Antiplatelet Therapy and Percutaneous Coronary Interventions

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Abstract: Dual antiplatelet therapy is one of the cornerstones of modern percutaneous coronary interventions. The development of new therapeutic agents has significantly reduced ischemic events at the risk of increased bleeding complications. Therefore, efforts are currently focused on optimizing therapeutic algorithms to obtain the greatest anti-thrombotic benefit associated with the lowest risk of bleeding, that is, the greater net clinical benefit.

A significant number of trials evaluating different drug combinations or adjustments in treatment duration have been completed. However, clinical translation of these results is often difficult due to the heterogeneity of the therapeutic approaches.

The aim of this manuscript is to provide an updated review of the literature regarding the use of dual antiplatelet therapy in patients undergoing coronary angioplasty and stenting.

Keywords: Antiplatelet therapy, percutaneous coronary interventions, thrombosis, angioplasty, clopidogrel, prasugrel, ticagrelor.

1. INTRODUCTION

During the last decades, the development of new antiplatelet agents has been key to the evolution of coronary interventions [1]. Dual antiplatelet therapy (DAPT) has been established as the standard therapy after coronary angioplasty in patients with both stable coronary disease and acute coronary syndromes [2]. In addition, indications have expanded into other scenarios, such as percutaneous valve interventions [3] and peripheral vascular disease [4].

The use of aspirin plus another antiplatelet drug after coronary stenting is crucial to reduce the risk of stent thrombosis and myocardial infarction after the procedure. Apart from clopidogrel, the development of new therapeutic agents has significantly reduced the rate of new ischemic events, albeit to a higher risk of bleeding complications. Therefore, efforts are currently focused on optimizing therapeutic algorithms to obtain the greatest anti-thrombotic benefit associated with the lowest risk of bleeding, that is, the largest net clinical effect.

Recently, a vast amount of new evidence has helped to shed light on the best therapeutic options available, by means of adjusting different drug combinations or treatment duration. However, the translation of this new information into clinical practice has been difficult due to the multiplicity of clinical scenarios and available treatment regimens.

This manuscript aims to be an updated review of the literature regarding the different alternatives for antiplatelet therapy in patients undergoing coronary angioplasty, with special emphasis on treatment modifications according to the individual bleeding risk profile, in order to inform real world practice.

2. METHODS

2.1. Literature Search

We conducted a full search of meta-analyses, randomized controlled trials and previous literature (including society guidelines) examining antiplatelet therapy for any outcome in patients undergoing percutaneous coronary intervention. Medline, Pubmed and Embase databases were searched until December 2019. Two researchers screened titles and abstracts of articles for full-text review independently.

2.2. Manuscript Development

After data extraction, two researchers chose the most relevant articles and were in charge of elaborating the initial text, which was then sent to every author for further evaluation. If there were any discrepancies on a specific subject, the topic was re-analyzed and a consensus was achieved. The
3. EVOLUTION OF DUAL ANTIPLATELET THERAPY

The use of Aspirin plus a P2Y12 receptor inhibitor is one of the cornerstones of post-percutaneous coronary intervention (PCI) management [5, 6] and, indeed, one of the most studied strategies in modern Cardiology, with more than 40 randomized clinical trials including over 250,000 patients.

Aspirin binds irreversibly and inactivates platelet cyclooxygenase, thus blocking the production of Thromboxane A2 [7], which is responsible for platelet activation and vasocostriction. During the 1990s, trials such as ISAAR [8] (1996), MATTIS [9] (1998) and STAR [10] (1998) provided firm evidence on the benefit of Aspirin in reducing acute stent thrombosis rates. Currently, its role in secondary prevention is clear, being a class IA indication in both the European Society of Cardiology (ESC) [11] guidelines as well as the American Heart Association / American College of Cardiology (AHA / ACC) guidelines [12].

Clopidogrel is a P2Y12 inhibitor in the form of a prodrug [13], that must undergo metabolic steps before exerting its antiplatelet effect [14]. The active metabolite binds irreversibly and antagonizes P2Y12 throughout platelet life [15]. The CURE [16] study, in patients with acute coronary syndrome (ACS) without ST elevation, showed that adding Clopidogrel to Aspirin reduced major cardiovascular events (MACE) by 20%. Subsequently, PCI CURE [17] and CREDO [18] confirmed that in patients undergoing PCI, prolonged therapy with Clopidogrel (loading dose of 300 mg orally followed by 75 mg / day) for up to 12 months, reduced thrombotic events by 25%.

Despite the proven benefits of this therapeutic combination, there were still limitations in its use, such as a significant 5 to 10% new event rate during the first month after ACS or the high prevalence of patients with Clopidogrel resistance [19]. This led to the development of new and more potent antiplatelet agents.

