Review Article

Optimum Antithrombotic Therapy in Patients Requiring Long-Term Anticoagulation and Undergoing Percutaneous Coronary Intervention

Nayan Agarwal, Dhruv Mahtta, Cecil A. Rambarat, Islam Elgendy, and Ahmed N. Mahmoud

Department of Medicine, University of Florida, Gainesville, FL, USA

Correspondence should be addressed to Ahmed N. Mahmoud; ahmed.mahmoud@medicine.ufl.edu

Received 30 June 2017; Accepted 14 November 2017; Published 25 March 2018

Academic Editor: Farhad Kamali

Copyright © 2018 Nayan Agarwal et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Management of patients on long-term anticoagulation requiring percutaneous coronary intervention is challenging. Triple therapy with oral anticoagulant and dual antiplatelet therapy is the standard of care. However, there is no strong evidence to support this strategy. There is emerging data regarding the safety and efficacy of dual therapy with oral anticoagulant and single antiplatelet therapy in these patients. In this comprehensive review we highlight available evidence regarding various antithrombotic regimens' efficacy and safety in patient with coronary artery disease undergoing percutaneous coronary intervention with long-term anticoagulation therapy requirements.

1. Background

Patients with mechanical heart valves, a prior systemic thromboembolic event and atrial fibrillation/flutter (AF), often require long-term anticoagulation [1, 2]. About 20% to 30% of these patients have concomitant ischemic heart disease requiring percutaneous coronary intervention and stent implantation (PCI) [3–5]. This would mandate the use of dual antiplatelet therapy (DAPT) (aspirin and an adenosine diphosphate antagonist) for prevention of stent thrombosis and adverse events following PCI [6]. It is often a clinical dilemma, whether to use dual therapy (DT) with either oral anticoagulant (OAC) and single antiplatelet therapy (SAPT) or DAPT or triple therapy (TT) with OAC and DAPT in these patients [7].

Although primary intent of TT is to decrease the incidence of major adverse cardiac events (MACE), especially stent thrombosis, it has been found to be associated with a high annual risk of bleeding [8, 9], which in turn is strongly associated with recurrent hospitalization and increased morbidity and mortality [10, 11]. Recently, new evidence has emerged questioning the benefit of TT and suggesting a regimen of dual therapy (DT) with OAC and a single antiplatelet (SAPT) agent might be equally efficacious to TT with a lower incidence of major bleeding [8, 9, 12]. There is also emerging evidence that use of DAPT in these patients is associated with similar outcomes to TT with less bleeding [13, 14]. Hence, we attempted to review the available evidence with regard to different antithrombotic regimes in patients on long-term OAC requiring PCI.

2. Pathophysiology of Thrombogenesis in AF and in Acute Coronary Syndrome/PCI Patients

AF is the most common indication for OAC in patients on OAC requiring PCI. AF significantly increases the risk of thromboembolism [1, 15]. The type of thrombus in AF is mainly fibrin rich where platelets play a smaller role [16, 17]. Loss of atrial contraction causes stasis of blood flow in left atrium. There is also increased local expression in the dysfunctional atrial endocardium of prothrombotic molecules, such as tissue factor [18] and Von Willebrand factor (VWF) [19]. This indicates that inhibition of coagulation remains the mainstay in preventing AF related thromboembolism.

The pathogenesis of coronary thrombosis in patients with coronary artery disease (CAD) and those undergoing PCI...
is considered to be largely platelet driven. Under normal
circumstances the endothelium is antithrombotic by express-
ing inhibitors of platelet activation, like nitric oxide (NO) and
prostacyclin (PGI2), coagulation inhibitors, like tissue
factor pathway inhibitor, and heparin sulphate, in addition
to tissue-type plasminogen activator promoting fibrinolysis.
However, when superficial erosions occur, the endothelium is
activated towards hemostasis, becoming prothrombotic with
expression of VWF and plasminogen activator inhibitor-1, in
addition to reduced expression of NO and PGI2 [20].
This promotes platelet activation, which in turn can activate
coaulation on the platelet surface. This suggests that platelet
inhibition is the mainstay for avoiding plaque rupture or
coronary stent induced coronary thrombosis.

3. Antithrombotic Regimens

3.1. Triple Therapy. Aspirin has always been cornerstone
in treating ACS and/or PCI, OAC is needed for stroke
prevention in AF, mechanical heart valves, and previous
thromboembolism, and a P2Y12 inhibitor is essential for
prevention of stent thrombosis. Current American College
of Cardiology (ACC)/American Heart Association (AHA)
[6] and European Society of Cardiology [4] guidelines both
recommend TT in patients with an indication for anticoag-
ulation undergoing PCI. However, this approach may result
in excess major bleeding, with rates of 2.2% within the first
month and 4 to 12% within the first year of treatment [21].
These guidelines are based mostly upon observational trials
and expert opinion due to the scarcity of randomized data.
However, the guidelines emphasize that the treatment period
should be as short as possible because of the increased bleed-
ing risk over time. The ISAR-TRIPLE (Intracoronary Stenting
and Antithrombotic Regimen-Testing of a 6-Week Versus a
6-Month Clopidogrel Treatment Regimen in Patients With
Concomitant Aspirin and Oral Anticoagulant Therapy Fol-
lowing Drug-Eluting Stenting) [22] failed to show a benefit
of 6 months of TT over 6 weeks with regard to composite
death, myocardial infarction, definite stent thrombosis,
stroke, or major bleeding. An explanation for this finding may
be that approximately one-half of all bleeding events occurred
in the first 6 weeks after PCI, when both groups received the
same therapy consisting of aspirin, clopidogrel, and OAC.

