS,” “percutaneous coronary intervention,” “PCI,” “myocardial infarction,” “stent thrombosis,” “bleeding,” “hemorrhage,” and related terms. The search strategy was designed to be highly sensitive, retrieving all potentially relevant studies. Reference lists of included studies and relevant systematic reviews were also screened for additional eligible studies.

Selection Process

Two evaluators conducted an independent assessment of the titles and abstracts of all obtained records in accordance with the established eligibility criteria. Studies that potentially met inclusion criteria or where eligibility was unclear proceeded to full-text review. Full-text articles were independently assessed by both reviewers. Conflicts were addressed through deliberation and collective agreement.

Data Collection Process

Data extraction was performed systematically using a standardized form. Extracted data included: - Study characteristics: First author, year, country, study design, sample size, follow-up duration - Population characteristics: Age, sex distribution, clinical presentation (ACS type or elective PCI), proportion with ACS, diabetes prevalence, prior MI - Intervention details: P2Y12 inhibitor type(s), DAPT duration in each group, aspirin dose, P2Y12 inhibitor loading and maintenance doses - Outcome data: Ischemic events (MI, stent thrombosis, stroke, CV death, MACE) with effect sizes (hazard ratios, odds ratios, relative risks) and 95% confidence intervals; bleeding events with definitions and effect sizes - Quality indicators: Funding sources, conflicts of interest, study limitations.

Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers using validated tools: - For RCTs: Cochrane Risk of Bias tool 2.0 (RoB 2.0), evaluating bias arising from randomization

process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results - For observational studies: Newcastle-Ottawa Scale (NOS), assessing selection of study groups, comparability of groups, and ascertainment of outcomes. Research investigations that achieved a score of 7 or above on a 9-point scale were classified as possessing high quality.

Synthesis Methods

With the understanding of the inherent variability linked to study designs, populations involved, interventions conducted, and how outcomes are defined, we implemented a narrative synthesis method. The studies were categorized based on design (randomized controlled trials versus observational studies) and by the nature of the comparison (extended versus standard duration of dual antiplatelet therapy; clopidogrel versus more potent P2Y12 inhibitors). Effect sizes accompanied by 95% confidence intervals were extracted and systematically organized. Trends pertaining to ischemic and bleeding outcomes were qualitatively described, with particular focus on patient demographics, duration of dual antiplatelet therapy, and the type of P2Y12 inhibitor administered.