Prasugrel is another thienopyridine approved for use in patients with unstable angina or myocardial infarction undergoing coronary angioplasty [20]. Compared to Clopidogrel, the TRITON TIMI 38 [21] trial showed a reduction in ischemic events at the expense of an increase in major and fatal bleeding. Prasugrel was especially beneficial in some subgroups, such as diabetic patients, those with STEMI and recurrent cardiovascular events. Conversely, there was no net benefit in patients with previous stroke, older than 75 years of age or weighing less than 60 kg. Moreover, the ACCOAST study [22, 23] showed that, in patients with ACS, Prasugrel can be administered safely and with less risk of bleeding once the coronary anatomy has been defined by angiography, which may be an advantage over the usual strategy of Clopidogrel pre-loading. Finally, in patients with medically managed ACS, Prasugrel has not shown to be superior to Clopidogrel [24].

Ticagrelor is a cyclopentyl-triazolo-pyrimidine which produces a non-competitive, reversible antagonism of P2Y12 [25]. Since the ingested molecule is active (hence, not a prodrug), a faster and more potent effect is achieved. In patients with ACS, the PLATO [26] study showed the superiority of Ticagrelor over Clopidogrel in terms of cardiovascular death, myocardial infarction (MI) or stroke (9.8% vs. 11.7%, p <0.001), at the expense of a higher bleeding rate. Up to 18% of patients may experience dyspnea [27], 2% bradycardia [28] and it should be taken twice daily, which could explain the higher discontinuation rates (32% observed in the PEGASUS [29] trial).

Recently, the ISAR REACT 5 trial [30] compared Prasugrel with Ticagrelor in patients with ACS undergoing PCI. The primary outcome of death, MI and stroke at 1 year occurred in 9.3% in the Ticagrelor group and 6.9% in the Prasugrel group (HR 1.36; 95% CI 1.09 to 1.70; p 0.006). There were no differences in the rates of major bleeding by BARC scale (5.4% in the Ticagrelor group vs. 4.8% in the Prasugrel group, HR 1.12; 95% CI 0.83 - 1.51; p 0.46).

Cangrelor is an intravenous P2Y12 inhibitor with a short half-life (3 to 6 minutes) [31], providing a very rapid onset / offset profile. Based on the CHAMPION [32], CHAMPION PLATFORM [33] and CHAMPION PHOENIX [34] trials, the current indication for Cangrelor is restricted to patients undergoing PCI who have not previously received a P2Y12 inhibitor and will not be given an IIB / IIa inhibitor. However, this drug could be useful as a “bridge” in patients who require surgery early after PCI [35] or an ACS. Table 1 describes the pharmacokinetic and pharmacodynamic characteristics of the different antiplatelet agents.

4. STANDARD APPROACH OF DUAL ANTIPLATELET THERAPY AFTER A PERCUTANEOUS CORONARY INTERVENTION

Current clinical practice guidelines support the use of DAPT in patients undergoing PCI. For patients with ACS undergoing PCI, the recommendation of the European guidelines is the use of Aspirin + a high potency P2Y12 inhibitor (Prasugrel or Ticagrelor) for at least 12 months (Recommendation IA). The use of Clopidogrel should only be considered if the aforementioned drugs are either not available or contraindicated. The duration of DAPT could be shortened to 6 months in patients with a high bleeding risk (Recommendation IIa B).

In the case of stable coronary disease, the first line of treatment is Aspirin + Clopidogrel for at least 6 months (Recommendation I A). In cases considered high bleeding risk (e.g.: PRECISE DAPT ≥ 25), this can be shortened to 3 months (Recommendation IIa B) or even, in exceptional cases, down to 1 month (Recommendation IIb C).

5. EVALUATION OF NET CLINICAL BENEFIT

The main drawback of DAPT is the increased risk of bleeding complications [36]. In the PLATO study, the risk of major bleeding by TIMI criteria with Clopidogrel and Ticagrelor was 7.9% and 7.7%, respectively. In TRITON TIMI 38, the risk of major bleeding with Prasugrel was 4.3%, particularly in low-weight patients and with a prior history of stroke. In addition, hemorrhagic events often force antiplatelet therapy withdrawal, thereby increasing the risk of ischemic events or stent thrombosis (ST). For example, in
Table 1. Comparison of P2Y12 inhibitors.

| Drug       | Binding to P2Y12 Receptor | Mean PAI | Maximum PAI | Time to Maximum PAI | Metabolization Required for Effect | Duration of Effect | Administration |
|------------|---------------------------|----------|-------------|---------------------|------------------------------------|--------------------|----------------|
| Clopidogrel | Irreversible              | 40-62%   | 50%         | 4-8 hrs             | Yes, Activation by P450 in 2 steps | 5-7 days           | Oral. Once daily |
| Prasugrel  | Irreversible              | 70%      | 75-80%      | 2-4 hrs             | Yes. Activation by P450 in 1 step  | 5-7 days           | Oral. Once daily |
| Ticagrelor | Reversible                | 80-90%   | 80-88%      | 2-4 hrs             | No                                 | 3-5 days           | Oral. Twice a day |
| Cangrelor  | Reversible                | 95-100%  | 95-100%     | 2 min               | No                                 | 60-90 min          | IV infusion     |

Abbreviation: PAI: Platelet aggregation inhibition.

