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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

Advances in Antiplatelet and Anticoagulant Therapies for NSTE-ACS

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Abstract

The treatment of patients requiring anticoagulation who develop acute coronary syndrome (ACS) and/or require percutaneous coronary intervention (PCI) must balance the reduction in major adverse cardiovascular events, stroke, and major bleeding. The development of direct oral anticoagulants (DOACs) for the treatment of atrial fibrillation has ushered in an era of potential treatment options for these complex patients.

Purpose of Review To review the clinical evidence underlying the use of DOACs for the treatment of patients with atrial fibrillation and ACS or PCI.

Recent Findings Three trials studied this particular patient population; WOEST showed that dual therapy with warfarin and clopidogrel decreased hemorrhage at 1 year compared with standard triple therapy (19.4 vs. 44.4% HR 0.36; 95% CI 0.26–0.50; $P < 0.0001$), without increasing thromboembolic events (11.1 vs. 17.6% HR 0.60; 95% CI 0.38–0.94; $P = 0.025$). PIONEER AF-PCI showed that 10–15 mg rivaroxaban plus $P2Y_{12}$ inhibitor for 12 months significantly lowered bleeding rates than standard triple therapy (16.8 vs. 26.7% HR 0.59; 95% CI 0.47–0.76; $P < 0.001$) and had equivalent rates of MACE. Finally, REDUAL-PCI compared two different doses of dabigatran (110 mg twice daily and 150 mg twice daily) plus $P2Y_{12}$ inhibitor with standard triple therapy and reported reduced ISTH bleeding with both doses; HR 0.52 with 110 mg dabigatran (95% CI 0.42–0.63, $P < 0.001$) and HR 0.72 with 150 mg dabigatran (95% CI 0.58–0.88; $P = 0.002$). The rate of the composite of thromboembolic events, death, or unplanned revascularizations was similar between pooled dabigatran dual therapy and triple therapy groups (13.7 vs 13.4% HR 1.04; 95% CI 0.84–1.29; $P = 0.005$).

Summary Recent evidence shows that DOACs plus one antiplatelet agent can decrease bleeding in patients with atrial fibrillation undergoing PCI for ACS. Although not powered to detect non-inferiority or superiority, large studies suggest rivaroxaban 10–15 mg plus $P2Y_{12}$ inhibitor for 12 months or dabigatran 150 mg twice daily plus P2y12 inhibitor for 12 months will have similar rates of MACE and stent thrombosis as triple therapy. In patients who have contraindications to DOACs, the strategy of INR-adjusted warfarin plus clopidogrel appears to be safer than warfarin plus dual antiplatelet therapy.

Keywords Antiplatelet therapy · Anticoagulation · Atrial fibrillation · Acute coronary syndrome · Bleeding

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Introduction

Approximately 8 million Americans have suffered a myocardial infarction (both STEMI and NSTE-ACS), and there are 720,000 new and 335,000 recurrent heart attacks estimated to occur this year. The death rate attributed to coronary heart disease has declined by 34% from 2005 to 2015, largely due to implementation of evidence-based therapies, preventive medicine, and lifestyle modification. However, coronary heart disease remains the leading cause of death in the USA, accounting for over 366,800 deaths annually, and it causes

significant economic burden on the healthcare system [1]. Moreover, atrial fibrillation affects between 2.7 million to 6.1 million Americans, with majority of those afflicted over the age of 60. Prevalence of atrial fibrillation is expected to double over the next 25 years as well [2]. Given the high prevalence of both of these diseases, it is likely that more patients will be affected by both acute coronary syndrome (ACS) and atrial fibrillation.

Non-ST segment elevation acute coronary syndrome (NSTE-ACS) is often the result of atherosclerotic plaque rupture or erosion leading to platelet activation and aggregation, and generation of thrombin. The cornerstone of therapy for NSTE-ACS has been antiplatelet therapy and antithrombin therapy and, in patients with moderate-to-high risk clinical features, invasive risk stratification. This combination of treatment strategies must balance the reduction in ischemic events with the risk of bleeding. The balance of ischemia and hemorrhage is more acute in ACS patients who require chronic anticoagulation, like those with atrial fibrillation. Management of these patients must also involve strategies to reduce the risk of long-term thromboembolic events. An increasing number of patients with atrial fibrillation are also undergoing PCI, and the reduction in the risk of stent thrombosis must also be addressed. This paper will review the therapeutic options and combinations for ACS patients with atrial fibrillation undergoing PCI and will also discuss appropriate duration of therapy.

Antiplatelet Therapy for NSTE-ACS

Antiplatelet therapy for NSTE-ACS consists of both oral and parenteral agents. Oral agents consist of inhibitors of platelet activation, while parenteral agents consist of inhibitors of platelet aggregation (e.g., the glycoprotein IIb/IIIa) and activation (e.g., cangrelor). The available anticoagulants and antiplatelet agents and their sites of action are shown in Fig. 1.

Aspirin

Aspirin irreversibly blocks cyclooxygenase (COX-1) enzyme inhibiting production of thromboxane A2 and prevents platelet aggregation. Guidelines recommend that all patients with NSTEMI should be given 162–325 mg of non-enteric coated aspirin as soon as possible, with a maintenance dose of 81–162 mg/day continued indefinitely thereafter [4]. If aspirin is given as part of dual antiplatelet therapy (DAPT), then a daily dose of 81 mg (75–100 mg/day) is preferred [5]. Patients allergic to aspirin should be given a loading dose of clopidogrel followed by daily maintenance. If aspirin is used with ticagrelor, then 81 mg daily dose is recommended based on indirect data on efficacy and safety [6]. The issue of the appropriate dosage of aspirin for secondary prevention is being studied in the large pragmatic ADAPTABLE trial [NCT02697916]. Moreover, a recent meta-analysis suggests that heavier people need a greater daily dose of aspirin for primary prevention of cardiovascular events. It showed that low-dose aspirin (75–100 mg/day) prevented cardiovascular events only in people weighing < 70 kg; those weighing greater than 70 kg required > 325 mg/day for cardiovascular benefits [7]. In addition, the availability of more potent oral antiplatelet agents may obviate the long-term use of aspirin. Several large-scale trials, such as the GLOBAL LEADERS [NCT0181313435] and the TWILIGHT [NCT02270242] trials, are testing the approach of discontinuing aspirin after PCI and continuing ticagrelor as monotherapy.

P2Y12 Inhibitors

Clopidogrel

Clopidogrel is a thienopyridine that selectively and irreversibly binds the $P2Y_{12}$ receptor on platelet surface, preventing ADP-$P2Y_{12}$ receptor interaction and thereby inhibiting platelet activation throughout the lifespan of platelets (7–10 days). Clopidogrel needs to be converted to an active metabolite by the hepatic CYP450 enzymes to exert its effect [8].

The clopidogrel in unstable angina to prevent recurrent ischemic events (CURE) trial randomly assigned 12,562 patients with NSTE-ACS to aspirin vs aspirin plus clopidogrel (300 mg loading dose followed by 75 mg daily) and showed a 20% relative risk reduction in MACE in the DAPT (dual antiplatelet) group at the expense of increased non-CABG-related major bleeding [9]. The reduction in MACE was primarily driven by decreased rates of non-fatal MI in the DAPT group. Importantly, patients requiring oral anticoagulants were excluded from the trial. Current ACC/AHA guidelines recommend that clopidogrel in addition to aspirin should be given for 12 months to all patients with NSTE-ACS without contraindications regardless of invasive or conservative strategy. These guidelines currently recommend that if clopidogrel is chosen for treatment, it should be administered as a loading dose of 300–600 mg followed by maintenance dose of 75 mg daily; in patients undergoing PCI, a loading dose of 600 mg should be given for greater platelet inhibition [4].