RESULTS

Study Selection

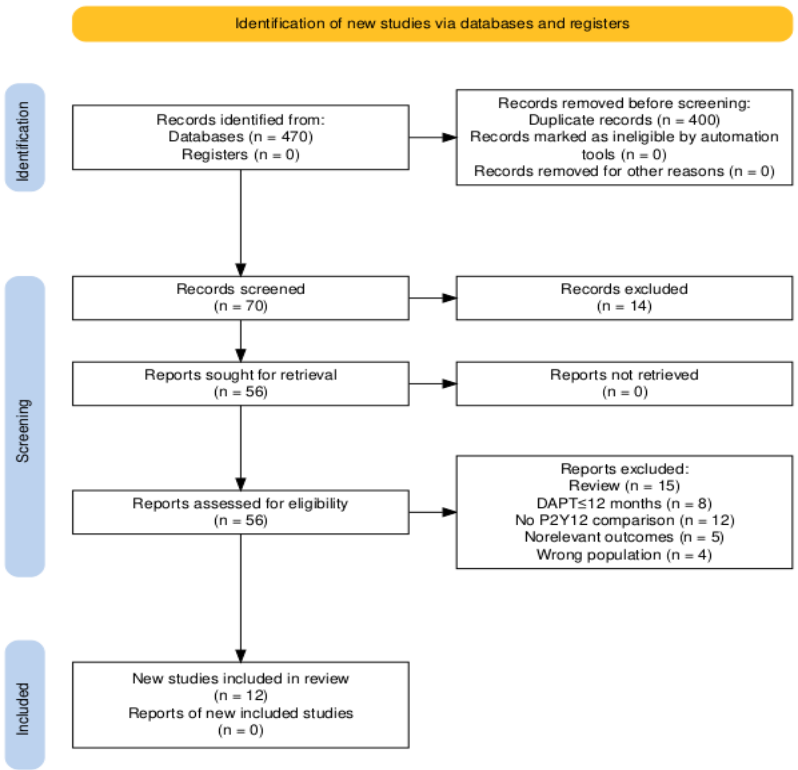

Figure 1. Diagram Flow Of Literature Search Strategy For This Systematic Review

The systematic search identified 470 records from all databases (Scispace Database: 430; PubMed: 20; Google Scholar: 20). After removing 400 duplicates, 70 unique records underwent title and abstract screening. Of these, 14 were immediately excluded as clearly not meeting criteria, and 56 proceeded to full-text eligibility assessment. After detailed evaluation, 44 studies were excluded for the following reasons: reviews or meta-analyses (n=15), DAPT duration ≤12 months only (n=8), no relevant comparison of P2Y12 inhibitors

or DAPT duration (n=12), no relevant ischemic or bleeding outcomes reported (n=5), and wrong population (n=4). Ultimately, twelve empirical investigations satisfied all specified inclusion criteria and were incorporated into the qualitative synthesisThe PRISMA flow diagram is presented in figure 1.

Study Characteristics

The twelve studies incorporated in this analysis consisted of two randomized controlled trials (both originating from the STOPDAPT-2 program) and ten observational studies (comprising eight registry-based cohort studies and two prospective multicenter cohorts), which collectively enrolled a total of 89,813 participants. The analysis was released in the interval covering 2020 to 2024. In terms of the geographical distribution of the research, a total of eight studies were conducted in China, whereas Japan contributed two, South Korea one, and France one. The studies recorded a median participation of 4,046 individuals, with a range stretching from 708 to 53,399. The follow-up timeframe extended between 12 and 67 months, presenting a median of 29 months. Table 1 provides a comprehensive summary of the characteristics of the studies that were included.

Table 1. Characteristics of Included Studies

Study	Design	Country	N	Population	ACS %	Age (y)	Male %	Follow-up (mo)
(Watanabe et al., 2024)	RCT	Japan	3,005	PCI with DES	Mixed	68.5	77.3	60
(Obayashi et al., 2022)	RCT	Japan	5,997	PCI with DES	Mixed	68.3	77.5	12
(Kim et al., 2023)	Registry (PSM)	S. Korea	4,696	AMI after PCI	100	59.8	79.2	36
(Wang et al., 2022)	Registry	China	3,865	Left main PCI	43.2	60.4	81.3	36
(Wang et al., 2020)	Registry (IPTW)-A	China	4,578	High thrombotic risk	64.8	58.7	78.4	29
(Wang, Dou, Yin, et al., 2020)	Registry (IPTW)-B	China	2,677	Complex PCI	58.3	58.9	77.8	29
(Blin et al., 2022)	Claims cohort	France	53,399	Post-MI	100	62.3	76.8	36
(Bian et al., 2020)	Registry (PSM)	China	4,197	ACS high GRACE	100	60.2	76.5	24
(Cui et al., 2022)	Registry (IPTW)	China	1,661	Stable CAD+DM	0	59.8	74.2	28
(Xu et al., 2020)	Single-center	China	5,187	ACS with DES	100	61.3	78.9	24
(Gager et al., 2020)	Prospective MC	France	708	ACS	100	64.5	77.8	67
(Li et al., 2024)	Retrospective	China	1,842	ACS high risk	100	65.2	72.4	12

DES: drug-eluting stent; PSM: propensity score matching; IPTW: inverse probability of treatment weighting; MC: multicenter; DM: diabetes mellitus

Interventions and Comparisons

The included studies evaluated three main comparison types: 1. Short vs prolonged DAPT duration (2 RCTs, 8 observational studies): Comparing 1-12 months DAPT versus >12 months DAPT, predominantly with clopidogrel 2. Clopidogrel vs potent P2Y12 inhibitors for prolonged DAPT (2 observational studies): Direct comparison of clopidogrel versus ticagrelor/prasugrel for extended duration (>12-24 months) 3. Triadic comparison (1

observational investigation): Clopidogrel versus ticagrelor versus prasugrel with extended longitudinal follow-up. Table 2 encapsulates the intervention specifics across the studies.