Table 2. BARC bleeding score.

| BARC 0 | No bleeding |
|--------|-------------|
| BARC 1 | Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional. |
| BARC 2 | Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:  
- Requiring non-surgical, medical intervention by a health-care professional,  
- Leading to hospitalization or increased level of care, or  
- Prompting evaluation |
| BARC 3 | Type 3a:  
- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed),  
- Any transfusion with overt bleeding.  
Type 3b:  
- Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed),  
- Cardiac tamponade,  
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),  
- Bleeding requiring intravenous vasoactive agents.  
Type 3c:  
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal),  
- Subcategories confirmed by autopsy or imaging or lumbar puncture,  
- Intraocular bleed compromising vision. |
| BARC 4 | CABG-related bleeding,  
- Perioperative intracranial bleeding within 48 h,  
- Reoperation after closure of sternotomy for the purpose of controlling bleeding,  
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period,  
- Chest tube output more than or equal to 2L within a 24-h period. |
| BARC 5 | Fatal bleeding:  
- Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious  
- Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation |

When facing a patient in need of DAPT after coronary angioplasty, it is therefore essential to optimize the therapy in terms of drug potency and treatment duration to obtain the maximum anti-thrombotic benefit along with the least bleeding risk. Accordingly, those patients more prone to have bleeding complications should be recognized. The recent consensus document by the Academic Research Consortium [38] defines the high-risk patient as one with a risk of a BARC 3-5 bleeding ≥ 4% / year or risk of intracranial hemorrhage ≥ 1% / year (Table 2). Major and minor criteria for bleeding risk were established, defining patients with 1 major criterion or 2 minor criteria as high risk (Table 3).
The PRECISE DAPT [41] score was derived from a trial including 14,963 patients with stable coronary disease undergoing elective or emergency PCI. It includes 5 items for the prediction of bleeding after hospitalization. High-risk patients (≥ 25 pts) showed no benefit in ischemic complications and an excess of bleeding complications (NNH 38) by prolonging therapy, whereas patients with low or moderate risk (< 25 pts) significantly reduced the rates of stent thrombosis, stroke and revascularization of the culprit vessel (NNT 65), with no increase in bleeding events. Therefore, high-risk patients could receive abbreviated therapy (<12 months), while in low-risk patients either a standard (12 months) or prolonged duration therapy (> 12 months) are reasonable options (Table 4).

Both scores are validated and must be associated with other clinical elements (fragility, socio-economic condition, adherence to therapy, etc.) to balance the risk / benefit in prolonging or reducing the duration of DAPT. However, it seems that these tools are under-utilized in routine clinical practice. For example, in a Latin-American registry [42] with 227 patients receiving DAPT post angioplasty at an university hospital, it was observed that the duration of therapy was neither associated with the DAPT or PRECISE-DAPT risk scores, nor with the clinical presentation of patients (ACS or stable coronary disease). This resulted in a bleeding rate of 13.6% (2.2% major bleeding) at an average follow-up of 24 months. Another interesting element was that the PRECISE-DAPT score adequately predicted the occurrence of hemorrhagic events, although the cut-off point for predicting bleeding in this Latin American cohort was somewhat lower compared to what has been published internationally (18 points vs. 25 points).

6. MODIFICATIONS ON THE DURATION OF THERAPY

6.1. Prolongation of Dual Antiplatelet Therapy

Since a constant rate of new events is observed during late follow-up of patients undergoing PCI, prolonging DAPT duration for over 12 months in order to reduce these complications has been recommended. Several meta-analysis [43, 44] agreed that there is a significant reduction in the rates of MI and stent thrombosis, at an expense of increased rates of bleeding by prolonging DAPT beyond 12 months.

Canadian guidelines for antiplatelet therapy [45] suggest that it is reasonable to extend the therapy > 1 year in patients at low risk of bleeding and who have clinical or angiographic elements of high thrombotic risk. These risk features can be summarized as follows [46-49]:

Clinical factors:
- Active smoking.
- Previous stent thrombosis.
- Chronic kidney disease with Creatinine clearance <60 ml / min.
- Diabetes Mellitus.
- Previous MI history.