Most of the studies evaluating the role of TT in patients
with an indication for OAC requiring PCI used warfarin as
the OAC [9, 23–26]. Although not supported by robust
clinical data, guidelines recommend a target international
normalized ratio (INR) to be between 2 and 2.5 when war-
farin is used [1, 6]. Data regarding newer oral anticoagulant
agents (NOACs) in patients requiring OAC and undergoing
PCI is scant. The dose of NOACs in TT is also debatable. The
ATLAS-ACS-TIMI 46 (Anti-Xa Therapy to Lower Cardio-
vascular Events in Addition to Standard Therapy in Subjects
with Acute Coronary Syndrome-Thrombolysis in Myocardial
Infarction 51) [27] demonstrated that standard 20 mg dose
of rivaroxaban when added to DAPT in ACS patients sig-
ificantly increased bleeding. In ATLAS-ACS TIMI 51 trial
[28] a very low dose of rivaroxaban (2.5 mg twice daily)
was associated with lower rates of death from cardiovascular
causes, myocardial infarction, and stroke compared to DAPT
alone in ACS patients without an increase in fatal bleeding,
but this low dose of 2.5 mg twice daily has not been studied
for prevention of stroke in AF patients. The usage of apixaban
for ACS was first explored in the Apixaban for Prevention of
Acute Ischemic and Safety Events (APPRAISE) trial, which
did not show a benefit with apixaban in addition to standard
post-ACS treatment but resulted in significantly increased
bleeding [29]. Dabigatran also increased the risk of bleeding
when added to DAPT in ACS patient [30]. The ACC/AHA
guidelines have not made any specific recommendations
regarding NOACS. European guidelines [4] give NOACS the
same level of recommendation as warfarin and suggest using
lower dose (dabigatran 110 mg twice daily, rivaroxaban 15 mg
daily, or apixaban 2.5 mg twice daily) for patients requiring
TT.

Role of rivaroxaban was investigated in PIONEER-
AF PCI (Open-Label, Randomized, Controlled, Multicenter
Study Exploring Two Treatment Strategies of Rivaroxaban
and a Dose-Adjusted Oral Vitamin K Antagonist Treatment
Strategy in Subjects with Atrial Fibrillation who Undergo
Percutaneous Coronary Intervention) [12] as triple therapy,
which showed a rivaroxaban based strategy resulting in
similar efficacy with less bleeding compared to warfarin based
strategy. Most recently, efficacy of DT with dabigatran versus
TT was assessed by a team of researchers from the RE-DUAL
PCI (Randomized Evaluation of Dual Therapy with Dabiga-
tran versus Triple Therapy Strategy with Warfarin in Patients
with nonvalvular atrial fibrillation that have undergone PCI
with Stenting) trial [31]. This was multicentered, randomized-
control trial consisting of 2725 patients where the primary
end point was major or clinically relevant nonmajor bleeding
event while the secondary endpoint consisted of thromboem-
bolic events. At their mean follow-up period of 14 months,
the authors concluded the risk of bleeding being lower among
the patients in the DT with dabigatran cohort as compared to
patients who received TT. DT with dabigatran was also shown
to be noninferior to TT with regard to thromboembolic events.
Future randomized studies such as Rivaroxaban and
Ticagrelor in Atrial Fibrillation (RT-AP) [32] and Apixaban
in Non-Valvular Atrial Fibrillation with a Recent Acute
Coronary Syndrome or Undergoing Percutaneous Coronary
Intervention (AUGUSTUS Trial) (NCT02415400) will pro-
vide more information on this subject.

There is paucity of data with regard to newer antiplatelet
agents (ticagrelor and prasugrel) in combination with OAC.
There are concerns that it can cause more bleeding compared
to clopidogrel [50]. However, such speculations regarding the
superiority or even inferiority of clopidogrel versus newer
antiplatelet agents have yet to be proven by clinical data from
randomized controlled trials. Nonetheless, at present both
ACC/AHA and ESC guidelines recommend using clopido-
grel, when TT is required.