Prasugrel

Prasugrel is a third generation thienopyridine which has a more rapid and potent platelet inhibition as compared with clopidogrel. It was studied in the TRITON-TIMI 38 trial where 13,608 ACS patients undergoing PCI were randomized to DAPT with aspirin and clopidogrel or prasugrel and were followed for 15 months. This study found a reduction in primary outcome of composite cardiovascular death, non-fatal

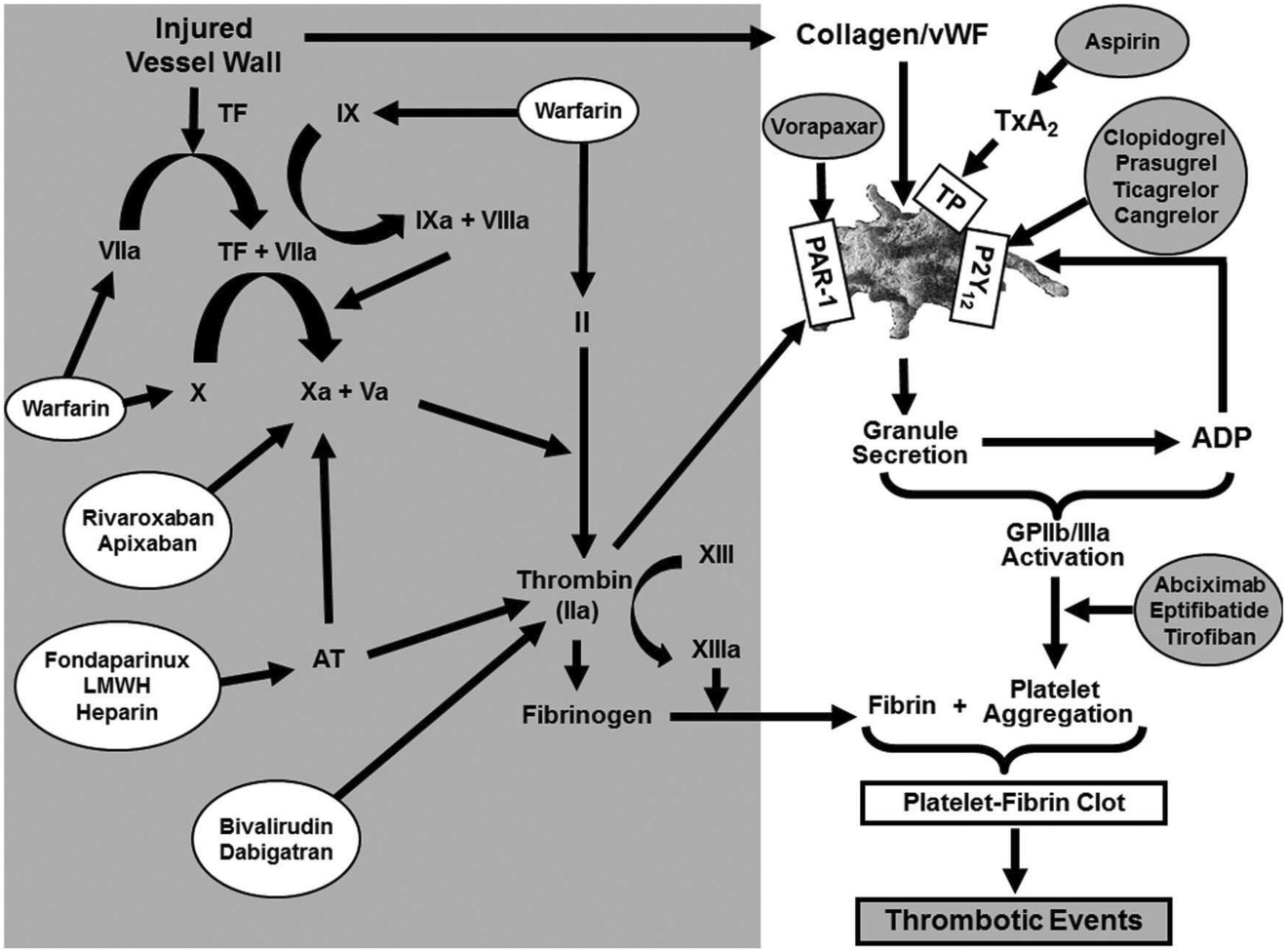

Fig. 1 Available antiplatelet agents and anticoagulants and their sites of action. (Reproduced from: Gurbel P A, Tantry US. Heart 2016, 102(11): 882–892, with permission from BMJ Publishing Group Ltd.) [3]

MI, or non-fatal stroke with prasugrel (9·9% prasugrel vs 12·1% clopidogrel; HR 0·81, 95% CI 0·73–0·90; $P < 0·001$), which was largely due to reduction in non-fatal MI. This was counterbalanced by a concomitant increase in the key safety endpoint of non-CABG-related major bleeding and life-threatening bleeding (1·4 vs 0·9%; $P = 0·01$) [10]. In contrast, TRILOGY-ACS randomly assigned 7243 medically managed patients with NSTE-ACS patients to clopidogrel or prasugrel and found no difference in ischemic outcomes or bleeding risks [11]. Given high risk for intracranial hemorrhage, prasugrel is contraindicated in patients with prior TIA or stroke because of net clinical harm with prasugrel in these patients. Moreover, a lower maintenance dose of 5 mg should be considered in high-risk patients 75 years of age or older and/or patients with a body weight < 60 kg [11]. Again, patients requiring oral anticoagulation were excluded from the TRITON and TRILOGY trials [12]. Guidelines for the use of prasugrel reflect these contraindications and recommend its use only in ACS patients undergoing PCI, not those treated medically.

Ticagrelor

Ticagrelor is a non-thienopyridine, reversibly binding, potent, and fast-acting inhibitor of $P2Y_{12}$ receptor. It was studied in the PLATO trial that randomized 18,642 STEMI or NSTE-ACE patients to aspirin and clopidogrel (300–600 mg followed by 75 mg daily) or ticagrelor (180 mg followed by 90 mg twice daily) and reported reduction in primary composite endpoint of vascular death, myocardial infarction, or stroke with ticagrelor at 12 months (9·8% ticagrelor vs 11·7% clopidogrel, HR 0·84, 95% CI 0·77–0·92, $P < 0·001$). The primary safety endpoint was major bleeding (including CABG-related bleeding) and showed no difference between the two treatments (11.6 vs. 11.2% (HR 1.04; 95% CI 0.95–1.13; $P = 0.43$). However, ticagrelor was associated with a significant increase in non-CABG-related bleeding (4·5 vs 3·8%, $P = 0·03$). Adverse effects of ticagrelor included increased dyspnea, bradycardia, and > 3 s ventricular pause on Holter monitoring during the first week, which disappeared by 30 days [13]. The results of PLATO were adopted into the most recent guidelines that

recommend using ticagrelor 180 mg loading dose followed by 90 mg twice daily as part of DAPT for 12 months in all patients with NSTE-ACS and favoring ticagrelor over clopidogrel [4]. As noted above, the dose of aspirin should be 81 mg when used concomitantly with ticagrelor.

Antiplatelet Therapy Management in ACS Patients Requiring Oral Anticoagulants

Patients who require oral anticoagulation (OAC), like those with atrial fibrillation, can also develop ACS. In these patients, anticoagulation is required for stroke prevention while antiplatelet therapy is required to prevent future major adverse cardiovascular events. The efficacy of combining DAPT with OAC was previously unclear, but the risk of bleeding was ostensibly higher than with each strategy alone. In the last few years, there have been several trials examining the optimal treatment antithrombotic strategy in these complex patients (Table 1). Agents studied include warfarin and the direct-acting oral anticoagulants (DOACs) dabigatran and rivaroxaban in combination with aspirin and clopidogrel. Very few patients in these trials received ticagrelor or prasugrel. The DOAC apixaban is currently being studied in the AUGUSTUS trial with results expected in 2019.

