CONTENTS

Safety and Efficacy of Bioresorbable Scaffolds in Daily Practice: Experience from a Single Center in Taiwan

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Abstract

Introduction: The bioresorbable material of the stent frame, capable of providing mechanical support and drug-delivery functions, has been developed in an attempt to improve long-term outcomes. However, publications about long-term outcomes of bioresorbable scaffolds (BRS) in Asia are still limited. This study is to investigate the long-term outcomes of bioresorbable scaffolds in a single tertiary medical center.

Method: Data regarding BRS placement in consecutive patients receiving percutaneous coronary intervention was collected from the cardiovascular center ofa single tertiary medical center from 2014 to 2017.

Result: A total of 138 cases were included during 3.5 years follow up. The mortality rate was 2.2%, whereby the cause of mortality in these 3 patients was not derived from coronary artery disease. One patient suffered acute myocardial infarction (0.7%). The rate of target lesion restenosis was 3.6% and that of target vessel restenosis was 2.9%.

Conclusion: This study demonstrated that BRS placement had low cardiac cause mortality and acute myocardial infarction at long-term follow up in a single tertiary medical center.

Keywords: acute myocardial infarction, bioresorbable scaffolds, coronary artery disease, percutaneous coronary intervention

INTRODUCTION

Cardiovascular disease, especially ischemic heart disease, is one of the leading causes of mortality and morbidity worldwide. Catheterization intervention with metallic drug-eluting stent

placement for coronary artery stenosis is the mainstream treatment option in the modern era. Moreover, the second generation of metallic drug-eluting stent has already been proven safe and effective for coronary artery disease treatment.[1,2] However, the development of late adverse events with permanent metallic stents may be caused by persistent inflammation, loss of normal vessel curvature, impaired vasomotion, strut fracture, ongoing tissue growth within the stent frame, and neoatherosclerosis.[3] Consequently, fully bioresorbable material has been developed for the stent frame, capable of providing both mechanical support and drug-delivery functions, in an attempt to improve long-term outcomes.

The clinical randomized trial revealed everolimus-eluting bioresorbable scaffolds (BRS), as compared with everolimus-eluting cobalt-chromium stents (EES), were within the pre-specified margin for non-inferiority with respect to target-lesion failure at one year in patients with noncomplex obstructive coronary artery disease.[4] However, the following trial revealed a higher rate of device-oriented composite endpoint due to target vessel myocardial infarction, including peri-procedural myocardial infarction in the BRS group.[5] The ABSORB III study showed a 2.3 percent rate of thrombosis within BRS versus 0.7 percent within the EES at 3 years.[6] Furthermore, the meta-analysis study and other long-term follow-up clinical results revealed that compared with metallic EES, the currently approved BRS is associated with higher rates of major adverse cardiac events and BRS thrombosis, from the non-US ABSORB II, ABSORB Japan, ABSORB China studies and US-based ABSORB III study.[7] Those results have ledthe U.S. Food and Drug Administration (FDA) to issue a safety alert for the Absorb BRS due to an increased rate of major adverse cardiac events observed in patients receiving the device, and they have recommended the reference vessel diameter ≥ 2.5 mm and ≤ 3.75 mm, with longer dual antiplatelet therapy to be considered in small heart vessels patients.

In Taiwan, BRS has been approved since 2014. Currently, there has been no long-term follow-up trial providing information about the safety and efficacy of BRS practice in Taiwan. This study is to investigate the long-term safety and efficacy of BRS in daily practice in Taiwan.

METHODS

Data Source

A totalof 138 consecutive patients, who had received BRS placements, were enrolled from the cardiovascular center of a tertiary medical center in Taiwan from 2014 to 2017, and analyzed. All patients met the diagnosis criteria of coronary artery disease with more than 70% stenosis compared with the reference vessel on coronary angiography. This study, approved by the Human Research Committee, contains comprehensive medical records of patients, offering researchers detailed data.

Study Population

Those who were admitted for coronary artery disease received complete basic laboratory, chest X-ray, and electrocardiography survey prior to percutaneous catheterization intervention. All patients were monitored at the hospitalfor at least 24 hours after the procedure.

Outcome Analysis

All enrolled patients were followed until death or 28th February 2018. To measure the outcome, both out patient department and hospital admission medical records were checked. The medical charts of patients were reviewed by two independent physicians. Patients lost to follow-up, as recognized from medical chart reviews, were contacted by telephone. Furthermore, follow-up questionnaire, including medication compliance, complications, and mortalities, was performed.

Statistical Analyses

Categorical data were reported as per-centages and evaluated by the Chi-square test. Continuous variables were reported as the mean

and standard deviation (SD) and compared by paired t-test. The Kaplan–Meier method was used to estimate cumulative survival. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULT

Descriptive Characteristics

A total of 138 patients with coronary artery disease receiving BRS were enrolled in this study. The clinical characteristics are displayed in Table 1. Most patients were male (N = 127; 92.%) and the average age was 58.7 ± 12.1 years old. Average body height and body weight was 167.4 ± 7.1 cm and 73.2 ± 10.5 kg, and body mass index was 26.1 ± 3.3 kg/m^2. Of the patients, 60.1% had hypertension (N = 83), 35.5% had diabetes mellitus (N = 49), 39.1% had dyslipidemia (N = 54), 11.6% had previous myocardial infarction (N = 16) and 55.8% had a family history of coronary artery disease (N = 77). Fifty patients (36.2%) were cigarette smokers (Table 1).