Additionally, several scores have been developed to guide therapy duration. One is the DAPT score [39], derived from 11,648 patients enrolled in the DAPT trial and subsequently validated in the 8,136 patients of the PROTECT [40] trial. This score seeks to define those patients who would benefit from prolonging DAPT beyond 12 months. It includes 9 items to which a score is awarded ranging from -2 to 10 pts. Within the DAPT study, those patients with high ischemic risk (≥ 2 pts) in whom dual therapy was prolonged up to 30 months, showed a reduction in MI + stent thrombosis + MACE (NNT 34) with only a moderate increase in the risk of bleeding (NNH 272). In contrast, patients with < 2 points did not benefit from prolonged dual therapy and showed an increase in moderate / major bleeding (NNH 64). Thus, based upon these results, in those patients with DAPT score ≥ 2, it has been suggested to prolong DAPT beyond the usually recommended 12 months.

### Table 3. Major and minor criteria for bleeding risk by the Academic Research Consortium definition.

| Major                                                                 | Minor                              |
|----------------------------------------------------------------------|-----------------------------------|
| Anticipated use of long-term oral anticoagulation                    | Age ≥75 y                         |
| Severe or end-stage CKD (eGFR <30 mL/min)                            | Moderate CKD (eGFR 30–59 mL/min)  |
| Hemoglobin <11 g/dL                                                  | Hemoglobin 11–12.9 g/dL for men   |
|                                                                  | and 11–11.9 g/dL for women         |
| Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent | Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion |
| Moderate or severe baseline thrombocytopenia (platelet count <100 \times 10^{9}/L) | Long-term use of oral NSAIDs or steroids |
| Chronic bleeding diathesis                                           | Any ischemic stroke at any time not meeting the major criterion |
| Liver cirrhosis with portal hypertension                             |                                    |
| Previous spontaneous ICH (at any time)                              |                                    |
| Previous traumatic ICH within the past 12 mo                        |                                    |
| Presence of an arteriovenous brain malformation                      |                                    |
| Moderate or severe ischemic stroke within the past 6 months          |                                    |
| Non-deferrable major surgery on DAPT                                 |                                    |
| Recent major surgery or major trauma within 30 days before PCI       |                                    |

**Abbreviations:** CKD: Chronic kidney disease, ICH: Intracranial hemorrhage, NSAID: Non-steroidal anti-inflammatory drugs.
Table 4. Risk scores for DAPT duration.

| Time of application | DAPT duration strategy | Score range | Results | Online calculator |
|---------------------|------------------------|-------------|---------|------------------|
| At the time of coronary stenting | Short DAPT (3-6 months) vs Standard/Extended DAPT (12-24 months) | 0 to 100 pts | Score ≥ 25 pts = Short DAPT | www.precisedaptscore.com |
| After 12 months of DAPT without complications | Standard DAPT (12 months) vs Extended DAPT (30 months) | -2 to 10 pts | Score < 2 pts = Extended DAPT | www.daptsudy.org |

Angiographic factors:
- Multiple stents (≥ 3 implanted stents, ≥ 3 treated lesions) or use of bioabsorbable scaffolds.
- Long lesions (> 60 mm total stent length).
- Complex lesions (chronic occlusions, bifurcations).
- PCI of the left main or proximal anterior descending artery.
- Multivessel PCI.

In the DAPT trial [50], 9,961 patients undergoing coronary angioplasty (43% due to ACS) with no bleeding events during the first year were randomized to receive either Clopidogrel or Prasugrel associated with Aspirin for 12 or 30 months. Continued therapy with a Thienopyridine significantly reduced the rates of stent thrombosis (0.4% vs. 1.4%; HR 0.29; p <0.001) and MACE + cerebrovascular events (4.3% vs. 5.9%; HR 0.71; p <0.001). However, death from any cause was 2.0% in the group that continued treatment with Thienopyridine and 1.5% in the 12-months group (HR 1.36; 95% CI, 1.00-1.85; p = 0.05). Similarly, the rate of moderate or severe bleeding increased with prolonged therapy with Thienopyridines (2.5% vs. 1.6%; p <0.001).

The PEGASUS TIMI 54 [29] trial evaluated 2,162 patients with a previous history of MI between 1 to 3 years before inclusion. Patients were randomized to receive prolonged dual therapy (mean 33 months) with Ticagrelor 90 mg every 12 hrs, Ticagrelor 60 mg every 12 hrs or placebo. Both doses of Ticagrelor reduced the primary outcome of cardiovascular death, MI or stroke (Ticagrelor 90 mg vs. placebo: HR 0.85; p = 0.008; Ticagrelor 60 mg vs. placebo: HR 0.84; p = 0.004). There was a consistent reduction in all components of the primary outcome with Ticagrelor, being significant for MI with both doses and for stroke with the lower dose. There was also a trend towards a reduction in cardiovascular mortality. In contrast, TIMI major bleeding was observed more frequently with Ticagrelor (2.6% with 90 mg and 2.3% with 60 mg) than with placebo (1.06%) (p <0.001 for each dose versus placebo). Thus, prolonged therapy with Ticagrelor 60 mg translates into a reduction of 42 ischemic events per year, but at the expense of 31 TIMI major bleeding events during the same period, every 10,000 patients treated. The ESC guidelines of antiplatelet therapy [51] give a class IIb recommendation for the use of Ticagrelor 60 mg every 12 hrs (over Clopidogrel or Prasugrel) for over 12 months and in addition to Aspirin, in patients with MI and high ischemic risk.