Warfarin

The question of safety and bleeding risks with triple therapy vs double therapy was first answered in the WOEST trial. This was an open-label, multicenter randomized control trial that studied 579 patients with an indication for vitamin K antagonist (atrial fibrillation in 69%, mechanical valve 10%, and other 20%) who had undergone PCI. Patients were randomized to receive warfarin (titrated to INR 2–3) and clopidogrel 75 mg vs. triple therapy with warfarin (INR 2–3), clopidogrel 75 mg and aspirin 80–100 mg daily. The primary endpoint was occurrence of any bleeding at 1 year according to the TIMI, GUSTO, and BARC criteria. The secondary endpoint

Table 1 Clinical trials of oral anticoagulants in ACS patients with atrial fibrillation undergoing PCI

Clinical trial	Study type	Number of patients	Intervention	Primary outcome	Secondary outcome
WOEST	Open-label randomized control trial	579	Warfarin + clopidogrel 75 mg vs. warfarin + clopidogrel 75 mg + aspirin 80–100 mg	Any bleeding at 1 year (TIMI, GUSTO, BARC) 19.4 vs. 44.4% HR 0.36; 95% CI 0.26–0.50; $P < 0.0001$	Composite of death, MI, stroke, stent thrombosis, or revascularization 11.1 vs. 17.6% HR 0.60; 95% CI 0.38–0.94; $P = 0.025$
PIONEER AF-PCI	Open-label randomized control trial	2124	Rivaroxaban (10–15 mg BID) + $P2Y_{12}$ inhibitor vs. rivaroxaban 2.5 mg BID + DAPT (1, 6, or 12 months) vs. warfarin + DAPT (1,6, or 12 months)	TIMI major/minor bleeding or bleeding requiring medical attention at 12 months 16.8 vs. 18.0 vs. 26.7% **Group 1 vs. 3**: HR 0.59; 95% CI 0.47–0.76; $P < 0.001$ **Group 2 vs. 3**: HR 0.63; 95% CI 0.50–0.80; $P < 0.001$	MACE (composite of cardiovascular mortality, MI or stroke) 6.5 vs. 5.6 vs. 6.0% Stent thrombosis 0.8 vs. 0.9 vs. 0.7%
REDUAL-PCI	Open-label randomized control trial	2725	Warfarin + aspirin + $P2Y_{12}$ inhibitor vs. dabigatran 110 mg BID + $P2Y_{12}$ inhibitor vs. dabigatran 150 mg BID + $P2Y_{12}$ inhibitor	ISTH major or clinically relevant non-major bleeding 110 mg vs triple: 15.4 vs 26.9% HR 0.52; 95% CI 0.42–0.63; $P < 0.001$ 150 mg vs triple: 20.2 vs 25.7% HR 0.72; 95% CI 0.58–0.88; $P = 0.002$	Composite of thromboembolic events, death, or unplanned revascularization (pooled dabigatran vs. triple) 13.7 vs 13.4%, HR 1.04, 95% CI 0.84–1.29, $P = 0.005$ for non-inferiority
AUGUSTUS	Open-label, 2 × 2 factorial, randomized control trial	4600	$P2Y_{12}$ inhibitor + apixaban + aspirin vs. $P2Y_{12}$ inhibitor + apixaban + placebo vs. $P2Y_{12}$ inhibitor + warfarin+ aspirin vs. $P2Y_{12}$ inhibitor + warfarin + placebo	Major or clinically relevant non-major ISTH bleeding (results pending)	All-cause death and all-cause hospitalizations

was a composite of death, MI, stroke, stent thrombosis, or target vessel revascularization. The rate of the primary endpoint was 19.4% with double therapy and 44.4% with triple therapy (HR 0.36, 95% CI 0.26–0.5, $P < 0.001$). The secondary endpoint was reported in 11.1% in the double therapy group and 17.6% in the triple therapy group (HR 0.60, 95% CI 0.38–0.94, $P = 0.025$) [14]. Although the study was underpowered to detect differences in ischemic thrombotic events, this study changed practice guidelines in 2014, which gave Class IIb, level of evidence B rating to using oral anticoagulant and clopidogrel in patients with atrial fibrillation undergoing coronary revascularization with stents [15].

Hess et al. performed a large retrospective study using the ACTION-GWTG registry (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines) to study Medicare patients with atrial fibrillation or flutter who had an acute MI requiring admission and treatment with stenting. Among 4959 patients who met criteria, 1370 were discharged on triple therapy using Warfarin, aspirin, and $P2Y_{12}$ inhibitor; the rest were discharged on dual antiplatelet therapy. The primary outcome was MACE at 2 years, defined as death, readmission for MI, or stroke (ischemic or hemorrhagic). The primary safety outcome was bleeding readmission within 2 years after index hospitalization. The authors discovered that patients in both arms had a similar risk of MACE at 2 years (adjusted hazard ratio HR 0.99, 95% CI 0.86 to 1.16, $P = 0.94$). However, triple therapy was associated with a significantly greater risk of bleeding requiring hospitalization (adjusted HR 1.61, 95% CI1.31 to 1.97, $P < 0.0001$), and greater risk of intracranial hemorrhage (adjusted HR 2.04, 95% CI 1.25 to 3.34, $P < 0.01$) [16].

Rivaroxaban

Rivaroxaban is an oral selective, reversible direct factor Xa inhibitor, and thereby prevents conversion of prothrombin to thrombin thus inhibiting formation of fibrin clot and thrombin-mediated platelet activation. It is absorbed rapidly and can reach peak plasma concentrations in 2–4 h, and it can inhibit factor Xa for up to 24 h allowing for once-a-day dosing. It is hepatically metabolized via the CYP3A4/5 and CYP2J2 system and thus it should not be used in patients with moderate to severe hepatic impairment and associated coagulopathy. It should be avoided in ESRD and patients with severe chronic kidney disease (CrCL< 15 ml/min), and dose should be reduced from 20 mg to 15 mg/day in moderate to severe chronic kidney disease (CrCl 15–50 ml/min) [17].

Rivaroxaban was shown to be non-inferior to warfarin in preventing strokes and systemic embolism in the large pivotal ROCKET AF Trial of patients with non-valvular atrial fibrillation; additionally, there were no significant differences in the risk for major bleeding [18].

A sub-analysis of ROCKET AF trial studied 153 patients who underwent PCI while enrolled in the study and found that post PCI patients had a higher thrombotic, ischemic, and bleeding risk seen mostly within 6 months after PCI. Also, they observed that post PCI, DAPT was used in a variable manner in patients requiring oral anticoagulation, highlighting a need for systematic studies to offer guidance on patients on oral anticoagulant therapy undergoing PCI [19].

With respect to ACS, the ATLAS-ACS-TIMI-51 compared low-dose rivaroxaban, 2.5 mg twice daily, or 5 mg twice daily, with placebo, on the background of DAPT, in 15,526 patients with recent ACS. It showed that rivaroxaban reduced the primary outcome of cardiovascular death, MI, or ischemic stroke compared with placebo (HR 0.84; 95% CI 0.74–0.96; $P = 0.08$) but increased major TIMI non-CABG bleeding (2.1 vs. 0.6%, $P < 0.001$) [20]. The use of rivaroxaban in ACS patients undergoing PCI also reduced stent thrombosis (2.3% rivaroxaban vs. 2.9% placebo, HR 0.69; 95% CI 0.51–0.93; $P = 0.02$).

The ATLAS trial did not specifically include patients with atrial fibrillation. To study that population, the PIONEER AF-PCI randomized 2124 patients with atrial fibrillation undergoing PCI with stents in a 1:1:1 ratio to 15 mg rivaroxaban + $P2Y_{12}$ inhibitor for 12 months (group 1), low-dose rivaroxaban 2.5 mg twice daily and DAPT for prespecified duration of 1, 6, or 12 months (group 2), and lastly warfarin and DAPT for 1, 6, or 12 months (group 3). The index event leading to PCI was ACS (both NSTE and STEMI) in 50% of the participants, and the $P2Y_{12}$ inhibitor was clopidogrel in 94% of patients. All participants continued to receive 12 months of trial drug with at least single antiplatelet agent once their respective 1- or 6-month DAPT period was over. The primary outcome was clinically significant bleeding according to TIMI criteria, and the secondary endpoint was MACE (a composite of death from cardiovascular causes, myocardial infarction, or stroke) at 12 months. The rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving warfarin (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3 (HR for group 1 vs. group 3, 0.59; 95% CI, 0.47 to 0.76; $P < 0.001$; HR for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; $P < 0.001$). Additionally, the rates of MACE were similar in all three groups (6.5% in group 1, 5.6% in group 2, and 6.0% in group 3 ($P > 0.05$ for both comparisons). The rates of stent thrombosis were 0.8% in group 1, 0.9% in group 2, and 0.7% in group 3 (HR for group 1 vs. group 3, 1.20; 95% CI, 0.32–4.45; $P = 0.79$; HR for group 2 vs. group 3, 1.44; 95% CI, 0.40–5.09, $P = 0.59$). However, the total number of MACE was small and the trial was not powered to establish superiority or non-inferiority [21•].