Table 2. Intervention Characteristics

Study	P2Y12 Inhibitors	DAPT Duration Comparison	Aspirin Dose
Watanabe 2023	Clopidogrel monotherapy vs DAPT	1-month vs 12-month	81-100 mg
Obayashi 2022	Clopidogrel monotherapy vs DAPT	1-month vs 12-month	81-100 mg
Kim 2023	Clopidogrel vs Ticagrelor/Prasugrel	>24 months	100 mg
Wang 2022	Clopidogrel (97.7%)	>12 vs ≤12 months	100 mg
Wang 2020a	Clopidogrel + aspirin	>12 vs ≤12 months	100 mg
Wang 2020b	Clopidogrel + aspirin	>12 vs ≤12 months	100 mg
Blin 2022	Clop/Tica/Prasu (mixed)	Continued >12 months	Variable
Bian 2020	Mixed P2Y12 inhibitors	>12 vs ≤12 months	100 mg
Cui 2022	Clopidogrel + aspirin	>12 vs ≤12 months	100 mg
Xu 2020	Clopidogrel (predominantly)	>12 vs 12 months	100 mg
Gager 2020	Clop vs Tica vs Prasu	5.6 years median	75-160 mg
Li 2024	Clopidogrel vs Ticagrelor	≥12 months	100