3.2. Dual Therapy with OAC and SAPT. There are several
studies that evaluated the role of DT of OAC and SAPT
with TT [9, 12, 24–26, 33–42]. The WOEST [9] (what is the
optimal antiplatelet and anticoagulant therapy in patients
with oral anticoagulation and coronary stenting) was the first
| Study/author | Design | Year | Number of patients | Male (%) | TT | DT | Follow-up (months) | Indication for PCI | INR | Indication for anticoagulation |
|-------------|--------|------|-------------------|----------|----|----|------------------|-------------------|-----|-------------------------------|
| RE-DUAL PCI [31] | RCT | 2017 | 2725 | 76% | $w + a + c, w + a + t$ | $d^+ (c$ or $t)$ [44%], $d^+ (c$ or $t)$ [56%] | 14 | ACS, CAD | 2.0–3.0 | AF |
| De Vecchis et al. [33] | R* | 2016 | 98 | 45% | $w + a + c$ | $w + c$ [NR], $w + a$ [NR] | 12 | ACS, CAD | NR | AF, mechanical valve, VTE, dilated cardiomyopathy |
| PIONEER [12] | RCT | 2016 | 1415 | 74% | $w + a + c$ [96%], $w + a + p$ [1%], $w + a + t$ [3%] | $R + c$ [93%], $R + p$ [2%], $R + t$ [5%] | 12 | ACS, CAD | 2.0–3.0 | AF |
| ORBIT-AF [34] | P* | 2016 | 1827 | 72% | $w + a + c, w + a + p, d + a + c, d + a + p$ | $w + a$ [NR], $w + c$ [NR], $w + p$ [NR], $d + a$ [NR], $d + c$ [NR], $d + p$ [NR] | 24 | CAD | NR | AF |
| AFCAS [24] | P* | 2014 | 914 | 70% | $w + a + c$ | $w + c$ [100%] | 12 | ACS, CAD | 1.8–3 | AF |
| WARSTENT [25] | P* | 2014 | 401 | 26% | $w + a + c$ | $w + c$ [NR], $w + a$ [NR] | 12 | ACS, CAD | 1.8–4.5 | AF, apical thrombus, apical aekinesis, VTE, mechanical valve |
| Braun et al. [35] | R* | 2015 | 266 | 77% | $w + a + c$ | $w + t$ [100%] | 3 | ACS | 2.0–3.0 | AF, apical thrombus, apical aekinesis, VTE, mechanical valve |
| Lamberts et al. [36] | P* | 2013 | 12165 | 61% | $w + a + c$ | $w + c$ [27%], $w + a$ [73%] | 12 | ACS, CAD | NR | AF |
| WOEST [9] | RCT | 2013 | 573 | 80% | $w + a + c$ | $w + c$ [100%] | 12 | ACS, CAD | 2 | AF, mechanical valve, VTE, apical aeurysm, PAD, EF <30% |
| Rubboli et al. [37] | P* | 2012 | 632 | 73% | $w + a + c$ | $w + a$ [100%] | 12 | ACS, CAD | NR | AF, VTE, mechanical valve, dilated cardiomyopathy, ischemic heart disease, cardiac thrombus, CVA, LV aeurysm, biological heart valve |
| Persson et al. [38] | R* | 2011 | 1177 | 76% | $w + a + c$ | $w + c$ [45%], $w + a$ [55%] | 12 | ACS | NR | NR |
| Gao et al. [39] | P* | 2010 | 622 | 71% | $w + a + c$ | $w + c$ [87%] or $w + a$ [13%] | 12 | ACS, CAD | 1.8–2.5 | AF |
| MUSICA [40] | P* | 2009 | 405 | 81% | $w + a + c, LMWH$ + $a + c$ | $w + c$ [80%], LMWH + $c$ [4%], $w + a$ [13%], LMWH + $a$ [2%] | 6 | ACS, CAD | NR | AF, mechanical valve, CVA |
| Sørensen et al. [41] | R* | 2009 | 40812 | 63% | $w + a + c$ | $w + c$ [0.5%], $w + a$ [2%] | 18 | ACS | NR | NR |
| GRACE [26] | P* | 2007 | 800 | 70% | $w + a + c$ | $w + c$ [51%], $w + a$ [49%] | 6 | ACS | NR | AF, STEMI, VTE, mechanical valve |
| Karjalainen et al. [42] | R* | 2007 | 239 | 74% | $w + a + c$ | $w + c$ [58%], $w + a$ [42%] | 12 | ACS, CAD | 2–2.5 | AF, mechanical valve, VTE, CVA |

a = aspirin; ACS = acute coronary syndrome; AF = atrial fibrillation; c = clopidogrel; CAD = coronary artery disease; CVA = cerebral vascular accident; d = dabigatran (110 mg BID); $d^+$ = dabigatran (150 mg BID); DT = dual therapy; LMWH = low molecular weight heparin; NR = not reported; p = prasugrel; P* = prospective trial; PAD = peripheral artery disease; R = rivaroxaban; R* = retrospective trial; RCT = randomized-control trial; t = ticagrelor; TT = triple therapy; VTE = venous thromboembolism.
randomized study which tested the hypothesis of using DT with OAC and SAPT in patients with an indication for long-term OAC undergoing PCI. The combination of conventional therapy of warfarin, aspirin, and clopidogrel was tested against the combination of warfarin and clopidogrel over 1 year in 573 patients. DT arm had significantly less bleeding compared to TT (19.4% versus 44.4%, HR 0.36, \(p < 0.0001\)) and need for transfusion (3.9% versus 9.5%, OR 0.39, \(p = 0.011\)). The secondary end points of death, MI, stroke, and stent thrombosis were lower in DT compared to TT but did not reach statistical significance. In PIONEER-AF [12] the DT of OAC and clopidogrel was superior to OAC and aspirin regarding their use at this time. Table 2 illustrates outcomes with dual therapy compared with triple therapy after PCI.