Dabigatran

Dabigatran is a prodrug that is rapidly converted to its active form by plasma and hepatic esterases. The active form is a selective, reversible, direct thrombin inhibitor which inhibits both free and fibrin-bound thrombin. Dabigatran has a rapid onset of action and reaches peak plasma concentration in 2 h. Its half-life is 12 to 17 h and is increased to 15–18 h in patients with mild to moderate renal impairment; thus, its dose needs to be reduced in patient with impaired kidney function (e.g., creatinine clearance 15–28 ml/min). It has not been studied in patients with severe renal or hepatic impairment; its use should be avoided in this population. Additionally, dabigatran has a black box warning of increased risk of thrombotic events upon premature discontinuation [22].

Dabigatran was first compared with warfarin in RELY trial, which studied rates of thromboembolic events and major bleeding in 18,113 patients with non-valvular atrial fibrillation. Patients were randomized to receive either dabigatran at 150 mg twice daily, 110 mg twice daily, or warfarin titrated to INR 2.0–3.0 and were followed for 2 years for the occurrence of stroke or systemic embolism. RELY showed that dabigatran given at 110 mg twice a day was non-inferior to warfarin (1.53% with dabigatran 110 mg vs. 1.69% with warfarin, RR 0.91, 95% CI 0.74–1.11, $P < 0.001$ for non-inferiority) and had lower rates of major bleeding (2.71% with dabigatran 110 mg vs. 3.36% in warfarin). Additionally, dabigatran given at 150 mg twice a day was superior to warfarin at preventing the primary outcome of stroke or systemic embolization (1.11% with dabigatran 150 mg vs. 1.69% with warfarin, RR 0.66, 95% CI 0.53–0.82, $P < 0.001$), and had similar rates of major hemorrhage [23].

REDEEM was a phase II study of 1861 patients with recent ACS who were randomized to twice daily treatment with escalating doses of dabigatran in addition to standard DAPT compared with placebo. It showed that dabigatran was associated with a dose-dependent increase in the primary outcome of major clinically relevant minor bleeding at 6 months, but the study was not powered to detect reductions in ischemic events [24]. An ACS indication for dabigatran was not pursued with a phase 3 trial.

The REDUAL-PCI trial addressed the issue of the safety of dabigatran with antiplatelet therapy among patients undergoing PCI. It was a prospective, randomized trial of 2725 patients with non-valvular atrial fibrillation who have undergone PCI with stenting. It randomized patients in 1:1:1 ratio to receive triple therapy (warfarin, clopidogrel, or ticagrelor, and aspirin), dual therapy with dabigatran 110 mg twice daily and clopidogrel or ticagrelor, or dual therapy with dabigatran 150 mg twice daily and clopidogrel or ticagrelor. The indication for PCI was ACS in approximately 50% of patients. The primary outcome was the rate of ISTH major bleeding or clinically relevant non-major bleeding; patients were followed for 14 months. In the triple therapy group, aspirin was discontinued after 1 to 3 months (1 if BMS and 3 after DES), and all patients received $P2Y_{12}$ for 12 months. The primary endpoint was lower in the 110 mg dual therapy group than in the triple therapy group (15.4% with 110 mg dabigatran vs. 26.9% with warfarin, HR 0.52 (95% CI 0.42–0.63); $P < 0.001$), and it was lower in the 150 mg dual therapy group (20.2% with 150 mg dabigatran vs. 25.7% with warfarin, HR 0.72 (95% CI 0.58–0.88); $P = 0.002$). Secondary efficacy analyses were the composite of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularizations, and rates were similar between pooled dabigatran dual therapy and triple therapy groups (13.7 vs 13.4%, HR 1.04, 95% CI 0.84–1.29, $P = 0.005$ for non-inferiority). However, once removing unplanned revascularizations, there was a 1.1% non-significant increase in rates of thromboembolism and death in the pooled dual therapy group (HR 1.17, 95% CI 0.90–1.53, $P = 0.11$ for non-inferiority). Importantly, the study was not statistically powered for thrombotic events [25•].

Apixaban

Apixaban is an oral, reversible, direct-acting factor Xa inhibitor. It reaches peak plasma concentration in 3–4 h and has a half-life of 12 h allowing it to be dosed twice a day. Although there are no dosage adjustment recommendations from the manufacturer, it should be avoided in patients with creatinine clearance < 25 ml/min. The recommended dose for patients with non-valvular atrial fibrillation is 5 mg twice daily, and this dose needs to be halved in patients who meet at least two of the following criteria: weight < 60, age > 80, and serum creatinine > 1.5 [26].

The ARISTOTLE AF trial ($N = 18,201$) showed that patients with atrial fibrillation treated with apixaban had lower rates of ischemic or hemorrhagic stroke, systemic embolism, and lower ISTH major bleeding as compared with warfarin [27].

With respect to apixaban's role in secondary prevention after ACS, the APPRAISE-2 trial was done comparing apixaban with placebo in addition to standard DAPT for high-risk patients who recently had an ACS (STEMI or NSTEMI). Patients were treated either with 5 mg twice daily of apixaban or placebo in addition to standard antiplatelet therapy, with a primary outcome of MACE and a primary safety endpoint of TIMI major bleeding. However, the study was terminated prematurely due to increased bleeding in the Apixaban cohort with no significant reduction in ischemic events [28].

Two trials are studying apixaban in patients with atrial fibrillation undergoing percutaneous coronary intervention. The SAFE-A study aims to find optimal duration of triple antithrombotic therapy by comparing 1- vs. 6-month $P2Y_{12}$

inhibitor therapy in combination with aspirin and apixaban, in 600 patients with atrial fibrillation who undergo DES implantation. The primary endpoint is incidence of all bleeding complications occurring at 12 months and secondary endpoints include rates of ischemic stroke and stent thrombosis [29].

AUGUSTUS is a multicenter, international trial aiming to study 4600 patients with atrial fibrillation who develop ACS and/or undergo PCI, by randomizing them using a 2 × 2 factorial design to either apixaban or warfarin and aspirin or placebo. All patients will receive $P2Y_{12}$ inhibitor and will be followed for 6 months, as this is the time period when risk of ischemic events is highest. Primary outcomes include major or clinically relevant non-major ISTH bleeding, and key secondary outcomes include all-cause death and all-cause hospitalizations. Other secondary outcomes of interest include rates of death, MI, stroke, stent thrombosis, urgent revascularization, and first hospitalization for any cause. AUGUSTUS will not exclude patients with a history of prior stroke, TIA, anemia, or prior gastrointestinal bleeding potentially allowing for greater generalizability of results [30].

Chiarito et al. did a meta-analysis of six studies that compared DOAC plus DAPT with DAPT alone in patients with ACS and reported a differential in outcome based on type of ACS (STEMI vs. NSTE-ACS). The primary efficacy endpoint was the composite of cardiovascular death, myocardial infarction, and stroke, and the prespecified primary safety endpoint was major TIMI bleeding. The primary efficacy endpoint was significantly lower in the patients treated with DOAC in addition to DAPT compared with those treated with DAPT alone (OR 0.85; 95% CI, 0.77–0.93; $P < 0.01$); however, the DOAC plus DAPT group also had a higher risk of major bleeding compared (OR 3.17; 95% CI, 2.27–4.42; $P < 0.01$).

Four of the trials reported outcomes based on type of ACS (STEMI vs. NSTE-ACS); and when stratified by type of ACS, there was a difference in results. In patients with STEMI, DOAC plus DAPT significantly lowered the risk of primary efficacy endpoint as compared with DAPT alone (OR 0.76; 95% CI 0.66–0.88; $P < 0.01$), whereas there was no significant difference in the NSTE-ACS group (OR 0.92; 95% CI 0.78–1.09; $P = .361$). Triple therapy groups had higher rates of bleeding regardless of type of ACS. One suggested explanation for this difference in outcome between STEMI and NSTEMI is the presence of higher thrombotic burned and increased coagulation cascade activation after STEMI [31•].