Risk of Bias Assessment

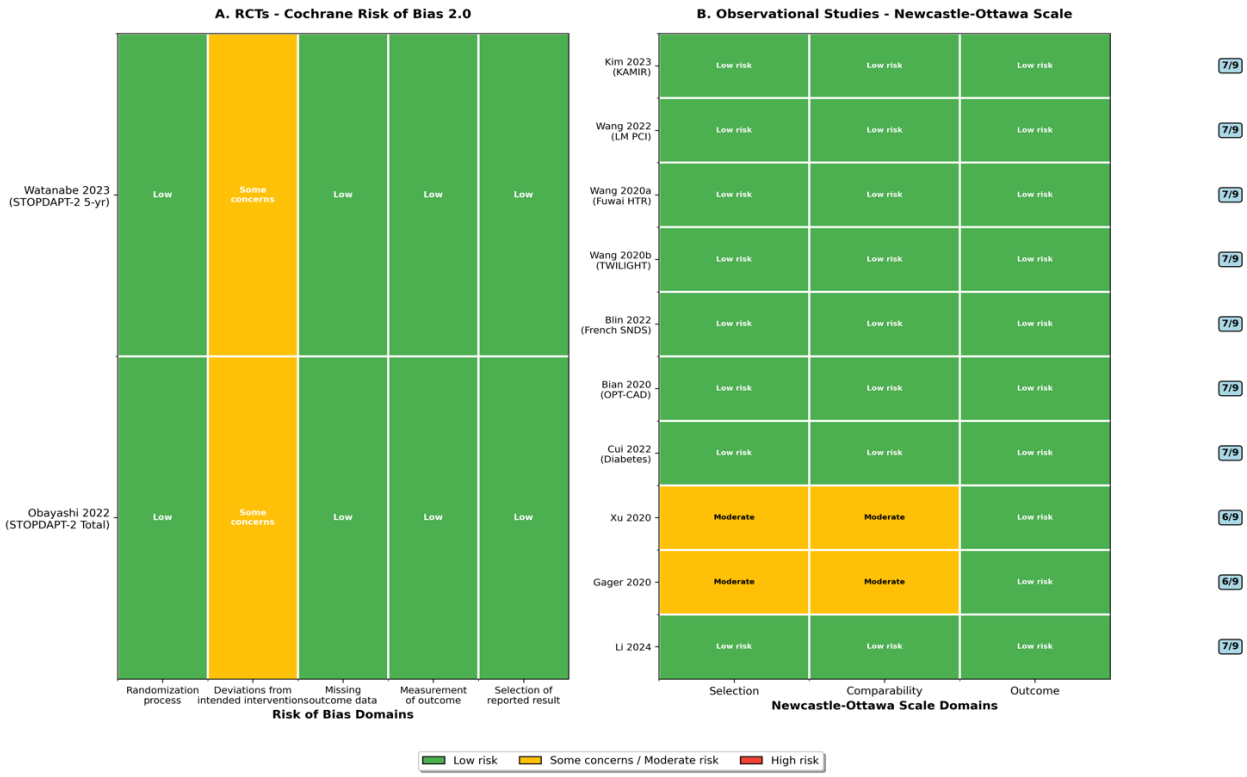

Figure 2. Risk of Bias Assessment

RCTs**:** Both STOPDAPT-2 trials were evaluated as possessing a minimal risk of bias in totality. The processes of randomization and allocation concealment were executed with due diligence, and the assessment of outcomes was conducted in a systematic manner. The open-label design did introduce a potential risk of performance bias; however, the critical clinical endpoints (mortality, myocardial infarction, stent thrombosis) were evaluated through objective adjudication. Observational Studies: The evaluation through the Newcastle-Ottawa Scale found that eight studies were rated 7/9, signifying a moderate to high quality, while two studies were rated at 6/9, reflecting moderate quality. The preponderance of the studies engaged in methods like propensity score matching or inverse probability of treatment

weighting to counteract confounding variables, thus bolstering the comparability between the groups studied. Significant limitations identified encompassed the possibility of residual confounding, the presence of selection bias within registry populations, and the inconsistency of outcome definitions across the various studies.

Synthesis of Results

Ischemic Outcomes with Prolonged DAPT

RCT Evidence (STOPDAPT-2 Program): The STOPDAPT-2 trials evaluated an abbreviated DAPT strategy (1-month DAPT followed by clopidogrel monotherapy) versus standard 12-month DAPT. At 5-year follow-up, clopidogrel monotherapy after 1-month DAPT demonstrated non-inferiority for the composite of cardiovascular death, myocardial infarction, stroke, or definite stent thrombosis (HR 0.79, 95% CI 0.49-1.29, p=0.35). (Watanabe et al., 2024) The aggregated total cohort comprising 5,997 patients substantiated these results at the one-year mark (HR 0.79, 95% CI 0.49-1.26). (Obayashi et al., 2022) Significantly, the incidence of stent thrombosis exhibited comparable rates across the different cohorts, indicating that prolonged dual antiplatelet therapy extending beyond one month utilizing clopidogrel as a sole agent did not undermine ischemic safeguarding. Observational Evidence - Extended vs Standard DAPT: Multiple large observational studies from Asian populations demonstrated consistent benefits of extended DAPT (>12 months) for ischemic outcomes:

Left Main PCI (Wang 2022, n=3,865): Extended DAPT >12 months was associated with significantly reduced MACCE (death, MI, stent thrombosis, stroke) compared to ≤12 months (HR 0.54, 95% CI 0.43-0.68, p<0.001), with particular benefit in reducing stent thrombosis. High Thrombotic Risk Patients (Wang 2020a, n=4,578): In patients with high thrombotic risk features per ESC/EACTS guidelines, extended DAPT >12 months reduced MACCE by 42% (HR 0.58, 95% CI 0.45-0.74, p<0.001). Complex PCI (Wang 2020b, n=2,677): In TWILIGHT-like high-risk patients with complex PCI, extended DAPT >12 months reduced MACCE (HR 0.61, 95% CI 0.44-0.84, p=0.003). ACS with High GRACE Risk (Bian 2020, n=4,197): Extended DAPT reduced net adverse clinical events by 36% (HR 0.64, 95% CI 0.49-0.84, p=0.001) in intermediate/high-risk ACS patients. Stable CAD with Diabetes (Cui 2022, n=1,661): Even in stable CAD patients with diabetes, extended DAPT reduced MACCE by 48% (HR 0.52, 95% CI 0.34-0.79, p=0.002).