Laboratory data showed hemoglobin at 14.0 ± 1.5 g/dL, glycated hemoglobin (HbA1c) at 6.6 ± 1.5%, blood sugar at 138.4 ± 64.2 mg/dL, creatinine at 1.1 ± 0.4 mg/dL, low-density lipoprotein-cholesterol (LDL-C) at 94.7 ± 28.9 mg/dL and high-density lipoprotein (HDL-C) at 41.7 ± 12.0 mg/dL (Table 1). The percentage of antiplatelet therapy is shown in Table 1, including aspirin (97.8%), clopidogrel (55.0%) and ticagrelor (43.4%). In these patients, the average duration of antiplatelet therapy use was 566.6 ± 370.4 days for aspirin, 351.96 ± 311.78 days for clopidogrel and 513 ± 330.16 days for ticagrelor (Table 1).

Angiographic and Procedure Characteristics

Regarding lesion characteristics on coronary angiography, there were 20.3% type A lesions (N = 28), 32.6% type B1 lesions (N = 45), 26.1% type B2 lesionsand 21.0% type C lesions (N = 29). The Syntax score was 13.0 ± 7.8. Furthermore, chronic total occlusion lesions accounted for 10.9% of

Table 1. Baseline Characteristicsof Patients Who Received Bioresorbable Scaffolds

Characteristics	N = 138
Gender (Male ratio)	N = 127 (92.0%)
Age (years)	58.7 ± 12.1
Body mass index; BMI (kg/m^2)	26.1 ± 3.3
Height (cm)	167.4 ± 7.2
Weight (kg)	73.2 ± 10.5
Comorbidities	
Hypertension	N = 83 (60.1%)
Diabetes Mellitus	N = 49 (35.5%)
Dyslipidemia	N = 54 (39.1%)
Family History of coronary artery disease	N = 77 (55.8%)
Previous myocardial infarction	N = 16 (11.6%)
Previous ischemia stroke	N = 0 (0.0%)
Peripheral artery disease	N = 1 (0.7%)
Coronary artery bypass grafting	N = 3 (2.2%)
End stage renal disease	N = 0 (0.0%)
Heart failure	N = 1 (0.7%)
Cigarette smoking	N = 50 (36.2%)
Lab Data	
Hemoglobin (g/dL)	14.0 ± 1.5
Creatinine (mg/dL)	1.1 ± 0.4
Hemoglobin A1c; HbA1C (%)	6.6 ± 1.5
Blood sugar (mg/dL)	138.4 ± 64.2
Glutamate pyruvate transaminase (U/L)	35.2 ± 26.7
Cholesterol (mg/dL)	165.0 ± 41.5
High-density lipoprotein; HDL (mg/dL)	41.7 ± 12.0
Low-density lipoprotein; LDL (mg/dL)	94.7 ± 28.9
Triglyceride (mg/dL)	140.1 ± 96.9
Antiplatelet therapy	
Aspirin (Percentage)	N = 135 (97.8%)
Average duration (days)	566.57 ± 370.43
Clopidgrel (Percentage)	N = 76 (55.0%)
Average duration (days)	351.96 ± 311.78
Ticagrelor (Percentage)	N = 60 (43.4%)
Average duration (days)	513.00 ± 330.16

lesions; 12.3% of patients had ostial lesions (N = 17), 25.4% had bifurcation lesions (N = 35) and only 2 lesions were left main bifurcation lesions (Table 2).

In the study, a total of 209 bioresorbable scaffolds were deployed. The frequency of BRS sizes was 18.2% for 2.5 mm (N = 72), 47.4% for 3.00 mm (N = 72) and 34.4% for 3.5 mm (N = 72). The frequency of BRS lengths was 3.8% for 12 mm (N = 8), 20.1% for 18 mm (N = 42), 29.7% for 23 mm (N = 62) and 46.4% for 28 mm (N = 97) (Table 2). During the percutaneous catheter intervention procedure, 94.7% of patients received balloon post-dilatation after BRS implantation and 60.1% of patients received intravascular image guide, including optical coherence tomography (N = 55, 39.9%) and intravascular ultrasound (N = 28, 20.3%) (Table 2).

OutcomeAnalysis

A total of 138 cases were included during the 3.5 years follow-up. The mortality rate was 2.2% (N = 3) (Figure 1), whereby the cause of mortality in these 3 patients was not derived from coronary artery disease. One patient suffered acute myocardial infarction (0.7%) (Figure 2). The rate of target lesion restenosis was 3.6% (N = 5) (Figure 3) and the rate of target vessel restenosis was 2.9% (N = 4) (Figure 4).