Summary and Future Direction

Patients with ACS requiring PCI who have another indication for oral anticoagulation, like atrial fibrillation, represent a challenging population in whom the balance between ischemia and hemorrhage must be weighed carefully. There are four recent and ongoing trials which offer guidance in managing this tenuous balance. WOEST showed that holding aspirin and continuing patients on warfarin and clopidogrel decreased hemorrhage at 1 year without increasing thromboembolic events. Studies with DOACs such as PIONEER AF-PCI showed that 10–15 mg rivaroxaban plus $P2Y_{12}$ inhibitor for 12 months had significantly lower bleeding rates than standard triple therapy and had equivalent rates of MACE and stent thrombosis. Similarly, REDUAL-PCI compared two different doses of dabigatran plus $P2Y_{12}$ inhibitor with standard triple therapy and again showed decreased bleeding rates with both doses of dabigatran. Although the composite endpoint of thromboembolic events, death, or unplanned revascularizations was similar between standard therapy and the pooled dabigatran doses, the incidence was 1% lower in the 150 mg dual therapy group. Although none of these trials were powered to detect thrombotic events (non-fatal MI, non-fatal stroke, or cardiovascular mortality), largely limited by sample size needed to detect a difference, the pooled data suggest greater generalizability. Moreover, the ongoing AUGUSTUS will be the first trial to compare two double therapies ($P2Y_{12}$ + warfarin with $P2Y_{12}$ + apixaban) and thus may provide more data to guide clinical practice.

Compliance with Ethical Standards

Conflict of Interest Anish Badjatiya and Sunil V. Rao declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Percutaneous Coronary Intervention of Chronic Total Occlusions in Patients with Diabetes Mellitus: a Treatment-Risk Paradox

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Abstract

Purpose of Review Diabetes mellitus (DM) is highly prevalent among patients undergoing percutaneous coronary intervention (PCI) for chronic total occlusions (CTOs). This review aims to summarize the available evidence on CTO recanalization in patients with DM.

Recent Findings Coronary artery bypass grafting (CABG) surgery is the recommended revascularization modality for patients with DM and multivessel coronary artery disease (CAD). However, the optimal management strategy in diabetic patients with CTO and single-vessel disease or prior CABG remains a clinical dilemma. Contemporary, large-scale, observational registries support the notion that CTO PCI, if performed at high-volume CTO PCI centers by highly experienced operators, conveys similar high procedural success and low complication rates in patients with and without DM. Although DM patients have more frequently CTOs and may derive greater benefit from complete revascularization, they are less frequently exposed to CTO PCI than non-DM patients (*treatment-risk paradox*).

Summary CTO PCI performed by highly experienced operators constitutes a safe and effective treatment option for selected diabetic CTO patients who are not candidates for CABG. Randomized studies are warranted to compare long-term outcomes of CTO PCI and medical therapy in this high-risk subset.

Keywords Chronic total occlusion · Percutaneous coronary intervention · Diabetes mellitus · Coronary revascularization

Abbreviations

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CTO	Chronic total occlusion
DES	Drug-eluting stent
DM	Diabetes mellitus
MACE	Major adverse cardiac events
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
TLR	Target lesion revascularization
TVR	Target vessel revascularization

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Introduction

Percutaneous coronary intervention (PCI) for chronic total occlusions (CTOs) is a rapidly evolving area of interventional cardiology. If performed at high-volume CTO PCI centers and by highly experienced operators, the latest refinements in CTO PCI equipment and techniques, including the recent introduction of the *hybrid* approach which entails a tailored strategy based on angiographic characteristics (i.e., antegrade vs. retrograde approach and wire escalation vs. dissection reentry crossing techniques) [1], enabled high procedural success rates (85–90%) while maintaining acceptable low major

complications rates (~3%) [2–5]. These results have contributed to a renewed interest for CTO PCI and the increase in the number of CTO recanalizations, as well as in the patient and lesion complexity approached [3–6].

Diabetes mellitus (DM) is highly prevalent among patients with coronary artery disease (CAD) [7] and is associated with greater atherosclerotic burden, including diffuse, small-vessel, and multivessel disease, coronary artery calcifications, and higher rates of left main coronary stenoses and CTOs [7–10]. The presence of DM is considered as a major determinant when selecting the optimal myocardial revascularization strategy (i.e., PCI vs. coronary artery bypass grafting [CABG]) in patients with multivessel CAD [11, 12•, 13]. Compared with individuals without DM, diabetic patients undergoing PCI with newer-generation drug-eluting stents (DES) have increased long-term major adverse cardiac events (MACE) rates, driven by higher rates of repeat revascularization, irrespective of the underlying CAD complexity [14–16]. Although, even with CABG surgery, DM is associated with an increased risk of complications [17, 18], current evidence from dedicated randomized controlled trials (RCTs), subgroup analyses of RCTs, and observational data consistently favors CABG as the revascularization modality of choice for patients with DM and multivessel CAD [11, 12•]. Nevertheless, PCI remains an established alternative treatment for selected diabetic patients with CTO and single-vessel disease or prior CABG [11, 12•]. This review aims to provide an overview of the currently available evidence on CTO recanalization in patients with DM, with a special emphasis on procedural success, periprocedural complications, and long-term MACE rates.

Specificities of Coronary Artery Disease in Diabetes Mellitus

DM is present in 20 to 30% of patients undergoing myocardial revascularization [11, 12•]. The accelerated atherosclerotic burden observed in diabetic individuals is believed to result from the combination of prothrombotic and proinflammatory states, systemic endothelial dysfunction, and metabolic disorders, including hyperglycemia, dyslipidemia, obesity, insulin resistance, and oxidative stress [7]. Compared with non-diabetic individuals, patients with DM have more extensive and complex coronary atherosclerotic disease, including multivessel, diffuse, and small-vessel CAD and coronary artery calcifications, and a twofold higher rate of CTOs [8–10]. The greater burden of anatomical coronary complexity observed in patients with DM as compared with non-DM individuals results in more challenging myocardial revascularization and higher degrees of residual jeopardized myocardium by the means of both PCI and CABG surgery [7, 19].

Complete myocardial revascularization was consistently associated with favorable long-term clinical outcomes, including lower mortality, myocardial infarction (MI), and repeat revascularization rates among patients with complex or multivessel CAD undergoing both PCI and CABG surgery [20, 21]. This was found to be true also for DM patients, as incomplete revascularization was associated with a higher risk of long-term MACE including death, MI, stroke, or repeat revascularization, among patients with DM compared with diabetic individuals completely revascularized, irrespective of the revascularization modality [19, 22]. In a post hoc analysis of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial including 751 diabetic patients undergoing myocardial revascularization by the means of PCI using bare-metal stents or first-generation DES ($n = 487$), or CABG surgery ($n = 264$) [19], complete revascularization was achieved in only 38% of patients, whereas mildly and moderately to severely incomplete revascularization occurred in 47% and 15% of patients, respectively. Compared with patients incompletely revascularized, complete anatomical revascularization was associated with lower rates of the composite outcome of death, MI, or stroke, as well as repeat revascularization, irrespective of the revascularization strategy (PCI or CABG) [19]. Previous studies suggest that complete revascularization among patients with multivessel CAD is more commonly achieved with CABG surgery than with PCI [19, 20, 23•]. In the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial, the significantly lower rates of complete revascularization observed among patients who underwent PCI compared with CABG surgery (34.3% vs. 64.8%, $p < 0.001$, respectively) resulted from extremely low CTO PCI procedural success rates achieved with PCI as compared with CABG surgery (49.4% vs. 68.1%, respectively) [23•]. The presence of a CTO was shown to be the strongest independent predictor of incomplete revascularization among patients with complex or multivessel CAD treated by PCI (hazard ratio (HR) 2.70, 95% CI 1.98–3.67, $p < 0.001$) [23•]. Among CTO patients undergoing PCI, heavy coronary artery calcifications and long lesions, which are observed more frequently among patients with DM than in non-diabetic individuals [8–10], were also independent predictors of incomplete myocardial revascularization [23•].

Current evidence supports CABG surgery over PCI as the preferred revascularization modality for diabetic patients with multivessel CAD [11, 12•, 13, 24, 25]. In the SYNTAX trial [24], PCI with first-generation DES in patients with complex multivessel CAD resulted in significantly higher rates of MACE, including all-cause death, MI, or stroke, as well as repeat revascularization, at 5 years compared with CABG. More recently, CABG surgery was found to be superior to PCI with mostly first-generation DES on the background of optimal medical therapy with respect to the composite

outcome of all-cause death, nonfatal MI, or stroke at 5 years in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial [25]. Notwithstanding, the optimal revascularization strategy for selected diabetic patients with single-vessel CTO or recurrent disease after CABG remains a clinical dilemma, and PCI is frequently proposed to this high-risk patient subset.