As noticed in Table 1, the OAC was warfarin in majority of the studies, except for PIONEER, where rivaroxaban was used. Antiplatelet in the DT arm was clopidogrel in majority of studies, though aspirin was also used in several observational studies. Karjalainen et al. [42] demonstrated that combination of warfarin and aspirin resulted in more strokes and stent thrombosis compared to combination of warfarin and clopidogrel. Similarly in a network meta-analysis Liu et al. [46] demonstrated that the combination of OAC and clopidogrel was superior to OAC and aspirin with regard to major adverse cardiac events, stroke, MI, and all-cause mortality. Similar results were also seen in Danish registry [36] as discussed above. Newer antiplatelets (ticagrelor and prasugrel) were used only in about 15% of patients in PIONEER-AF; hence there is insufficient data regarding their use at this time. Table 2 illustrates outcomes of DAPT compared with TT following PCI.

The ESC guidelines [1] recommend an initial 4-week-6-month TT based on CHADVASC and HAS-BLED score and then DT of OAC (warfarin or NOAC) and clopidogrel. WOEST [9] trial noticed that most bleeding episodes happened during the initial 180 days after PCI. Similar time frames for increased bleeding were seen in other studies of antiplatelet therapies [51, 52]. Hence, omission of the initial 4-week-6-month TT can result in reduction in bleeding as evidenced by WOEST [9] and PIONEER-AF [12]. In Table 3, we summarize the current guidelines pertaining to the use

### Table 2: Outcomes with dual therapy compared with triple therapy after PCI.

| Study/author      | MACE (%)  | Mortality (%)  | Stent thrombosis (%) | Total bleeding (%) | Major bleeding (%) |
|-------------------|-----------|----------------|----------------------|--------------------|-------------------|
|                   | [\(p\ value\)] | [\(p\ value\)] | [\(p\ value\)] | [\(p\ value\)] | [\(p\ value\)] |
| RE-DUAL PCI [31]  | NR        | 4.9/5.6 [0.56]\* | 0.8/1.5 [0.15] | 42.9/27.1 [<0.001] | 9.2/5.0 [<0.001] |
| De Vecchis et al. [33] | 271/12.9 [0.32] | 8.3/0 [0.26] | 2/0 [0.59] | 16.7/19.4 [0.90] | 8.3/6.5 [0.89] |
| PIONEER [12]      | 6.0/6.5 [0.75] | 1.9/2.4 [0.52] | 0.7/0.8 [0.79] | 26.7/16.8 [<0.01] | 3.3/2.1 [0.23] |
| ORBIT-AF [34]     | NR        | 4.1/5.4 [0.57] | NR | NR | 5.68/5.85 [0.66] |
| AFCAS [24]        | 22/18 [0.72] | 11/7 [0.54] | 1/3 [0.60] | 18/16 [0.66] | 10/7 [0.43] |
| WARSTENT [25]     | 16/15 [0.98] | 5/0 [0.45] | 1/0 [0.76] | 11/5 [0.34] | 4/5 [0.84] |
| Braun et al. [35] | NR        | 3.2/3.8 [NS] | 0/0 [NS] | NR | 7/7.5 [NS] |
| Lamberts et al. [36] | NR | 8.9/7.1 [NS] | NR | 14.3/10.9 [NS] | 0.9/0.5 [NS] |
| WOEST [9]         | NR        | 6.3/3.5 [0.03] | 3.2/1.4 [0.17] | 44.4/19.4 [<0.01] | 5.6/3.2 [0.16] |
| Rubboli et al. [37] | 32/24.6 [0.19] | 9.9/10.2 [0.78] | 2.7/2.0 [0.77] | NR | 5.0/2.6 [0.32] |
| Persson et al. [38] | NR | 3.0/4.2 [0.43] | NR | 4.7/1.3 [0.02] | 2.7/0.3 [0.03] |
| Gao et al. [39]   | 8.8/14.9 [0.01] | 4.4/5.8 [0.17] | 0.7/1.7 [0.73] | 11.8/7.4 [0.038] | 2.9/2.5 [0.73] |
| MUSICIA [40]      | 23.7/26.1 [0.001] | 6.8/10.9 [0.06] | 4.0/8.7 [0.04] | 15.5/13 [0.02] | 4.3/6.5 [0.29] |
| Sørensen et al. [41] | NR | [NS] | NR | 3.2/1.6 [NS] | NR |
| GRACE [26]        | NR        | 5.1/6.5 [0.47] | NR | NR | 5.9/4.6 [0.46] |
| Karjalainen et al. [42] | 21.9/11 [0.003] | 8.7/1.8 [0.003] | 4.1/1.3 [0.09] | NR | 8.2/2.6 [0.01] |