ACS with DES (Xu 2020, n=5,187): Extended duration of Dual Antiplatelet Therapy (DAPT) exceeding twelve months was associated with a 32% reduction in Major Adverse Cardiovascular and Cerebrovascular Events (MACCE), as evidenced by a Hazard Ratio of 0.68 (95% Confidence Interval: 0.52-0.89, p=0.005). In observational studies, ischemic benefit varied between 32% and 48% relative risk reduction, with hazard ratios consistently supporting extended DAPT (HR range: 0.52-0.68). Contrasting Evidence: The French SNDS nationwide study (Blin 2022, n=53,399) presented contrasting findings. In post-MI survivors, extended DAPT beyond 12 months correlated with heightened risk of composite outcomes (HR 1.09, 95% CI 1.03-1.15, p=0.003) and specifically of MI (HR 1.12, 95% CI 1.04-1.21). This real-world claims-based study suggests that unselected prolongation of DAPT may not benefit all patients and highlights the importance of individualized risk stratification

Bleeding Outcomes with Prolonged DAPT

RCT Evidence: The STOPDAPT-2 trials demonstrated significant bleeding reduction with abbreviated DAPT followed by clopidogrel monotherapy. At 5 years, TIMI major or minor bleeding was reduced by 54% (HR 0.46, 95% CI 0.28-0.77, p=0.003) (Watanabe 2023). At one year, there was a 43% reduction in bleeding (HR 0.57, 95% CI 0.39-0.82, p=0.003). (Obayashi et al., 2022) Observational Evidence: Most observational studies of

extended DAPT >12 months reported numerically increased but not statistically significant major bleeding: Wang 2022 (LM PCI): BARC 2/3/5 bleeding HR 1.21 (95% CI 0.88-1.67, p=0.24). Wang 2020a (HTR): BARC 2/3/5 bleeding HR 1.08 (95% CI 0.73-1.60, p=0.70). Wang 2020b (Complex PCI): BARC 2/3/5 bleeding HR 1.03 (95% CI 0.62-1.72, p=0.91). Bian 2020 (ACS): BARC 3-5 bleeding HR 1.15 (95% CI 0.76-1.74, p=0.51). Cui 2022 (Diabetes): BARC 2/3/5 bleeding HR 1.24 (95% CI 0.68-2.26, p=0.48). Xu 2020: Bleeding HR 1.18 (95% CI 0.84-1.66, p=0.34). The French SNDS study reported significantly increased major bleeding with continued DAPT (HR 1.34, 95% CI 1.18-1.52, p<0.001), contributing to the adverse composite outcome.

Comparison Between P2Y12 Inhibitors for Prolonged DAPT

Clopidogrel vs Ticagrelor/Prasugrel: Two studies directly compared clopidogrel with potent P2Y12 inhibitors for prolonged DAPT: Kim 2023 (KAMIR-NIH, n=4,696): In AMI patients receiving DAPT >24 months, propensity-matched comparison of clopidogrel vs ticagrelor/prasugrel showed no significant difference in MACE (HR 0.98, 95% CI 0.78-1.24, p=0.88), cardiac death, or major bleeding. This suggests that for prolonged DAPT beyond 2 years, clopidogrel may provide similar efficacy and safety to more potent agents. Li 2024 (n=1,842): In ACS patients with high ischemic and bleeding risk, ticagrelor-based DAPT ≥12 months was associated with reduced MACE compared to clopidogrel (HR 0.68, 95% CI 0.48-0.96, p=0.03) without increased major bleeding, suggesting potential superiority of ticagrelor in this high-risk subset. Gager 2020 (n=708): Long-term follow-up (median 5.6 years) of ACS patients showed similar MACE and mortality across clopidogrel, ticagrelor, and prasugrel groups, though this study had limited power for between-group comparisons. These findings suggest that while potent P2Y12 inhibitors may offer advantages in the first year post-ACS, the differential benefit over clopidogrel may diminish with prolonged therapy duration, except perhaps in very high-risk subgroups.