CTO and Diabetes Mellitus

CTOs are observed in 16 to 52% of patients undergoing coronary angiography [26••]. Despite the lack of definitive randomized evidence on the beneficial effects of CTO PCI compared with optimal medical therapy, observational cohort studies demonstrated that successful CTO PCI, as opposed to a failed procedure, is associated with improved clinical outcomes including lower risk of mortality, MACE, residual angina, and the need for CABG surgery [26••, 27]. Nonetheless, CTO PCI remains widely underused worldwide with the exception of dedicated high-volume CTO PCI centers [26••], as the majority of CTO patients are currently treated with either CABG surgery or medical therapy alone [26••, 28]. The probable explanation for this finding is that, compared with non-CTO PCI, CTO recanalization is a complex procedure requiring dedicated skillset and equipment, which is associated with lower procedural success rates, higher major complications risk, and increased radiation exposure to patient and operator [29]. Among patients undergoing CTO recanalization, DM is common with a prevalence ranging from 27 to 45% in large contemporary registries [30••, 31••, 32••]. Among patients with complex or multivessel CAD undergoing PCI, the presence of CTO was shown to negatively impact the degree of revascularization completeness and long-term clinical outcomes, including mortality, repeat revascularization, or stent thrombosis [23•]. These findings do apply more to DM patients because of the twofold higher prevalence of CTOs observed in patients with DM compared with non-diabetic individuals [8]. Whereas DM confers per se significantly worse prognosis in CAD patients undergoing coronary revascularization compared with non-diabetic individuals, additional cardiovascular risk factors and comorbidities that individually negatively impact cardiovascular outcomes are also more prevalent in DM patients. Baseline clinical and angiographic characteristics of patients with and without DM included in most contemporary large-scale CTO PCI registries are summarized in Table 1. Overall, diabetic patients undergoing CTO PCI had a higher baseline cardiovascular risk profile than non-diabetic individuals. Importantly, patients with DM were more likely to have a history of prior CABG, which has been invariably associated with lower success rates following CTO PCI [33–35].

CTO PCI and Diabetes Mellitus

Although, as mentioned, CTOs are more prevalent among patients with DM [8], CTO PCI is performed less commonly in diabetic patients compared with non-diabetic individuals [36, 37]. The fact that high-risk patients are less frequently treated than lower risk individuals, a so-called *treatment-risk paradox*, is not new in the field of PCI [7]. Diabetic patients remain at increased risk for long-term MACE following PCI even with newer-generation DES, driven by higher rates of target lesion revascularization (TLR), irrespective of the underlying CAD complexity [16]. However, data concerning the impact of DM on long-term clinical outcomes after CTO PCI in patients with DM in the DES era are scant. In the absence of dedicated trials, the evidence is limited to subgroup analyses of large-scale, prospective, observational studies [30••, 31••, 32••, 38–44]. Notwithstanding, interpretation of these data is limited by the number of diabetic patients included, the low proportion of patients with more advanced DM such as insulin-dependent diabetic subjects, and the short-term follow-up period, precluding therefore any definitive conclusion with respect to longer-term clinical outcomes after CTO PCI in diabetic patients.

Early Studies

Early evidence reporting on the clinical outcomes of patients with DM undergoing CTO PCI was mostly limited to small single-center, observational studies and demonstrated conflicting results. In a single-center registry, clinical outcomes of 506 diabetic patients who underwent CTO PCI were compared with 506 patients with DM undergoing PCI of a non-CTO using propensity score matching [38]. Whereas angiographic success rates were significantly lower in diabetic CTO patients (75% vs. 93%, $p < 0.001$), rates of in-hospital MACE, a composite of death, urgent CABG, Q wave MI, or target vessel revascularization (TVR) were similar between CTO and non-CTO diabetic patients (3.2% vs. 2.6%, $p = 0.57$) [38]. Five-year survival rates were not different between CTO and non-CTO diabetic subjects (75% vs. 79%, $p = 0.20$) and there were no significant differences with respect to in-hospital (success 1.6% vs. failure 2.4%, $p = 0.70$) or 1-year mortality (success 22.2% vs. failure 26.8%, $p = 0.30$) among diabetic CTO patients according to angiographic CTO PCI success [38]. In a single-center registry including 163 patients (diabetics, $n = 34$; non-diabetics, $n = 129$) who underwent successful CTO PCI [39], rates of in-hospital MACE, a composite of death, Q wave, or urgent TVR were significantly higher among diabetic patients compared with patients without DM (23.5% vs. 7.8%, $p = 0.02$), mainly driven by a significantly increased risk of repeat revascularization (20.6% vs. 7%, $p = 0.04$) in subjects with DM [39]. However, long-term MACE rates were not statistically different between

Table 1 Baseline characteristics of patients with and without diabetes mellitus included in recent large contemporary CTO PCI registries

Characteristics	PROGRESS CTO registry [32••]			Sanguinetti et al. [33]			OPEN-CTO registry [34]		
	Diabetes ($n = 584$)	No diabetes ($n = 724$)	p value	Diabetes ($n = 362$)	No diabetes ($n = 958$)	p value	Diabetes ($n = 412$)	No diabetes ($n = 588$)	p value
Age (years)	65.3 ± 9.6	65.7 ± 10.6	0.26	65.5 ± 10.4	62.2 ± 11.6	< 0.0001	65.5 ± 9.9	65.3 ± 10.6	0.79
Male gender (%)	82.5	85.5	0.13	82.3	86.7	0.04	76.5	83.2	0.008
BMI (kg/m^2)	31.3 ± 6.4	29.2 ± 5.7	0.001	28.7 ± 4.6	26.7 ± 4.0	< 0.0001	32.2 ± 6.4	29.2 ± 5.4	< 0.001
Hypercholesterolemia (%)	96.4	92.8	0.005	63.3	63.5	0.94	NR	NR	NR
Hypertension (%)	NR	NR	NR	72.8	54.0	< 0.0001	NR	NR	NR
Current smoker (%)	26.3	29.6	0.29	21.8	28.6	0.01	12.3	14.3	0.37
Prior MI (%)	41.9	42.2	0.92	22.7	21.8	0.74	53.6	44.7	0.005
Prior PCI (%)	65.4	64.4	0.69	NR	NR	NR	68.9	63.4	0.07
Prior CABG (%)	38.1	31.0	0.007	10.2	6.4	0.01	42.2	32.5	0.001
PAD (%)	18.9	12.8	0.003	NR	NR	NR	21.6	14.6	0.004
LVEF (%)	NR	NR	NR	55.7 ± 9.0	57.0 ± 9.6	0.04	49.8 ± 13.7	51.8 ± 13.8	0.06
J-CTO score	2.6 ± 1.2	2.5 ± 1.2	0.82	1.5 ± 0.8	1.3 ± 0.9	0.02	2.4 ± 1.3	2.3 ± 1.2	0.03
CTO length (mm)	NR	NR	NR	18.3 ± 13.4	18.2 ± 14.9	1.00	63.7 ± 29.1	59.1 ± 27.9	0.01
CTO vessel (%)			0.34						0.48
Left anterior descending artery	22.8	23.6		31.2	31.1	0.97	19.2	21.9	
Left circumflex artery	21.6	18.3		25.4	21.6	0.14	17.2	16.7	
Right coronary artery	55.6	58.1		42.8	47.2	0.16	62.4	60.9	

Values are mean ± standard deviation. *NR* not reported, *BMI* body mass index, *CABG* coronary artery bypass grafting, *CTO* chronic total occlusion, *J-CTO* Japan chronic total occlusion, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention

both groups at a mean follow-up of 15 months (35.3% vs. 28.5%) [39].