NR = not reported; NS = statistically nonsignificant; number preceding ‘/’ denotes TT (triple therapy) and number proceeding ‘/’ denotes DT (dual therapy). TT/DT; for RE-DUAL PCI: TT/DT\* = Therapy with Dabigatran 110 mg BID; TT/DT\* = Therapy with Dabigatran 150 mg BID.
Table 3: Guideline recommendations regarding triple therapy.

| Class of evidence | 2016 European Society of Cardiology Guidelines on AF [43] | 2014 European Consensus on AF and PCI [4] | 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease [6] | 2014 ACC/AHA Guidelines on NSTEMI [44] | 2013 ACC/AHA Guidelines on STEMI [45] |
|-------------------|----------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------|----------------------------------------|
| Summary and synthesis of guideline, expert consensus documents, and comprehensive review article recommendations | (1) Keep TT duration as short as possible (2) Consider target INR 2.0–2.5 when warfarin is used as part of TT (3) Clopidogrel is the P2Y12 inhibitor of choice (4) PPIs should be used in patients with history of GI bleeding and those who are at high risk of bleeding while being on TT | (1) After ACS or PCI: OAC monotherapy after initial 12 months (2) After elective PCI: OAC monotherapy after initial 6 months in patients with high bleeding risk | (1) Minimize duration of TT to limit risk of bleeding (2) Addition of PPI therapy in patients with prior history of GI bleeding who are started on TT |
| (I) | (IIa) Stable CAD with elective PCI: 1 month of TT (2) Stenting after ACS: 1–6 months of TT (3) ACS without stenting: up to 12 months of DT (4) In general, minimize duration of TT and after completion of TT, DT until 12 months after PCI or ACS | (1) Stable CAD with elective PCI: 1–6 months of TT (2) ACS: 1–6 months of TT (3) After completion of TT, DT until 12 months after PCI or ACS (4) Consider lower INR goal for warfarin (2.0–2.5) when part of TT | Consider addition of PPI therapy in patients without prior history of GI disturbances who are started on TT |
| (IIb) | DT with OAC + clopidogrel may be considered as an alternative therapy in selective patients | (1) DT with OAC + clopidogrel may be considered as an alternate to TT in selected patients (2) ACS: 6–12 months of TT if low bleeding risk (3) DT beyond 12 months after ACS in selected cases (LM lesions, proximal LAD lesions, recurrent MIs, etc.) (4) When using DOAC as part of TT, we may consider lower tested dose of DOAC for stroke prevention in AF | Consider lower INR goal (2–2.5) for patients receiving ASA and P2Y12 inhibitor | Consider lower INR goal (2–2.5) for patients receiving ASA and P2Y12 inhibitor |
| (II) | Ticagrelor and Prasugrel should not be part of TT | | | |

AF = atrial fibrillation, PCI = percutaneous coronary intervention, ACC/AHA = American College of Cardiology/American Heart association, NSTEMI = non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction, TT = triple therapy, INR = international normalized ratio, PPI = proton pump inhibitor, GI = gastrointestinal, ACS = acute coronary syndrome, OAC = oral anticoagulant, CAD = coronary artery disease, DT = dual therapy, LM = left main, LAD = left anterior descending, MI = myocardial infarction, DOAC = direct oral anticoagulant, and ASA = aspirin.
Table 4: Meta-analyses comparing outcomes of dual with triple therapy.

| Study/author          | Year | Patient population                                           | Number of patients | Comparison | Results                                                                 |
|-----------------------|------|----------------------------------------------------------------|-------------------|------------|------------------------------------------------------------------------|
| Agarwal et al. [8]    | 2017 | Patients with an indication for long-term anticoagulation undergoing PCI | 7,276             | TT versus DT | (1) Less major bleeding with OAC + SAPT                                   |
|                       |      |                                                                |                   |            | (2) Comparable outcomes between OAC + SAPT and TT for MACE, MI, stent thrombosis, CV mortality |
| Liu et al. [46]       | 2016 | Patients with indication for OAC and undergoing PCI or medically managed ACS | 22,842            | Network meta-analysis of TT, OAC + C, OAC + A, DAPT | (1) OAC + C had the lowest rate of MACE, CVA, MI, all-cause mortality, and major bleeding |
| Barbieri et al. [47]  | 2016 | Patients undergoing PCI that required long-term OAC              | 21,716            | TT versus DT | (1) As compared to DT, the use of TT was associated with significant reduction in overall mortality, recurrent MI, and ischemic stroke |
|                       |      |                                                                |                   |            | (2) Patients with TT were found to have a higher incidence of bleeding |
| D'Ascenzo et al. [48] | 2015 | Patients with indication for OAC and undergoing PCI or medically managed ACS | 7,182             | TT versus DAPT, TT versus OAC + C | (1) Major bleeding: DAPT and OAC + C both had less incidence as compared to TT |
|                       |      |                                                                |                   |            | (2) MACE: no benefit of TT over OAC + C or DAPT                         |
| Gao et al. [49]       | 2015 | Patients taking OAC with coronary stent implantation            | 9,185             | TT versus OAC + C | (1) Lower incidence of MACE with OAC + C                                |
|                       |      |                                                                |                   |            | (2) Comparable outcomes between OAC + C and TT for all-cause mortality, MI, ST, ischemic thrombosis, and major and minor bleeding |