DISCUSSION

This study is the first study to show the long-term safety and efficacy of BRS in daily practice in Taiwan. In 3.5 years follow-up, there were few major adverse cardiac events, including cardiovascular death, myocardial infarction, target lesion restenosis, and target vessel restenosis.

BRS was developed to dissolve fully within patients' vessels, and within three years of implantation, with the intent of bypassing any negative side effects sustained from a metal stent. In the ABSORB III randomized trial, the Absorb BRS proved noninferior to the Xience device with regard to the occurrence of target

Table 2. Angiographic and Procedure Characteristics

Coronary Angiography Findings (N=138)	
Lesion type	
A	N= 28 (20.3%)
B1	N= 45 (32.6%)
B2	N= 36 (26.1%)
C	N= 29 (21.0%)
Left mainbifurcation lesion	N= 2 (1.4%)
Ostial lesion	N= 17 (12.3%)
Bifurcation lesion	N= 35 (25.4%)
Chronic total occlusion	N= 15 (10.9%)
Syntax score	13.0 ± 7.8
Bioresorbable Scaffolds (N=209)	
BRS size (mm)	
2.50	N= 38 (18.2%)
3.00	N= 99 (47.4%)
3.50	N= 72 (34.4%)
BRS length (mm)	
12	N= 8 (3.8%)
18	N= 42 (20.1%)
23	N= 62 (29.7%)
28	N= 97 (46.4%)
Post-BRS balloon dilatation	N=198 (94.7%)
Intravascular image guide	N=83 (60.1%)
Optical Coherence Tomography (OCT)	N=55 (39.9%)
Intravascular ultrasound (IVUS)	N=28 (20.3%)

BRS = bioresorbable scaffolds

lesion failure (TLF), target vessel myocardial infarction (TVMI) and ischemia-driven target lesion revascularization (TLR). The U.S. Food and Drug Administration approved Abbott's BRS device upon the release of these positive results, but recent reports from the Absorb III trials[6] have suggested increased instances of thrombosis and MI directly related to the dismantling process of the bioresorbable vascular scaffold. Around 2,000 cardiac patients took part in the ABSORB III study, all of whom were undergoing PCI. The Absorb BRS was deemed noninferior to the Xience stent for the study's primary endpoint of

Kaplan-Meier curve for cumulative survival rate
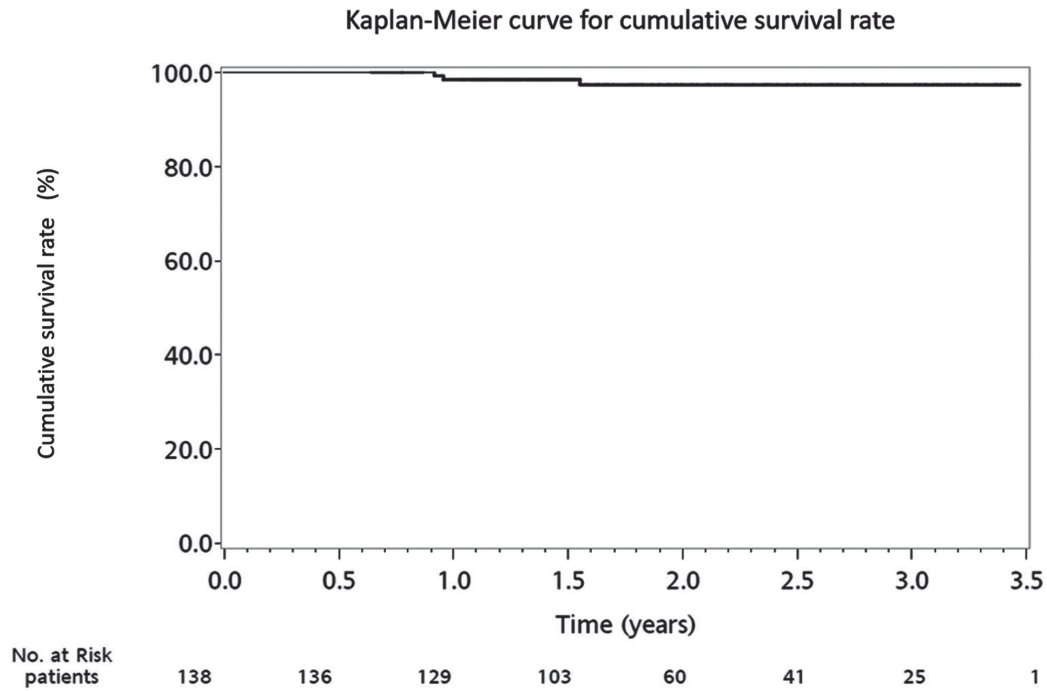
Figure 1. Kaplan-Meier curve forcumulative survival rate for patients after bioresorbable scaffolds (BRS) implantation.