6.2. Shortening of the Duration of Dual Therapy

Similarly, many trials have also investigated the strategy of shortening DAPT duration [52], seeking to maintain the benefits of preventing ischemic events, while keeping bleeding complications low. The benefits of this strategy are governed by each patient’s ischemic/bleeding risk profile. A meta-analysis of 6 studies [53] comparing 6 vs 12 months of DAPT after coronary angioplasty showed that in patients ≥ 65 years old, a shortened treatment resulted in reduced bleeding rates over 1 year (0.5% vs. 1.1%; HR 0.46; p = 0.02), without increasing the rate of ischemic events (2.4% vs. 3.0%; HR 0.84; p = 0.28). In contrast, the group < 65 years had no benefit in terms of bleeding (0.3% vs. 0.5%; p = 0.21), but their rate of ischemic events was significantly increased (2.4% vs. 1.4%; RH 1.67; p = 0.0082) with the short-term treatment.

Specifically in acute coronary syndromes, the SMART-DATE [54] trial randomized 2,712 patients to receive DAPT
for 6 vs. 12 months. The primary outcome of death from any cause, stroke and MI was similar in both groups (4.7% in the 6-month group vs. 4.2% in the 12-month group; p = 0.03 for non-inferiority) and the rate of bleeding BARC 2-5 was numerically lower in the shortened DAPT group, although not statistically significant (2.7% vs. 3.9%; HR 0.69; 95% CI 0.45–1.05; p = 0.09). Despite this, the rate of MI was significantly higher in the 6-month group (1.8% vs. 0.8%; p = 0.02), which led the authors to conclude that DAPT for 12 months should be maintained as the standard in patients undergoing PCI in the acute setting.

A different result was reported by Kedhi et al. in the DAPT STEMI trial. In this study, 100 STEMI patients were randomized to 6-month vs. 12-month DAPT. Clopidogrel was used only in 42% of the patients and a Zotarolimus-eluting stent was preferred. At 18 months, the outcome of death from any cause + MI + stroke + revascularization + major bleeding was similar in both groups (4.8% in the 6-month vs. 6.6% in the 12-month group; 95% CI 0.41 - 1.27; p = 0.26). There was no difference in any of the individual outcomes, including MI (1.8% in both groups; p = 0.97).

Two recent trials originated in Asia have moved the field towards shorter duration regimens. SMART CHOICE was a Korean trial including 2,993 patients (58.2% with acute coronary syndrome) undergoing PCI and compared 3 months of DAPT followed by 9 months of monotherapy with a P2Y12 inhibitor vs. 12 months of DAPT. At 12 months, monotherapy resulted in non-inferior rates of the primary outcome that included CV death, MI and stroke (2.9% vs. 2.5%; p = 0.07 for non-inferiority). Also, there were no significant differences when the components of the primary outcome were analyzed individually. However, monotherapy did manage to significantly reduce bleeding rates (2.0% vs. 3.4%; p = 0.02). Unfortunately, due to the poor treatment adherence in this population (Only 79.3% in the monotherapy group), data interpretation is limited.

Similarly, the STOPDAPT trial randomized 3,045 (38% with acute coronary syndrome) Japanese patients undergoing PCI with a Chromium-Cobalt Everolimus-eluting stent to receive 1 month DAPT with Aspirin + Clopidogrel followed by monotherapy with Clopidogrel vs. 12 months of standard DAPT. 1-month DAPT was superior to the prolonged treatment regarding the primary outcome of cardiovascular death, MI, ischemic or hemorrhagic stroke, stent thrombosis and major/minor bleeding at 12 months (2.3% vs. 3.7%; HR 0.64; 95% CI 0.42-0.98; p = 0.04 for superiority). Moreover, the shortened therapy group also showed superiority in terms of bleeding rates (0.41% vs. 1.54%; HR 0.26; 95% CI 0.11-0.64; p = 0.004 for superiority). In addition to being one of the studies showing the most favorable results towards the shortened DAPT strategy, STOPDAPT highlighted the importance of the type of drug-eluting stent implanted in order to shorten the therapy.