ACS = acute coronary syndrome; C = clopidogrel; CV = cardiovascular; CVA = cerebral vascular accident; DAPT = dual antiplatelet therapy; DT = dual therapy; MACE = major adverse cardiovascular event; MI = myocardial infarction; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; TT = triple therapy.
of DT and TT as recommended by ACC/AHA and ESC [4, 6, 43–45].

3.3. Dual Therapy with DAPT. DAPT is the cornerstone of therapy in patients with ACS and/or PCI. Aspirin alone has shown to reduce the incidence of stroke by 22% in AF [53, 54]. Can DAPT provide enough benefit in stroke protection? This hypothesis was tested in ACTIVE-W study [55] (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), which showed that, compared to warfarin only, the combination of aspirin and clopidogrel resulted in a significantly increased relative risk of 1.44 (1.18–1.76; p = 0.0003) of composite of stroke, systemic embolus, MI, or vascular death in patients with AF. Hence, DAPT is not considered effective for thromboembolic-prophylaxis in AF.

There are conflicting results on efficacy of DAPT in this cohort. A recent analysis published from National Cardiovascular Data Registry (NCDR) examined outcomes with DAPT versus TT in 4,959 patients > 65 years of age with acute MI and AF who underwent PCI [14]. Relative to DAPT, patients on TT had a similar risk of major adverse cardiac events (adjusted hazard ratio [HR]: 0.99 [95% CI: 0.86 to 1.16]), nonsignificantly lower risk of ischemic stroke (HR 0.66, 95% CI: 0.41–1.06), but significantly greater risk of bleeding requiring hospitalization (adjusted HR: 1.61 [95% CI: 1.31 to 1.97]), and greater risk of intracranial hemorrhage (adjusted HR: 2.04 [95% CI: 1.25 to 3.34]). In another single center retrospective study by Choi et al. [13], it was seen that, compared to TT, DAPT had less bleeding and no difference in composite of stroke, MI, or cardiac death. Danish registry study [36], Karjalainen et al. [42], Gao et al. [39], and Rubboli et al. [37] showed a higher risk of ischemic stroke, all-cause death, and major adverse cardiac events with DAPT compared to TT and OAC plus SAPT. The NCDR analysis [14] and results of Choi et al. [13] were underpowered to detect a difference in stroke and patients had less risk factors for stroke, which could undermine the benefits of TT compared to DAPT. Network meta-analysis by Liu et al. [46] demonstrated that DAPT was associated with worse outcomes compared with TT and OAC plus clopidogrel in this patient population. Table 4 summarizes the results of various meta-analyses comparing DAPT with TT.

4. Further Considerations for Treatment Strategies

Based on the review of available evidence, combination of OAC and clopidogrel and TT are most efficacious. Combination of OAC and clopidogrel results in less bleeding compared to TT. Several large meta-analyses (Table 3) have suggested that OAC + SAPT either resulted in lower incidence or had equivalent rates of MACE when compared to TT. DAPT and combination of OAC and aspirin are inadequate with higher incidence of stroke, MI, and stent thrombosis.

Major bleeding events and blood transfusions have been associated with increased risk of death in patients undergoing PCI [10, 56]. Majority of the patients with indication for OAC needing PCI are older [8, 56], who have higher thromboembolic risk, higher bleeding risk, and significant comorbidities [57]. Effect of nonmajor bleeding should not be underestimated in these patients, since even superficial or “nuisance” bleeding can lead to discontinuation of antiplatelet therapy, which may lead to subsequent thrombotic complications such as stent thrombosis [56, 58]. Hence, a strategy to reduce bleeding is even more important in these patients.

There are several questions that still remain. Firstly, what is the optimal therapy for patients undergoing PCI who are treated with OAC and clopidogrel, once clopidogrel is discontinued? Do these patients require OAC plus aspirin or OAC alone after discontinuation of P2Y12 inhibitor? Optimal treatment strategy in this scenario is currently unknown and the lack of randomized trials assessing this troubles the daily clinician. Two large registry based studies—Danish registry [59] and ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) [60]—demonstrated that, compared to warfarin monotherapy, combination of warfarin and aspirin was associated with higher bleeding risk without reducing ischemic end points. European guidelines recommend long-term therapy with OAC only (Class 1, LOE B) with combination of OAC and SAPT in selected patients, for example, left main PCI, bifurcation PCI, and recurrent MI (Class 2b, LOE C). Secondly, data regarding role of NOACs in TT or DT is insufficient. PIONEER-AF showed rivaroxaban was superior to warfarin. Future trials like RT-AF and AUGUSTUS will provide more data on this subject. Thirdly, the role of newer P2Y12 inhibitors like ticagrelor and prasugrel is also unclear due to lack of studies using the combination of OAC plus ticagrelor/prasugrel.