Kaplan-Meier curve for myocardial re-infarction free survival
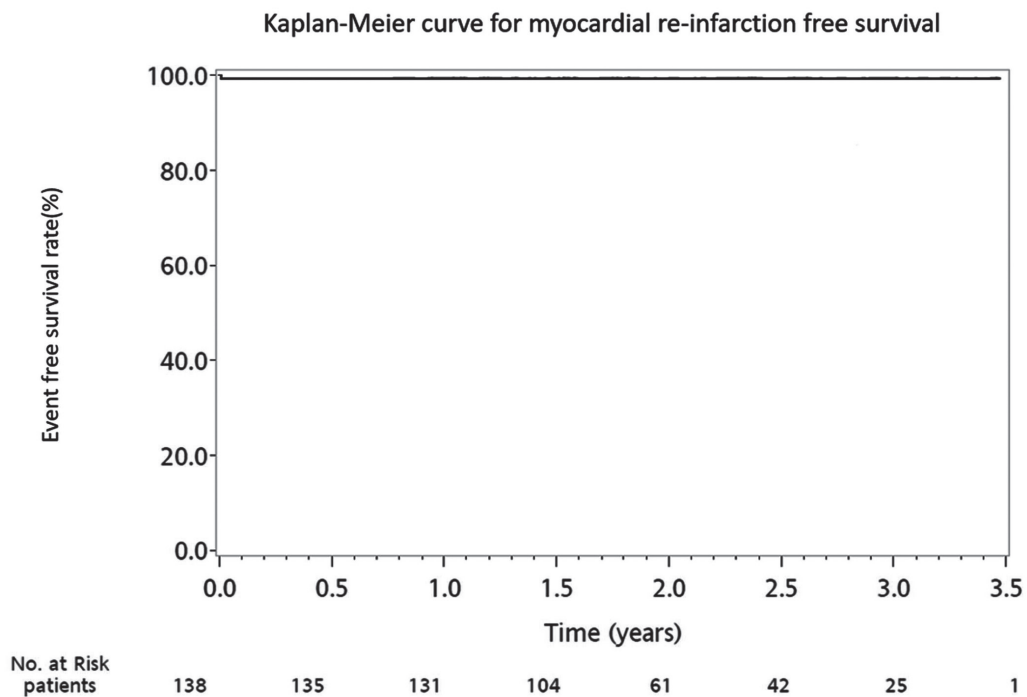
Figure 2. Kaplan-Meier curve for myocardial re-infarction free survival rate for patients after bioresorbable scaffolds (BRS) implantation.

Figure 3. Kaplan-Meier curve for target lesion revascularization (TLR) free survival rate for patients after bioresorbable scaffolds (BRS) implantation.

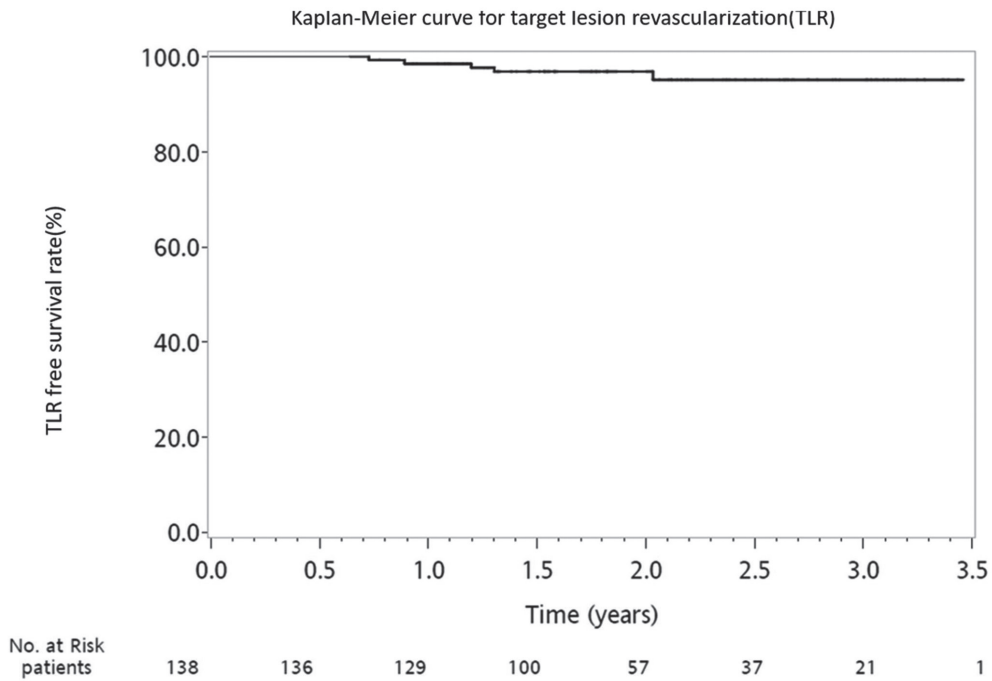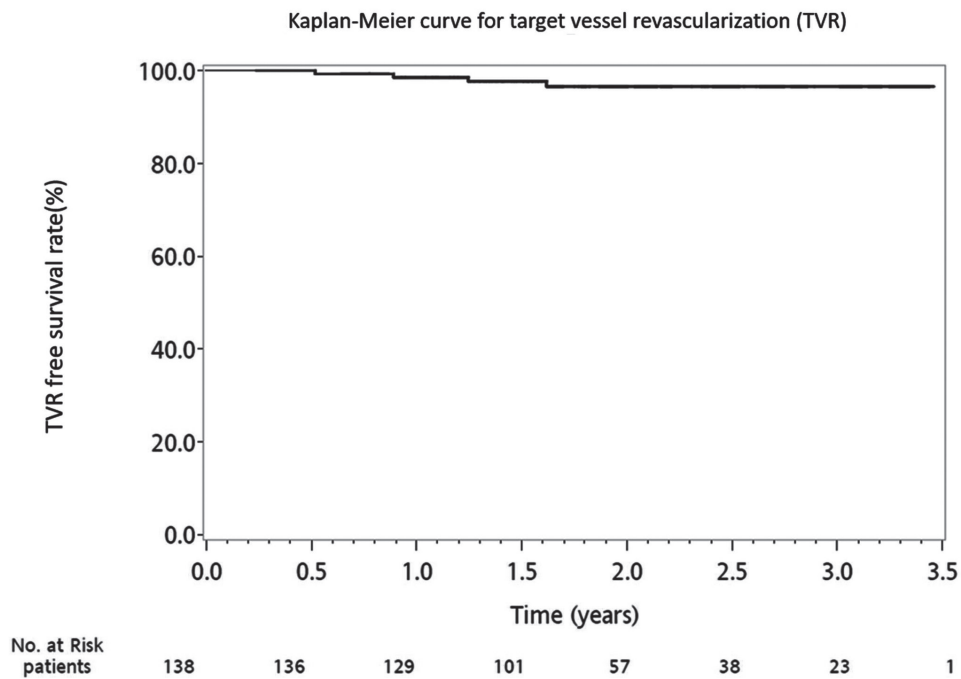
Figure 4. Kaplan-Meier curve for target vessel revascularization (TVR) free survival rate for patients after bioresorbable scaffolds (BRS) implantation.