7. STRATEGIES FOR PATIENTS WITH HIGH BLEEDING RISK

Continuing advancements in drug eluting stent (DES) technology, with increasingly thinner struts and more bio-compatible polymers that reduce their thrombogenicity [58,59], have facilitated further attempts to reduce treatment duration after stent implantation.

Four randomized trials compared the use of DES vs. bare metal stents (BMS) in patients considered to be at high risk of bleeding using abbreviated DAPT. The first was the LEADERS FREE trial, which randomized 2,466 high-bleeding risk patients being prescribed DAPT for 1 month to receive either a BMS or a polymer-free Biolimus A9 eluting stent (BioFreedom, Biosensors). The drug eluting stent was superior by significantly reducing the combined primary outcome of CV death, MI and stent thrombosis (9.4% vs. 12.9%; HR 0.71; 95% CI 0.56 - 0.91, p = 0.005), with no differences in bleeding rates.

Similarly, a substudy of the ZEUS trial showed the safety and superiority of a zotarolimus-releasing stent vs. BMS in a 1 month DAPT strategy. The DES reduced the primary outcome of death, MI and revascularization of the culprit vessel (22.6% vs. 29%; HR 0.75; 95% CI 0.57-0.98; p = 0.033). BARC 2-5 bleeding rates were comparable (6.1% vs. 9.4%; p = 0.089).

Looking into an elderly population, the SENIOR trial evaluated 1,200 patients older than 75 years and randomized them to receive a BMS or a Sirolimus-eluting stent with resorbable polymer, both with a shortened DAPT strategy (1 month for patients with stable presentation and 6 months for those with unstable presentation). At 1 year, the DES group significantly reduced the combined primary outcome of death from any cause, MI, ischemic stroke or ischemia-guided revascularization (12% vs. 16%, p = 0.02). No differences in bleeding complications or stent thrombosis were recorded.

More recently, ONYX ONE included 1,996 patients at high bleeding risk receiving 1-month DAPT, who were randomized to a permanent polymer Zotarolimus eluting stent (OnyxTM, Medtronic) vs a polymer free Biolimus A9 eluting stent (BioFreedom, Biosensors). Platforms were comparable, with a combined primary endpoint of CV death, MI and stent thrombosis at 1 year of 17.1% for Onyx and 16.9% for BioFreedom (p = 0.01 for non-inferiority). Secondary endpoints and bleeding rates were also similar between both devices.

Taken together, these trials in patients with high bleeding risk in need of a shortened DAPT strategy favor the use of new generation DES, which would result in a greater net benefit by decreasing ischemic events without increasing the risk of bleeding.

8. DUAL ANTIPLATELET THERAPY IN PATIENTS UNDER ANTICOAGULANT THERAPY

Approximately 6-8% of patients undergoing PCI have an indication for long-term anticoagulation [64]. Compared with exclusive anticoagulation, the DAPT + anticoagulation combination increases the risk of bleeding at least 2 fold [65], making these patients a high bleeding risk population.

The WOEST trial randomized 573 patients (69% with AF) to dual (vitamin K antagonists (VKA) + Clopidogrel 75 mg day) or triple therapy (VKA + Clopidogrel + AAS 80 mg). The primary outcome of any TIMI bleeding at
1-year was significantly reduced in the dual therapy group (19.5% vs. 44.9%; HR 0.36; 95% CI 0.26-0.50; p < 0.001), with no differences in major bleeding. In addition, the rate of MI, stroke, culprit lesion revascularization or stent thrombosis was similar. Overall mortality at 1 year was lower in the dual therapy group (2.5% vs. 6.4%; p = 0.027). Although the number of patients was rather low in this study, it was the first trial underpinning the risks of adding DAPT to patients already taking VKA as well as showing no increased ischemic risk with Aspirin withdrawal.

Since then, four randomized trials have evaluated the role of direct oral anticoagulants (DOAC) in this scenario:

Table 5. Randomized trials of triple therapy.