5. Conclusions

The efficacy of TT in patients on OAC needing PCI has never been proven. This combination increases bleeding risk, which can result in adverse patients’ outcomes. New evidence, from randomized controlled trial, nationwide registries, observational studies, and meta-analysis, indicates the great potential of the combination of OAC and clopidogrel without aspirin to improve clinical outcomes in comparison with triple therapy. Therefore, OAC combined with clopidogrel seems to be a reasonable alternative to triple therapy in patients on long-term OAC who undergo PCI.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] C. T. January, L. S. Wann, J. S. Alpert et al., “2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society,” Circulation, vol. 130, no. 23, pp. e199–e267, 2014.

[2] R. A. Nishimura, C. M. Otto, R. O. Bonow et al., “2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force
on Practice Guidelines,” *Circulation*, vol. 129, no. 23, pp. 2440–2492, 2014.

[3] A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry,” *Europace*, vol. 16, no. 6, pp. 941–941, 2014.

[4] G. Y. H. Lip, S. Windecker, K. Huber et al., “Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: A joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS),” *European Heart Journal*, vol. 35, no. 45, pp. 3155–3179, 2014.

[5] S. Kralev, K. Schneider, S. Lang, T. Süsadelbe, and M. Borggrefe, “Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography,” *PLoS ONE*, vol. 6, no. 9, Article e24964, 2011.

[6] G. N. Levine, E. R. Bates, J. A. Bittl et al., “ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy for Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery,” *Circulation*, vol. 134, pp. e123–155, 2016.

[7] G. Y. H. Lip, K. Huber, F. Andréotti et al., “Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/ stenting: A consensus document of the European Society of Cardiology Working Group on thrombosis, endorsed by the European Heart Rhythm Association [EHRA] and the European Association of Percutaneous Cardiovascular Interventions [EAPCI],” *Thrombosis and Haemostasis*, vol. 103, no. 1, pp. 13–28, 2010.

[8] N. Agarwal, A. Jain, A. N. Mahmoud et al., “Safety and Efficacy of Dual Versus Triple Antithrombotic Therapy in Patients Undergoing Percutaneous Coronary Intervention,” *American Journal of Medicine*, vol. 130, no. 11, pp. 1280–1289, 2017.

[9] W. J. M. Dewilde, T. Oirbans, F. W. A. Verheugt et al., “Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial,” *The Lancet*, vol. 381, no. 9872, pp. 1107–1115, 2013.

[10] B. J. Doyle, C. S. Rihan, D. A. Gastineau, and D. R. Holmes Jr., "Bleeding, Blood Transfusion, and Increased Mortality After Percutaneous Coronary Intervention. Implications for Contemporary Practice," *Journal of the American College of Cardiology*, vol. 53, no. 22, pp. 2019–2027, 2009.

[11] A. K. Chhatriwalla, A. P. Amin, K. F. Kennedy et al., "Association between bleeding events and in-hospital mortality after percutaneous coronary intervention,” *Journal of the American Medical Association*, vol. 309, no. 10, pp. 1022–1029, 2013.

[12] C. M. Gibson, R. Mehran, C. Bode et al., "Prevention of bleeding in patients with atrial fibrillation undergoing PCI,” *The New England Journal of Medicine*, vol. 375, no. 25, pp. 2423–2434, 2016.

[13] H. Choi, J. Ahn, S. H. Kang et al., "Prevalence, Management, and Long-Term (6-Year) Outcomes of Atrial Fibrillation Among Patients Receiving Drug-Eluting Coronary Stents,” *JACC: Cardiovascular Interventions*, vol. 10, no. 11, pp. 1075–1085, 2017.

[14] D. Pahaljani and A. Mehta, *Yearbook of Cardiology* 2016, Jaypee Brothers Medical Publishers (P) Ltd., 2016.

[15] G. Y. Lip and H. S. Lim, “Atrial fibrillation and stroke prevention,” *The Lancet Neurology*, vol. 6, no. 11, pp. 981–993, 2007.

[16] W. E. Wysokinski, S. G. Owen, D. N. Fass, D. D. Patrzalek, L. Murphy, and R. D. McBane II, “Atrial fibrillation and thrombosis: immunohistochemical differences between in situ and embolized thrombi,” *Journal of Thrombosis and Haemostasis*, vol. 2, no. 9, pp. 1637–1644, 2004.

[17] T. Watson, E. Shantsila, and G. Y. Lip, “Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited,” *The Lancet*, vol. 373, no. 9658, pp. 155–166, 2009.

[18] Y. Nakamura, K. Nakamura, K. Fukushima-Kusano et al., “Tissue factor expression in atrial endothelia associated with nonvalvular atrial fibrillation: Possible involvement in intracardiac thrombogenesis,” *Thrombosis Research*, vol. 113, no. 3, pp. 137–142, 2003.