In the Multinational CTO Registry including 1742 patients (diabetics, $n = 395$; 23%; insulin-dependent diabetics, $n = 164$, 42% of the diabetic population) [40], the procedural success rates were similar in patients with versus without DM (69.6% vs. 67.9%, $p = 0.53$). Among diabetic patients, successful CTO PCI was associated with lower long-term mortality rates (10.4% vs. 13.0%, $p < 0.05$) and reduced need for CABG (2.4% vs. 15.7%, $p < 0.01$) at a median follow-up of 3 years [40]. Multivariate analysis identified insulin-dependent DM as an independent predictor of all-cause mortality among patients with DM (HR 2.25, 95% CI 1.04–4.87, $p = 0.04$) [40]. In a subanalysis of the multicenter, randomized CIBELES trial including 207 patients (diabetics, $n = 75$; insulin-dependent diabetics, 21%) undergoing successful CTO PCI with DES [41], the cumulative survival rates free from MACE (86.3% vs. 87.5%, $p = 0.80$), death (97.3% vs. 99.2%, $p = 0.27$), MI (100% vs. 97.7%, $p = 0.19$), and TVR (88.7% vs. 88.2%, $p = 0.90$) were similar between patients with and without DM at 12 months follow-up. Conversely, in a large-scale Korean multicenter CTO registry including 2865 patients (977 diabetic patients, 34%) who underwent CTO PCI with DES [42], successful CTO PCI (83% of the overall patient population), defined as reduction in angiographic minimum diameter stenosis to < 30% in presence of thrombolysis in myocardial infarction (TIMI) grade 2 flow, was associated with significantly the higher crude rates of TLR (6.1% vs. 3.9%, $p = 0.02$), TVR (7.2% vs. 4.8%, $p = 0.02$), MACE (10.3% vs. 7.7%, $p = 0.01$), and the combined endpoint of cardiac death, MI, or TLR (7.7% vs. 5.5%, $p = 0.02$) among patients with DM compared with non-diabetic individuals. Among diabetic patients, the all-cause mortality (6.1% vs. 1.9%, $p = 0.02$), TLR (11.3% vs. 4.6%, $p = 0.007$), TVR (12.2% vs. 5.9%, $p = 0.025$), MACE (17.4% vs. 9.2%, $p = 0.012$), and combined endpoints of cardiac death, MI, or TLR (8.0% vs. 5.9%, $p = 0.003$) and cardiac death, MI, or TVR (16.5% vs. 8.0%, $p = 0.008$) rates were significantly more frequent in patients with insulin-dependent than non-insulin-dependent DM [42]. In a multivariate analysis, DM was an independent predictor for the 1-year TLR (odds ratio (OR) 2.20, $p = 0.001$) and MACE (OR 1.68, $p = 0.002$), whereas insulin-dependent DM was an independent predictor for the 1-year all-cause death (OR 3.19, $p = 0.04$), TLR (OR 2.93, $p = 0.005$), TVR (OR 2.44, $p = 0.02$), MACE (OR 2.21, $p = 0.01$), and combined endpoints of cardiac death, MI, or TLR (OR 2.91, $p = 0.003$) and cardiac death, MI, or TVR (OR 2.35, $p = 0.009$) [42]. These findings persisted after

propensity score-matched analysis to account for differences in baseline demographic and lesion characteristics. The results of CTO registries reporting the initial experience of CTO PCI in diabetic versus non-diabetic patients were pooled in a recent meta-analysis of 7 trials (one randomized trial, 6 observational studies) including a total of 4571 patients (1915 subjects with type 2 DM) undergoing CTO PCI [43]. While acute procedural results were not reported, the all-cause mortality (OR 1.56, 95% CI 1.05–2.31, $p = 0.03$), MACE (OR 1.30, 95% CI 1.06–1.58, $p = 0.01$), and repeat revascularization (OR 1.30, 95% CI 1.06–1.59, $p = 0.01$) were significantly higher in CTO diabetic patients at long-term follow-up (≥ 1 year) [43].

Recent Studies

Recently, several studies reported the outcome results of contemporary cohorts of diabetic patients undergoing CTO PCI in high-volume centers by experienced operators using mostly the *hybrid* approach (Table 2). In a recent analysis of the large-scale, multicenter Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS CTO) registry [30••] including 1308 patients (mean age 65.5 years) with ($n = 584$, number of insulin-dependent DM patients not reported) and without DM ($n = 724$) undergoing CTO PCI at 11 US high-volume centers, both technical (90.7% vs. 90.3%, $p = 0.80$) and procedural (89.3% vs. 89.1%, $p = 0.90$) success rates were similar among subjects with and without DM, despite adverse angiographic characteristics among diabetic patients (moderate-to-severe coronary calcifications, 61% vs. 56%, $p = 0.12$; proximal cap ambiguity, 33% vs. 30%, $p = 0.27$; Japan chronic total occlusion (J-CTO) score, 2.6 vs. 2.5, $p = 0.82$). The final successful crossing strategy was similar irrespective of the diabetic status (retrograde, 30% vs 27.7%; antegrade wire escalation, 45.8% vs. 47.2%; antegrade dissection re-entry, 24% vs. 25%, $p = 0.66$) [30••]. The CTO procedure duration and fluoroscopy time and fluoroscopy time were similar in both groups, but the radiation dose was higher, whereas contrast volume was lower, among diabetic subjects [30••]. Importantly, the in-hospital MACE (2.2% vs. 2.5%, $p = 0.61$), mortality (0.4% vs. 0.3%, $p = 0.51$), MI (1.3% vs 0.5%, $p = 0.11$), stroke (0.4% vs 0.1%, $p = 0.40$), emergency PCI (0.3% vs 0.3%, $p = 0.82$) or need for CABG surgery (0% vs. 0%), and emergency pericardiocentesis (0.6% vs 0.6%, $p = 0.99$) rates were similarly low in patients with and without DM [30••].

In a prospective, single-center, high-volume CTO PCI registry including 1320 consecutive patients (diabetics, $n = 362$; insulin-dependent DM patients not reported) [31••], the procedural success rates were numerically lower, despite statistically not significant, among subjects with DM compared with non-diabetic patients (69.8% vs. 75%, $p = 0.07$) despite a higher prevalence of multivessel CAD (64.4% vs. 59.4%, $p = 0.09$), prior CABG (10.2% vs. 6.4%, $p = 0.01$), and significantly more complex disease (J-CTO score, 1.45 vs. 1.34, $p = 0.02$) in the diabetic subgroup. Cardiac tamponade occurred similarly in both diabetic and non-diabetic groups (0.8% vs. 1.4%, $p = 0.43$) [31••]. Whereas all-cause (23.1% vs. 22.2%, $p = 0.16$) and cardiac (11.3% vs. 10.7%, $p = 0.08$) mortality rates did not significantly differ between successful and failed CTO PCIs among non-diabetic patients, unsuccessful CTO PCI was associated with significantly higher risk of all-cause (54.9% vs. 23.2%, $p < 0.001$) and cardiac (31.0% vs. 13.1%, $p < 0.001$) mortality in patients with DM at a median follow-up of 4.2 years [31••]. These findings suggest superior clinical benefits of successful CTO PCI in diabetic patients compared with non-diabetic subjects and a *treatment-risk paradox* (i.e., higher risk patients, more benefit from the procedure but the procedure is less frequently performed). By multivariate analysis, the presence of DM (HR 2.44, 95% CI 1.52–3.83, $p < 0.001$), decreased left ventricular ejection fraction (HR 0.96, 95% CI 0.94–0.99, per percent decrease, $p = 0.004$), and increased age (HR 1.06, 95% CI 1.03–1.08, per year increment, $p < 0.0001$) were found independent predictors of cardiac death at follow-up [31••]. Interestingly, the authors found a significant interaction between the presence of DM and procedural outcomes with lower cardiac mortality rates after failed PCI between diabetic and non-diabetic patients (24.7% vs. 9.3%, $p < 0.0001$), suggesting a preferential benefit of complete revascularization in the diabetic population [31••].