one-year target lesion failure (TLF), recording a risk difference of just 1.7 percent between the two devices. Device thrombosis was recorded in 1.5 percent of BRS patients and 0.7 percent of EES patients after those first 12 months. Three years into the study results varied more widely—the device-oriented primary endpoint was observed in 13.4 percent of BRS subjects compared to 10.4 percent of EES patients. Between one and three years after treatment, TLF occurred in 7 percent and 6 percent of all BRS and EES patients, respectively. BRS patients also recorded higher rates of target vessel failure, death, myocardial infarction, TVMI, and revascularization. Factors like a prior cardiovascular intervention, diabetes, and vessel size were all found to be independent predictors of adverse outcomes in BRS-treated patients. Scaffold thrombosis events seemed to be clustered in very small vessels prior to the one-year treatment mark, the researchers wrote, while between one and three years thrombosis presented itself mainly invessels more appropriately sized for the scaffold device.

To our knowledge, late thromboembolism events were most related to multifactorial origins, including the patient, antithrombotics, procedural issues, the lesion and the device.[9,10] Attention to technical details may also improve results when percutaneous catheter intervention (PCI) is performed with BRS. Because both the number of stents and the stent length enhance the risk of thromboembolism events, refraining from excessive overall stent length and from stent overlap is judicious. Moreover, proper deployment of the BRS should be ensured, with care taken to fully expand it over its entire length, particularly incalcified lesions, and residual dissections should be avoided as when deploying drug-eluting stents (DES). Among patients with these larger vessels, the TLF rate was 9.4% among the Absorb-treated patients and 7.0% among the Xience-treated patients, a difference that was not statistically significant (HR 1.35; 95% CI 0.93-1.96).[6] Similarly, in those with an RVD $\geq$ 2.25 mm, the 2-year rate of definite/probable ST was

1.3% and 0.6% in the Absorb- and Xience-treated patients, respectively. Again, this difference was not statistically significant. An additional analysis of the data showed that when physicians followed the PSP protocol (predilatation, appropriate sizing, and post-dilatation), the rates of TLF and ST in the Absorb BRS arm were much closer to rates observed with the Xience stent.

In this study, we did not notice any remarkable recurrent stent thromboembolism events during 3.5 years follow-up. The main reasons for the lack of major cardiac events in this study might be that most BRS used i more than 3.00 mm in size with optimal technique by post-stent balloon dilatation. Moreover, intravascular images were used in more than half the cases to assess the proper reference lumen size, lesion type, and length. Appropriate use of intravascular images increases the accuracy of chosenstent size and length. Dual antiplatelet therapy (DAPT) in all cases continued for at least one year after the procedure. All of the above might explain why there were relatively few major cardiac eventsin this study.

However, there are some limitations to this study. First, the sample size is small, and second, there is no control group in this study. Further comprehensive, prospective, randomized control trials should be under taken in Taiwan.