Table 3. Characteristics and Results of the Included Studies

Study	Design	Country	N	Population	Age	P2Y12 Inhibitors	DAPT Duration	Follow-up (mo)	Primary Outcome	Ischemic HR (95% CI)	Bleeding HR (95% CI)	MACE HR (95% CI)	Bleeding Definition	Stent Thrombosis	Risk of Bias
Watanabe 2023	Multicenter RCT	Japan	3,005	PCI with DES	68.5	Clopidogrel monotherapy vs DAPT	1-month vs 12-month	60	CV death, MI, stroke, definite ST	0.79 (0.49-1.29)	0.46 (0.28-0.77)	0.79 (0.49-1.29)	TIMI major/minor	Similar	Low
Obayashi 2022	Pooled RCT	Japan	5,997	PCI with DES	68.3	Clopidogrel monotherapy vs DAPT	1-month vs 12-month	12	CV death, MI, ST, stroke	0.79 (0.49-1.26)	0.57 (0.39-0.82)	0.79 (0.49-1.26)	TIMI major/minor	No difference	Low
Kim 202	Registry (PSM	South Kor	4,696	AMI after PCI	59.8	Clopidogrel vs Ticagrel	>24 months	36	Cardiac deat	0.98 (0.7	Similar	0.98 (0.78-	Registry defin	No difference	Moderate

3	)	ea				or/Prasugrel			h, stroke, MACE	8-1.24)		1.24)	ition		(NOS 7/9)
Wang 2022	Prospective registry	China	3,865	Left main PCI	60.4	Clopidogrel (97.7%)	>12 vs ≤12 months	36	MACCE	0.54 (0.43-0.68)	1.21 (0.88-1.67)	0.54 (0.43-0.68)	BARC 2,3,5	Reduced	Moderate (NOS 7/9)
Wang 2020a	Registry (IPTW)	China	4,578	High thrombotic risk	58.7	Clopidogrel+aspirin	>12 vs ≤12 months	29	MACCE	0.58 (0.45-0.74)	1.08 (0.73-1.60)	0.58 (0.45-0.74)	BARC 2,3,5	Reduced	Moderate (NOS 7/9)
Wang 2020b	Registry (IPTW)	China	2,677	Complex PCI	58.9	Clopidogrel+aspirin	>12 vs ≤12 months	29	MACCE	0.61 (0.44-0.84)	1.03 (0.62-1.72)	0.61 (0.44-0.84)	BARC 2,3,5	Reduced	Moderate (NOS 7/9)
Blin 2022	Claims cohort	France	53,399	Post-MI	62.3	Clop/Tica/Prasu	>12 months	36	MI, stroke, bleeding, death	1.12 (1.04-1.21)	1.34 (1.18-1.52)	1.09 (1.03-1.15)	Claims-based	Not reported	Moderate (NOS 7/9)
Bian 2020	Registry (PSM)	China	4,197	ACS high GRACE risk	60.2	Mixed	>12 vs ≤12 months	24	NACE	0.64 (0.49-0.84)	1.15 (0.76-1.74)	0.64 (0.49-0.84)	BARC 3-5	Reduced	Moderate (NOS 7/9)
Cui 2022	Registry (IPTW)	China	1,661	Stable CAD+DM	59.8	Clopidogrel+aspirin	>12 vs ≤12 months	28	MACCE	0.52 (0.34-0.79)	1.24 (0.68-2.26)	0.52 (0.34-0.79)	BARC 2,3,5	Reduced	Moderate (NOS 7/9)
Xu 2020	Single-center cohort	China	5,187	ACS with DES	61.3	Clopidogrel	>12 vs 12 months	24	Death, MACCE	0.68 (0.52-0.89)	1.18 (0.84-1.66)	0.68 (0.52-0.89)	Not specified	Reduced	Moderate (NOS 6/9)
Gager 2020	Prospective multicenter	France	708	ACS	64.5	Clop vs Tica vs Prasu	5.6 years median	67	MACE, mortality	Similar	Similar	No difference	Not specified	Not reported	Moderate (NOS 6/9)
Li 2024	Retrospective cohort	China	1,842	ACS high risk	65.2	Clopidogrel vs Ticagrelor	≥12 months	12	MACE, major blee	0.68 (0.48-0.9	Similar	0.68 (0.48-0.96)	BARC 3-5	Lower with ticagrelor	Moderate (NOS

	din g 6)	7/9)