[19] K. Kumagai, M. Fukuchi, J. Ohta et al., “Expression of the von Willebrand Factor in Atrial Endocardium is Increased in Atrial Fibrillation Depending on the Extent of Structural Remodeling,” *Circulation Journal*, vol. 68, no. 4, pp. 321–327, 2004.

[20] K. W. Lee and G. Y. H. Lip, “Acute coronary syndromes: Virchow's triad revisited,” *Blood Coagulation & Fibrinolysis*, vol. 14, no. 7, pp. 605–625, 2003.

[21] J. S. Paikin, D. S. Wright, M. A. Crowther, S. R. Mehta, and J. W. Eikelboom, “Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents,” *Circulation*, vol. 121, no. 18, pp. 2067–2070, 2010.

[22] K. A. Fiedler, M. Maeng, and J. Mehilli, “Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial,” *Journal of the American College of Cardiology*, vol. 65, no. 16, pp. 1619–1629, 2015.

[23] M. Lamberts, J. B. Olesen, M. H. Ruwald et al., “Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study,” *Circulation*, vol. 126, no. 10, pp. 1185–1193, 2012.

[24] A. Rubboli, A. Schlitt, T. Kiviniemi et al., “One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: An analysis of the AF-CAS registry,” *Clinical Cardiology*, vol. 37, no. 6, pp. 357–364, 2014.

[25] A. Rubboli, F. Saia, A. Sciahba et al., “Outcome of patients on oral anticoagulation undergoing coronary artery stenting: Data from discharge to 12 months in the warfarin and coronary stenting (WAR-STENT) registry,” *The Journal of Invasive Cardiology*, vol. 26, no. 11, pp. 563–569, 2014.

[26] M. C. Nguyen, Y. L. Lim, A. Walton et al., “Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: Is it safe and effective to use
just one antiplatelet agent?" European Heart Journal, vol. 28, no. 14, pp. 1717–1722, 2007.

[27] J. L. Anderson, C. D. Adams, and E. M. Antman, "2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines," Circulation, vol. 127, no. 23, pp. e663–e828, 2013.

[28] J. L. Anderson, C. D. Adams, and E. M. Antman, "2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines," Circulation, vol. 127, no. 23, pp. e663–e828, 2013.

[29] R. De Vecchis, C. Cantatrione, and D. Mazzei, "Clinical Rel- evance of Anticoagulation and Dual Antiplatelet Therapy to the Outcomes of Patients With Atrial Fibrillation and Recent Percutaneous Coronary Intervention With Stenting," Journal of Clinical Medicine Research, vol. 8, no. 2, pp. 153–161, 2016.

[30] J. L. Anderson, C. D. Adams, and E. M. Antman, "2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines," Circulation, vol. 127, no. 23, pp. e663–e828, 2013.

[31] R. Sørensen, M. L. Hansen, S. Z. Abildstrom et al., "Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data," The Lancet, vol. 374, no. 9706, pp. 1967–1974, 2009.

[32] P. P. Karjalainen, P. Porela, A. Ylitalo et al., "Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting," European Heart Journal, vol. 28, no. 6, pp. 726–732, 2007.

[33] "Corrigendum to: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS," European Heart Journal, 2017.
[53] "Risk Factors for Stroke and Efficacy of Antithrombotic Therapy in Atrial Fibrillation," *JAMA Internal Medicine*, vol. 154, no. 13, p. 1449, 1994.

[54] R. G. Hart, O. Benavente, R. McBride, and L. A. Pearce, "Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis," *Annals of Internal Medicine*, vol. 131, no. 7, pp. 492–501, 1999.

[55] S. Connolly, J. Pogue, and R. Hart, "Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial," *The Lancet*, vol. 367, no. 9526, pp. 1903–1912, 2006.

[56] W. J. M. Dewilde, P. W. A. Janssen, F. W. A. Verheugt et al., "Triple therapy for atrial fibrillation and percutaneous coronary intervention: A contemporary review," *Journal of the American College of Cardiology*, vol. 64, no. 12, pp. 1270–1280, 2014.

[57] T. Gomes, M. M. Mamdani, A. M. Holbrook, J. M. Paterson, C. Hellings, and D. N. Juurlink, "Rates of hemorrhage during warfarin therapy for atrial fibrillation," *Canadian Medical Association Journal*, vol. 185, no. 2, pp. E121–E127, 2013.

[58] P. Roy, L. Bonello, R. Torguson et al., "Impact of "Nuisance" Bleeding on Clopidogrel Compliance in Patients Undergoing Intracoronary Drug-Eluting Stent Implantation," *American Journal of Cardiology*, vol. 102, no. 12, pp. 1614–1617, 2008.

[59] M. Lamberts, G. H. Gislason, G. Y. H. Lip et al., "Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: A nationwide cohort study," *Circulation*, vol. 129, no. 15, pp. 1577–1585, 2014.

[60] B. A. Steinberg, S. Kim, and J. P. Piccini, "Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation," *Circulation*, vol. 128, no. 7, pp. 721–728, 2013.