CONCLUSION

This study demonstrates that BRS implantation has low cardiac-cause mortality and acute myocardial infarction at long-term follow-up in a single tertiary medical center, which might be explained by relatively larger size of BRS, optimization of post-stent balloon dilatation, use of intravascular image and at least one-year dual-antiplatelet therapy.

LIST OF ABBREVIATIONS

ACS = Acute coronary syndrome
AMI = Acute myocardial infarction
BRS = Bioresorbable vascular scaffold
CABG = Coronary artery bypass grafting
CAD = Coronary artery disease
CTO = Chronic total occlusion
DM = Diabetes mellitus
ESRD = End-stage renal disease
HF = Heart failure
IVUS = Intravascular ultrasound
OCT = Optical Coherence Tomography
PCI = Percutaneous coronary intervention.
PAD = Peripheral artery disease
SD = Standard deviation
TLR = Target lesion revascularization
TVR = Target vessel revascularization

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Improvement of Outcomes in Acute Coronary Syndrome (ACS) by Getting with the Guidelines: From Taiwan ACS-full Spectrum Registry to Taiwan ACS-DM Registry

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Abstract

Acute coronary syndrome (ACS) including ST-elevation myocardial infarction, non-ST elevation myocardial infarction and unstable angina is a life-threatening disease. To improve the clinical outcome of ACS, many cardiology societies have developed clinical guidelines to provide evidence-based therapy. To identify current management of ACS nationwideat hospital admission, during in-hospital stay and 12 months post discharge, the Taiwan Society of Cardiology (TSOC) implemented the Taiwan ACS full-spectrum registry from 2008 to 2010, ACS-stent registry from 2012 to 2015, and ACS-DM registry from 2013 to 2015. Percutaneous coronary intervention has been performed in most ACS patients in Taiwan. In the Taiwan ACS-Full Spectrum Registry, medical therapy for ACS patients according to clinical guidelines is suboptimal, although door to balloon time improved significantly after implementation of the ACS full spectrum registry. Dual antiplatelet use at patient discharge significantly improved from 74.8% to 99.6% from implementation of the ACS-full spectrum registry to the ACS-stent registry. Angiotensin converting enzyme inhibitor/angiotensin receptor blocker improved from 63.0% to 77.5%, beta-blocker from 53.4% to 71.1%, statin use from 60.5% to 81.2%. Increased adherence to the ACS guideline from ACS-Full spectrum registry to ACS-DM registry was also found. Much improvement in clinical guideline adherence was observed in the ACS-DM registry after local guideline establishment. However, a discrepancy remains between real-world and guideline directed therapy with regard to renin-angiotensin system blockade, beta-blocker and statin use. Concerted efforts are needed to continue this positive trend.

Keywords: acute coronary syndrome, registry, guideline

Introduction

Cardiovascular (CV) disease remains the leading cause of death and premature death globally,[1,2] and is among the leading causes of death in the Asia-Pacific region.[3] Acute coronary syndrome (ACS) including ST-elevation myocardial infarction (STEMI), non-ST elevation

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myocardial infarction (NSTEMI) and unstable angina is a life-threatening condition of CV disease. CV events recur at a high frequency after an ACS event and lead to marked morbidity including frequent re-hospitalization and mortality.[4-6] Even after surviving discharge after ACS, one year mortality is high.[7] Many cardiology societies have developed clinical guidelines for ACS to improve outcome and care quality in ACS cases. In fact, getting with these guidelines or guideline-directed medical therapies has improved the clinical outcomes for ACS patients.[8,9]

Overall the incidence of acute myocardial infarction in Taiwan has remained constant at around 50 per 100,000 persons from 2009 to 2015.[10] However, the ratio of NSTEMI to STEMI incidence has increased from 2009 to 2015, especially in young patients under 55 years. To assess the current management of ACS nationwideat hospital admission, during in-hospital stay and 12 months post discharge, the Taiwan Society of Cardiology (TSOC) implemented the Taiwan ACS full-spectrum registry from 2008 to 2010, the ACS-stent registry from 2012 to 2015, and the ACS-DM registry from 2013 to 2015. After developing the registries, TSOC developed guidelines for the management of STEMI in 2012[11] and non-ST-segment elevation ACS in 2018.[12] In this review paper, the quality of care outcome for patients with ACS in Taiwan will be analyzed based on these three nationwide registries.