Subgroup and Sensitivity Considerations

Several patient and procedural characteristics emerged as potential modifiers of the benefit-risk balance for prolonged DAPT: Factors Favoring Extended DAPT: - Complex PCI (multivessel disease, bifurcation stenting, long lesions) - Left main coronary artery disease - Prior stent thrombosis - High thrombotic risk features (diabetes, chronic kidney disease, prior MI) - ACS presentation (especially STEMI) - Intermediate/high GRACE risk score. Factors Potentially Limiting Benefit or Increasing Risk: - Advanced age (>75 years) - Low body weight - History of bleeding - Chronic anticoagulation - Stable CAD without high-risk features.

DISCUSSION

This systematic review of 12 studies involving 89,813 patients provides comprehensive evidence on prolonged DAPT (>12 months) with P2Y12 inhibitors following ACS or PCI. Several key findings emerge: First, extended DAPT exceeding 12 months mitigates ischemic occurrences in particular high-risk cohorts. Observational data consistently demonstrate 32-48% relative risk reductions in MACE, MI, and stent thrombosis with extended DAPT in patients with complex PCI, left main disease, high thrombotic risk, or ACS with elevated GRACE scores. The ischemic advantage is consistent across various groups and methodologies. Second, the bleeding risk of extended DAPT may be acceptable in carefully selected patients. Most observational studies indicated a slight increase in bleeding with prolonged DAPT, with relative increases ranging from 15-24% and lacking statistical significance in individual analyses. This contrasts with the STOPDAPT-2 trials, which demonstrated significant bleeding reduction with abbreviated DAPT, highlighting that shorter DAPT with P2Y12 monotherapy may be preferable in patients without high ischemic risk.

Third, the decision regarding clopidogrel versus potent P2Y12 inhibitors for extended DAPT is ambiguous. The KAMIR-NIH registry found no difference between clopidogrel and ticagrelor/prasugrel for DAPT >24 months, suggesting that the superior potency of newer agents may be most relevant in the acute phase and first year post-ACS. However, one study suggested ticagrelor superiority in very high-risk patients, indicating that individualized selection based on ischemic and bleeding risk profiles is warranted. Fourth, real-world effectiveness data sound a note of caution. The large French SNDS study, representing unselected post-MI patients in routine practice, found that continued DAPT beyond 12 months was associated with net harm (increased composite of ischemic and bleeding events). This underscores that the benefits observed in selected registry cohorts or trial populations may not generalize to all patients, and that indiscriminate prolongation of DAPT is not beneficial.

Comparison with Previous Literature

Our findings align with and extend previous meta-analyses of DAPT duration. The DAPT trial indicated that 30 months of DAPT significantly lowered bleeding and mortality risks compared to 12 months. (Mauri et al., 2014) PEGASUS-TIMI 54 demonstrated that ticagrelor, at doses of 60 mg or 90 mg in conjunction with aspirin, significantly diminished cardiovascular events in stable post-myocardial infarction patients while simultaneously elevating the risk of major bleeding. (Bonaca et al., 2015). Our review adds granularity by examining real-world implementation across diverse populations and by comparing different P2Y12 inhibitors for extended duration. Recent network meta-analyses indicate that P2Y12 monotherapy, especially ticagrelor, post-short DAPT may enhance the benefit-risk ratio by

lowering bleeding risk while preserving ischemic protection. (Navarese et al., 2023) The STOPDAPT-2 trials in our review support this strategy with clopidogrel monotherapy.