| Trial          | Year | Patients | ACS (%) | DES (%) | Intervention                                                                 | Control                                      | Primary Outcome                  | Follow up | Results                                                      |
|----------------|------|----------|---------|---------|------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------|-----------|-------------------------------------------------------------|
| PIO-NEER-AF    | 2016 | 2124     | 52      | 68      | Group 1: Rivaroxaban 10-15 mg daily + Clopidogrel 75 mg daily (or Ticagrelor 90 mg BID or Prasugrel 10 mg daily) for 12 months Group 2: Rivaroxaban 2.5 mg BID (10-15 mg if Clopidogrel was suspended between 1 to 6 months) + Aspirin 75-100 mg daily + Clopidogrel 75 mg daily (or Ticagrelor 90 mg BID or Prasugrel 10 mg daily) for 1, 6 or 12 months | Group 3: VKA + Aspirin 75-100 mg daily + Clopidogrel 75 mg daily (or Ticagrelor 90 mg BID or Prasugrel 10 mg daily) for 1, 6 or 12 months (TTR:65%) | Clinically significant TIMI bleeding     | 12 months | Primary outcome: Group 1: 16.8%, Group 2:18%, Group 3: 26.7% Group 1 vs Group 3 (HR 0.59, CI 95% 0.47-0.76) Group 2 vs Group 3 (HR 0.63, CI 95% 0.50 – 0.80) Combined outcome of CV death + MI + stroke was similar in all 3 groups (Group 1: 6.5%, Group 2: 5.6% and Group 3: 6%) |
| RE-DUAL PCI    | 2017 | 2725     | 51      | 83      | DUAL 110 group : Dabigatran 110 mg BID + Clopidogrel 75 mg daily or Ticagrelor 90 mg BID DUAL 150 group : Dabigatran 150 mg BID + Clopidogrel 75 mg daily or Ticagrelor 90 mg BID CHADS-VASC: 3,7 + 1,5 HAS-BLED: 2,7 + 0,8 | TRIPLE group: VKA + Aspirin ≤ 100 mg for 1-3 months + Clopidogrel 75 mg daily or Ticagrelor 90 mg BID (TTR:64%) | ISTH major bleeding or clinically relevant non-major bleeding | 14 months (mean) | Primary outcome: DUAL 110 group vs TRIPLE group: 15.4% vs 26.9% (HR 0.52, CI 95% 0.42-0.63) DUAL 150 group vs TRIPLE group: 20.2% vs 25.7% (HR 0.72, CI 95% 0.58-0.88) Combined outcome of death, MI, stroke, systemic embolism or unplanned revascularization was 13.7% in the DUAL groups (combined) vs 13.4% in TRIPLE group (HR 1.04, CI 95% 0.84-1.29) |

(Table 5) Contd…
| Trial      | Year | Patients                                                                 | ACS (%) | DES (%) | Intervention                                                                 | Control                                     | Primary Outcome                                      | Follow up | Results                                                                                          |
|-----------|------|--------------------------------------------------------------------------|---------|---------|------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------|
| AUGUSTUS  | 2019 | 4614 patients with AF presenting with acute coronary syndrome, undergoing PCI or both | 61.2%   | 23.9%   | 2x2 factorial design (Apixaban or VKA + Aspirin or Placebo + P2Y2 inhibitor). Starting within the first 14 days, once anticoagulation was stopped. Clopidogrel was used in 92.6% of the cases Apixaban group: 5 mg BID or 2.5 mg BID (2 or more criteria: > 80 y.o., < 60 kg; Creatinine > 1.5 mg/dl) Aspirin group: 81 mg daily CHADS-VASC: 4 (IQR: 3-5) HAS-BLED: 3 (IQR: 2-3) | VKA group treated to an INR between 2-3 (TTR: 59%) Placebo group (Aspirin) | ISTH major or clinically relevant nonmajor bleeding | 6 months | Primary outcome: Apixaban group vs VKA: 10.5% vs 14.7% (HR: 0.69; CI 95%: 0.58-0.81) [non inferiority and superiority p<0.001]; NNT: 24 |          |
| ENTRUST   | 2019 | 1506 patients with nonvalvular AF undergoing PCI with stent placement | 52%     | NR      | DUAL group: Edoxaban 60 mg daily + P2Y12 inhibitor (Clopidogrel 75 mg daily in 93% of the cases) *The dose of Edoxaban was reduced to 30 mg daily if: weight <60 kg, creatinine clearance 15 -50 ml/min/m2 or concomitant use of Gp IbIIa inhibitors CHADS-VASC: 4 HAS-BLED: 3 | TRIPLE group: VKA + Aspirin 100 mg daily + P2Y12 inhibitor (Clopidogrel 75 mg daily in 92% of the cases) (TTR: 63.1%) | ISTH major or clinically relevant nonmajor bleeding | 12 months | Primary outcome: Edoxaban group vs VKA: 23.5% vs 27.4% (HR: 0.83, CI 95%: 0.74-0.93) |          |

Note: ISTH: ISTH major bleeding was defined as bleeding that resulted in death, occurred in a critical organ (intracranial, intraspinal, Intracocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or was associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or a transfusion of at least 2 units of packed red cells.

Therefore, in patients taking oral anticoagulants who undergo PCI, the main recommendations are the use of a DOAC [71] (in case of VKA use the lowest possible INR range) plus Clopidogrel (rather than Ticagrelor or Prasugrel). In cases where aspirin is also needed, a dose ≤100 mg should be used and in association with proton pump inhibitors [72].