Taiwan ACS Full Spectrum registry

The objective of the Taiwan ACS Full Spectrum registry was to identify the current management of ACS nationwideat hospital admission, during in-hospital stay, at discharge and 3, 6, 9 &12 months post discharge in the period from October 2008 to January 2010. Patients with age > 20 years admitted to the hospital within 24 hours of ACS were enrolled. Presentation of ACS accompanied or precipitated by co-

morbidity such as trauma, and previous enrolment in this trial or participation in an investigational drug study, were criteria for exclusion from this registry. A total of 3183 patients with ACS were recruited in 39 medical centers and regional hospitals throughout Taiwan, including northern, central, southern and eastern areas.[13] The ACS full spectrum included STEMI, NSTEMI, and unstable angina. This registry included 53% STEMI, 34% NSTEMI, and 12% unstable angina. For patients with STEMI, primary percutaneous coronary intervention (PCI) was performed in 97% whereas thrombolytic therapy was used in 3%. The median door to balloon time (D2B) was 96 min. With regard to pharmacological therapies, discharged prescriptions of dual antiplatelet therapy (DAPT) were 74.8%, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) 63.0%, beta blocker 53.4%, and statin 60.5%.[13] The 1-year usage of preventive medicine prescriptions at 1-year were DAPT 24.1%, ACEI/ARB 61.6%, beta-blocker 59%, and statin 61.1%. PCI was performed in 75% of patients with non-ST elevation ACS and was usually performed within the first 1-2 days. Bare metal stent (BMS) was used in 70.4% of STEMI patients and around 55% of non-ST elevation ACS patients. Drug-eluting stent (DES) was used in 21% of STEMI patients and 35% of non-ST elevation ACS patients.

There is an association between timely reperfusion therapy and clinical outcomes in STEMI. Primary PCI < 90 min produced better clinical outcomes, including less 30-day and 1-year mortality, less readmission for heart failure and myocardial infarction at 1 year than primary PCI > 90 min.[14] Different hospitals in Taiwan used different strategies to shorten D2B. These strategies included establishment of a regional network transfer system, a chest pain unit with an onsite cardiology team in the emergency room, direct emergency room tele-electrocardiographic triage of patients with chest pain, or a multiple-strategy approach.[15-18]

Taiwan ACS Stent registry

The objective of the Taiwan ACS Stent registry was to evaluate the practice patterns of ACS care in Taiwan from April 2012 to December 2015. The inclusion criteria were the same as the Taiwan ACS Full Spectrum registry except that only ACS patients who received PCI with stent implantation during hospitalization were included in the registry. A total of 2357 patients were recruited in 24 medical centers and regional hospitals throughout Taiwan. The registry included 54% STEMI and 46% non-ST elevation ACS. The median D2B time was 71 min in the Taiwan ACS Stent registry.[19]

As compared with the Taiwan ACS Full Spectrum registry, D2B in this registry was significantly shortened by 25 min (p < 0.0001), with a corresponding, significant increase (all p < 0.0001) in the percentage of patients with D2B < 90 min (46.7% to 63.3%, p < 0.0001) (Figure 1) between the 2 registries. With regard to pharmacological therapies, the in-hospital use of DAPT was 99.6%, ACEI / ARB 77.5%, beta

blocker 71.4%, and statin 81.2%. The use of secondary prevention medications all increased significantly (all p < 0.0001) between the Taiwan ACS Full Spectrum registry and the Taiwan ACS Stent registry. For STEMI and non-ST elevation ACS in the Taiwan ACS Stent registry, ACEI/ ARB were used in 77.5% and 67.6%, beta-blocker in 71.4% and 64.4%, and statin in 81.2% and 78.8%, respectively. The use of DAPT at 1-year after discharge was 34%.

PCI was performed in 100% of patients in the Taiwan ACS Stent registry. DES was used during primary PCI in 41% of STEMI patients and 62.9% of non-ST elevation ACS patients.

Taiwan ACS-DM registry

The prospective observational study of the Taiwan ACS-DM registry[20] aimed to explore the cardiovascular outcomes (including cardiovascular morbidity and mortality, non-fatal myocardial infarction, nonfatal stroke, unplanned coronary re-vascularization and heart failure hospitalization) in ACS patients with type 2 diabetes in Taiwan.
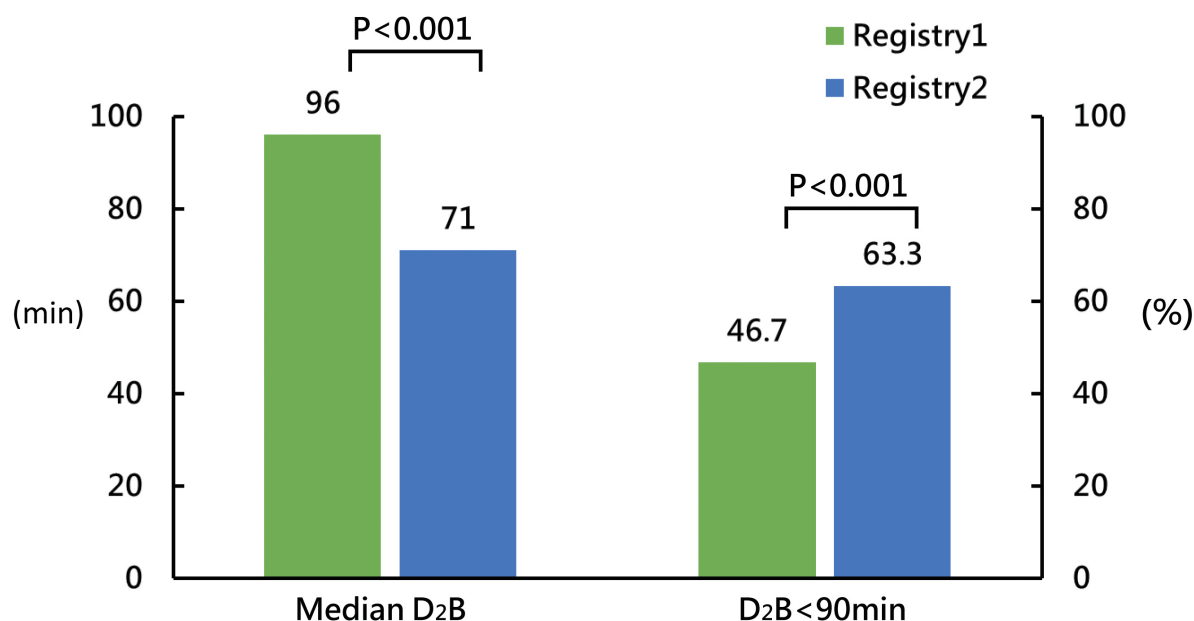