In the large-scale, the multicenter Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion (OPEN-CTO) registry including 1000 consecutive patients (diabetics, $n = 412$; insulin-dependent diabetics, $n = 154$) undergoing CTO PCI using the *hybrid* algorithm at 12 US high-volume centers [32••], crude technical success rates were significantly lower in patients with DM compared with non-diabetic subjects (83.5% vs. 88.1%, $p = 0.04$), but both lesion length (63.7 vs. 59.1 mm, $p = 0.01$) and CTO complexity (J-CTO score 2.4 vs. 2.3, $p = 0.03$) were significantly greater among diabetic patients compared with non-diabetics. After adjustment for differences in baseline clinical and angiographic characteristics, technical success rates were not statistically significant between diabetics and non-diabetics (relative risk [RR] 0.96, 95% CI 0.91–1.01, $p = 0.12$), resulting from adjustment for prior CABG, which was more prevalent among diabetic patients and was independently associated with lower technical success ($p < 0.001$) [32••]. These findings extend previous knowledge suggesting the negative impact of prior CABG, rather than the DM status itself, on CTO PCI technical success rates and clinical outcomes [33, 34], even when performed by experienced operators using the *hybrid* algorithm [35]. CTOs are present in ~ 50% of post-CABG patients undergoing coronary angiography and prior CABG further increases the complexity of CTOs, thus representing a technically highly challenging CTO patient subset [33–35]. These concerns are

Table 2 Recent large contemporary studies comparing clinical outcomes after CTO PCI in patients with and without diabetes mellitus

Study	Design	Number of patients			Success rates						Clinical outcomes
					Technical success rate			Procedural success rate			
		Total number of patients (*n*)	Diabetes (*n*, %)	Insulin-dependent diabetes (*n*, %)	Diabetes (%)	No diabetes (%)	*p* value	Diabetes (%)	No diabetes (%)	*p* value	
PROGRESS CTO [32••]	Prospective, multicenter, registry, 11 US centers (2012–2015)	1308	584 (44.6)	NR	90.7	90.3	0.80	89.3	89.1	0.93	• In-hospital MACE (composite of all-cause death, MI, recurrent symptoms requiring urgent TVR with PCI or CABG surgery, tamponade requiring either pericardiocentesis or surgery, or stroke prior to hospital discharge): 2.2% in diabetics vs. 2.5% in non-diabetics ($p = 0.61$) • In-hospital all-cause death (0.4% vs. 0.3%, $p = 0.51$), MI (1.3% vs. 0.5%, $p = 0.11$), stroke (0.4% vs. 0.1%, $p = 0.40$), emergency PCI (0.3% vs. 0.3%, $p = 0.82$), emergency CABG surgery (0%), and emergency pericardiocentesis (0.6% vs. 0.6%, p = 0.99) rates were similar between diabetics and non-diabetics, respectively.
Sanguinetti et al. [33]	Prospective single-center registry, one center in France (2004–2012)	1320	362 (27.4)	NR	NR	NR	NR	71.5	76.3	0.07	• Periprocedural major complications, including cardiac tamponade (1.4% vs. 0.8%, $p = 0.43$), were similar between diabetics and non-diabetics undergoing CTO PCI. • Among *diabetics*, all-cause death (54.9% vs. 23.2%, $p < 0.001$) and cardiac death (31.0% vs. 13.1%, $p < 0.001$), but not TLR (4.8% vs. 14.2%, $p = 0.23$), TVR (19.8% vs. 20.9%, $p = 0.78$), MI (5.2% vs. 3.0%, $p = 0.18$), and MACE (35.4% vs. 28.1%, $p = 0.13$) rates, were significantly higher in patients with failed as compared with successful CTO PCI at a median follow-up of 4.2 years, respectively. • Among *non-diabetics*, all-cause death (23.1% vs. 22.2%, $p = 0.16$), cardiac death (11.3% vs. 10.7%, $p = 0.08$), TLR (10.4% vs. 14.1%, $p = 0.63$), TVR (20.2% vs. 23.1%, $p = 0.77$), MI (11.4% vs. 5.1%, $p = 0.71$), and MACE (32.7% vs. 31.6%, $p = 0.08$) rates were similar between patients with failed and successful CTO PCI at a median follow-up of 4.2 years, respectively.
OPEN-CTO [34]	Prospective, multicenter registry, 12 US centers (2014–2015)	1000	412 (41.2)	154 (37.4)	83.5*	88.1*	0.04#	NR	NR	NR	• MACE (composite of all-cause death, periprocedural MI, emergency CABG surgery, stroke, or clinically significant perforation): 6.8% in diabetics vs. 7.1% in non-diabetics ($p = 0.832$). • In-hospital mortality (0.7% vs. 1.0%, $p = 0.743$), periprocedural mortality (0.2% vs. 0.7%, $p = 0.654$), periprocedural MI (2.7% vs. 2.6%, $p = 0.907$), and

Table 2 (continued)

Study	Design	Number of patients			Success rates						Clinical outcomes
					Technical success rate			Procedural success rate			
		Total number of patients (*n*)	Diabetes (*n*, %)	Insulin-dependent diabetes (*n*, %)	Diabetes (%)	No diabetes (%)	*p* value	Diabetes (%)	No diabetes (%)	*p* value	
											periprocedural stroke (0% in both groups), were similar between diabetics and non-diabetics, respectively. • Major procedural complications rates, including any perforation (9.5% vs. 8.3%, $p = 0.533$), pericardial effusion (2.2% vs. 2.9%, $p = 0.489$), hemodynamically significant pericardial effusion (44.4% vs. 52.9%, $p = 1.0$), emergent CABG (0.2% vs. 0.9%, $p = 0.409$), contrast nephropathy (1.2% vs. 0.2%, $p = 0.085$), and access site hematoma (3.9% vs. 4.6%, $p = 0.586$), were similar in patients with and without DM, respectively. • Adjusted SAQ AF (87.59 ± 1.68 vs. 88.05 ± 1.84, $p = 0.64$), SAQ QoL (74.50 ± 2.13 vs. 73.80 ± 2.33, $p = 0.58$), SAQ SS (83.01 ± 1.54 vs. 82.70 ± 1.68, $p = 0.73$), RDS (1.46 ± 0.14 vs. 1.46 ± 0.13, $p = 0.92$) through a follow-up period (30 days, 6 months or 12 months) were similar between diabetics and non-diabetics, respectively.

NR not reported. *Unadjusted rates. # Relative risk 0.96; 95% confidence interval 0.91 to 1.01; $p = 0.12$ after adjustment for clinical and angiographic characteristics (primarily driven by adjustment for prior CABG, which was independently associated with lower technical success, $p < 0.001$). *AF* angina frequency, *CTO* chronic total occlusion, *CABG* coronary artery bypass grafting, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *QoL* quality of life, *RDS* Rose Dyspnea Scale, *SAQ* Seattle Angina Questionnaire, *SS* summary score, *TLR* target lesion revascularization, *TVR* target vessel revascularization

of utmost importance considering that CABG remains the revascularization strategy of choice in patients with DM and multivessel CAD. Importantly, technical success rates were similar in diabetic patients requiring or not requiring insulin, suggesting that similar high technical success rates may be achieved from CTO PCI among non-diabetic, insulin-dependent diabetic, and non-insulin-dependent diabetic patients [32••]. Overall, there was no significant differences with respect to major procedural complications rates, including any perforation (9.5% vs. 8.3%), pericardial effusion (2.2% vs. 2.9%, of which nearly half were hemodynamically relevant in both groups), emergent CABG (0.2% vs. 0.9%), contrast nephropathy (1.2% vs. 0.2%), and access site hematoma (3.9% vs. 4.6%) in patients with and without DM, respectively [32••]. In-hospital MACE rates (6.8% vs. 7.1%, $p = 0.83$) were not different among patients with or without DM [32••]. Importantly, whereas the main indication to perform CTO PCI remains a relief of anginal symptoms [11, 12•], data reporting the impact of CTO PCI in diabetic patients with respect to short- and long-term health status outcomes compared with non-diabetic individuals are limited. Data from the OPEN-CTO registry demonstrate similar large and sustained symptom improvements with respect to angina burden, quality of life, and overall health status scores following CTO PCI over 1-year follow-up among patients with and without DM, even after adjustment for technical success, comorbidities, medications, and completeness of revascularization, including in the subgroup of diabetics requiring insulin [32••]. These results highlight the potential clinical impact of CTO PCI procedures among both diabetic and non-diabetic patients and support the use of CTO PCI with appropriate clinical indications irrespective of the DM status [44].

Conclusion

Evidence from contemporary, large-scale, observational registries supports the notion that CTO PCI, when performed at high-volume CTO PCI centers and by highly experienced operators, is a safe and effective treatment alternative to provide complete myocardial revascularization in selected CTO patients with DM. Importantly, in these studies, the degree of success of CTO PCI does not differ between DM and non-DM patients. Whereas CTO DM patients treated conservatively are at higher risk of adverse events compared with non-DM individuals, and incomplete revascularization negatively affects specifically DM patients, diabetic patients are less frequently exposed to CTO PCI. This *treatment-risk* paradox is concerning and deserves attention. Further randomized research is warranted to compare long-term outcomes of CTO PCI with newer-generation DES, CABG, and optimal medical therapy for the management of CTO patients with DM.

Compliance with Ethical Standards

Conflict of Interest Fabio Rigamont and Stéphane Noble declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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