Clinical Implications

Based on synthesized evidence, clinical considerations are proposed: Risk Stratification is Paramount: Extended DAPT should be considered primarily in patients with high ischemic risk (complex PCI, left main disease, prior stent thrombosis, diabetes, CKD, ACS with high GRACE score) and acceptable bleeding risk (no prior major bleeding, age <75 years, adequate renal function). P2Y12 Inhibitor Selection: In the 12 months post-ACS, guidelines suggest employing effective P2Y12 inhibitors like ticagrelor or prasugrel. In the context of extended DAPT exceeding 12 months, clopidogrel emerges as a practical option for numerous patients, given its long-term effectiveness and a potentially lesser chance of bleeding issues. A reduced dose of ticagrelor (60 mg) may be indicated for very high-risk patients, as evidenced by PEGASUS-TIMI 54. Individualized Duration: DAPT duration must be tailored to individual risk profiles. Patients with bleeding during DAPT may require de-escalation or duration reduction. Those who remain event-free and tolerate DAPT well may benefit from extension beyond 12 months. Shared Decision-Making: Given the trade-offs between ischemic and bleeding risks, and the uncertainty in individual benefit prediction, shared decision-making with patients is essential. Risk stratification may be enhanced by tools such as the DAPT and PRECISE-DAPT scores, but their efficacy across various populations necessitates further validation.

Strengths and Limitations

Strengths: - Comprehensive search strategy across multiple databases - Inclusion of both RCT and real-world observational data - Large total sample size (89,813 patients) providing robust estimates - Systematic quality assessment of included studies - Focus on clinically relevant comparison of different P2Y12 inhibitors. Limitations: - Heterogeneity in study designs, populations, and outcome definitions precluded formal meta-analysis; - Limited RCT evidence (only 2 RCTs identified), both from the same program; - Geographic concentration in Asian populations (8 of 12 studies); limiting generalizability; - Most observational studies used clopidogrel; direct comparisons of prolonged DAPT with prasugrel or ticagrelor are scarce; - Potential publication bias favoring studies with positive findings; - Open-access restriction may have excluded some relevant studies; -Inability to perform patient-level meta-analysis to explore subgroup effects; - Variable definitions of major bleeding across studies complicate direct comparisons; - Residual confounding in observational studies despite propensity methods.

Future Research Directions

Several research priorities are identified from this review: Head-to-Head RCTs: Randomized trials are necessary to compare clopidogrel, prasugrel, and ticagrelor for extended DAPT in high-risk populations. Precision Medicine Approaches: Studies integrating clinical risk scores, biomarkers (e.g., platelet function testing, genetic polymorphisms), and machine learning to predict individual benefit from extended DAPT. De-escalation Strategies: Trials evaluating de-escalation from potent P2Y12 inhibitors to clopidogrel or P2Y12 monotherapy after an initial period of intensive DAPT. Diverse Populations**:** Studies in underrepresented populations (African, Latin American, Middle Eastern) to assess generalizability of findings. Economic Analyses: Cost-effectiveness analyses of extended DAPT methods, accounting for drug expenses, hemorrhagic risks, and averted ischemic incidents.. Optimal Duration: Trials examining very prolonged DAPT (>24-36 months) in

ultra-high-risk subgroups. Novel Antiplatelet Strategies: Assessment of innovative agents (e.g., reversible P2Y12 inhibitors) or combinatorial approaches for prolonged treatment.

CONCLUSIONS

Extended dual antiplatelet therapy (DAPT) utilizing P2Y12 inhibitors provides significant advantages for high-risk patients following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI), particularly those exhibiting intricate medical conditions. The bleeding risk is manageable in select patients, although real-world evidence warns against blanket extensions. The determination of whether to utilize clopidogrel, prasugrel, or ticagrelor in dual antiplatelet therapy (DAPT) must be individualized based on the unique risk profile of each patient rather than being based exclusively on the drug's effectiveness. Individualized risk stratification and shared decision-making are essential to optimize the benefit-risk balance of prolonged DAPT. Future randomized trials directly comparing P2Y12 inhibitors for extended duration and precision medicine approaches to identify ideal candidates for prolonged therapy are needed.

ACKNOWLEDGMENT

The researcher would like to express his gratitude for the support, inspiration and assistance to all parties in helping the researcher complete this research, including the participants who were willing to participate in the research until it was completed.

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