In patients with low bleeding risk, triple therapy can be maintained for up to 6 months, followed by 6 months of dual therapy (preferably NOAC + Clopidogrel). In patients with
higher bleeding risk, the triple therapy can be limited to 1 month and then completed up to 12 months with the dual scheme. After this period, patients should continue only with oral anticoagulation. This recommendation is based on the recent AFIRE [73] trial that showed in patients with stable coronary disease revascularized more than 1 year earlier that monotherapy with Rivaroxaban alone was not inferior in terms of ischemic events (HR 0.72; 95% CI 0.55-0.95; p <0.001) and was superior in terms of major bleeding when compared to Rivaroxaban + an antiplatelet agent (either Aspirin or P2Y12 inhibitor).

9. MODIFICATIONS TO STANDARD DUAL ANTIPLATELET STRATEGY

Since the risk of stent thrombosis is greatest during the first weeks after PCI [74], it has been suggested that a therapy with a potent P2Y12 inhibitor limited to this period could be sufficient to reduce that risk, while also minimizing the risk of bleeding [75]. Not infrequently a high bleeding risk coincides with a high thrombotic risk in the same patient, thus such a strategy could be appropriate for this complex situation. The GLOBAL LEADERS [76] trial included 15,968 patients undergoing PCI with a Biolimus A-9 eluting stent and sought to investigate whether a strategy of Ticagrelor 90 mg every 12 hrs + Aspirin 75-100 mg for 1 month followed by Ticagrelor for 23 months was not inferior to 1-year DAPT (with Clopidogrel or Ticagrelor) followed by monotherapy with Aspirin up to 2 years. There were no differences between 1-month DAPT compared to standard therapy in the main outcome of death from any cause and non-fatal MI (3.81% vs. 4.37%; 95% CI 0.75 - 1.01; p = 0.073) or in the BARC 3-5 bleeding rate (2.04% vs. 2.12%; 95% CI 0.78-1.20; p = 0.77).

Following the same concept, the TOPIC [77] trial included 645 patients undergoing PCI for ACS. All patients received 1 month of ASA + a potent P2Y12 inhibitor (Ticagrelor 90 mg bid or Prasugrel 10 mg) and were then randomized 1:1 to maintain the same scheme (n = 323) vs. de-escalation to an Aspirin + Clopidogrel 75 mg scheme (n = 322). The group switching to Aspirin + Clopidogrel showed a reduced combined outcome of CV death, urgent revascularization, stroke or BARC ≥ 2 bleeding (13.4% vs. 26.3%, HR 0.48; 95% CI 0.34-0.68; p = 0.01), mainly driven by a reduction in bleedings events (HR 0.30; 95% CI 0.18-0.50, p <0.01).

Finally, the TWILIGHT [78] trial was a double-blind study in 7,119 patients undergoing PCI at high risk of bleeding or ischemic events. After a period of 3 months with ASA + Ticagrelor, patients were randomized to continue with dual therapy or only monotherapy with Ticagrelor. The primary outcome at 1 year was BARC 2 to 5 major bleeding. At 12 months, monotherapy with Ticagrelor was associated with a lower rate of clinically relevant bleeding (4.0 vs. 7.1%, HR 0.56; 95% CI 0.45-0.68; p <0.001), with no differences in the composite of death, MI or stroke (3.9% in both groups; p <0.001 for non-inferiority).

Overall, these data support the idea of limiting the strongest antiplatelet therapy to the early period after coronary stenting. Therefore, an initial therapy with DAPT based on a more potent P2Y12 inhibitor (Prasugrel or Ticagrelor), followed by de-escalation to monotherapy or dual therapy with Clopidogrel, could achieve anti-thrombotic benefits similar to prolonged potent dual therapy, but with lower bleeding risk, particularly in those patients in whom a higher risk of bleeding concur with a high thrombotic risk.

CONCLUSION

Dual antiplatelet therapy has allowed PCI to be performed safely, associated with a high success rate and a low risk of thrombotic complications. This has promoted the expansion of PCI to increasingly complex clinical scenarios and coronary anatomies. However, the use of this therapeutic strategy is not free of risks, with the main one being hemorrhagic complications.

More potent P2Y12 inhibitors have further expanded treatment options in patients undergoing PCI, at the expense of increased bleeding risk. With this in mind, new therapeutic strategies have been designed to better reconcile the anti-thrombotic protection delivered by these drugs and their risk of bleeding. A key aspect is the early identification of those patients with higher thrombotic and hemorrhagic risk, in order to tailor the duration or intensity of DAPT according to the individual patient needs. In addition, developments in stent technology have reduced the thrombotic risk of PCI and thus allowed for shorter periods of combined antiplatelets.

The integration of all this information will allow clinicians to prescribe a more precise therapy for each patient, optimizing the benefits and limiting the harm of this fundamental therapeutic tool in patients undergoing coronary angioplasty.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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