Figure 1. Comparison of median door-to-balloon time (D2B) and percentage of D2B < 90 min between the Taiwan ACS Full Spectrum registry (Registry 1) and the Taiwan ACS Stent registry (Registry 2).

Patients with a history of type 2 diabetes, confirmed on 2 occasions prior to the registry, and patients with age > 20 years who were diagnosed with ACS within 30 days of patient enrollment and type 2 diabetes (no matter whether newly or previously diagnosed) were recruited. For newly diagnosed diabetes mellitus (DM), diagnosis was based on the WHO criteria: i.e, fasting venous plasma glucose concentration > 7.0 mmol/L [126 mg/dL] or 2-hour post glucose load venous plasma glucose > 11.1 mmol/L [200 mg/dL]. This was a non-interventional prospective registry, and a total of 1534 eligible patients were enrolled from July 2013 to December 2015 in 27 medical centers and regional hospitals throughout Taiwan.

This registry included 29.5% STEMI, 48.9% NSTEMI, and 21.5% unstable angina.

In this registry, ACS with DM patients had higher prevalence of smoking, hypertension and dyslipidemia and also had higher prevalence of cardiovascular disease including prior stroke, prior MI, prior PCI, prior CABG and heart failure than patients in the Taiwan ACS Full Spectrum registry and the Taiwan ACS Stent registry (Table 1). PCI was performed in 79.6% of patients. Primary PCI was performed in 95.5% and fibrinolysis was performed in 1.8% of patients with STEMI. For NSTEMI and unstable angina, PCI was performed in 73.1% and 72.0%, respectively. With regard to pharmacological therapies, the rate of prescription at discharge of DAPT was 95.5%, ACEI/ARB 65.7%, beta blocker 64.8%, and statin 77%. The use of secondary prevention medicines in the Taiwan ACS-DM registry was similar to that in

Table 1. Clinical characteristics of three Taiwan ACS registry patients

	Registry 1 (2008-2010) (n = 3183)	Registry 2 (2012-2015) (n =2357)	Registry 3 (2013-2015) (n=1534)	P value
Age (years)	63.1 ± 13.6	60.0 ± 12.7	64.9+11.9	P<0.0001
Male, %	78.0 %	83.3%	71.3%	0.008
Risk factors				
Current smoker	42.0%	45.7%	51.6%	<0.0001
Hypertension	64.0%	63.7%	78.1%	<0.0001
Diabetes	36.0%	34.3%	100%	<0.0001
Hyperlipidemia	39.1%	44.4%	49.4%	<0.0001
Medical history				
Prior CAD	24.5%	30.8%	37.1%	<0.0001
Prior stroke	2.9%	6.0%%	10.8%	<0.0001
Prior MI	9.9%	8.2%	16.9%	<0.0001
Prior PCI	16.8%	15.7 %	26.3%	<0.0001
Prior CABG	2.7%	1.7%	5.5%	<0.0001
Prior HF	5.4%	3.3%	8.5%	<0.0001

The data were presented with mean ± standard deviation or percentages (%). Statistical analysis with ANOVA or chi-square was used.
Registry 1: Taiwan ACS Full Spectrum registry.
Registry 2: Taiwan ACS Stent registry.
Registry 3: Taiwan ACS-DM registry
CAD = coronary artery disease. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery bypass surgery. HF =heart failure.

the Taiwan ACS Stent registry, but was much better than that in the Taiwan ACS Full Spectrum registry (Figure 2). Medications prescribed at discharge for diabetic patients in the Taiwan ACS Full Spectrum registry showed that DAPT was 92.6%, ACEI/ARB 60.0%, beta-blocker 46.5%, and statin 49.7%. The rate of prescribed secondary preventive medicine was significantly higher in the Taiwan ACS-DM registry compared to the DM subgroup of the Taiwan ACS Full Spectrum registry.

Implications of the Taiwan nation-wide ACS registry

Reperfusion therapy and guideline-directed medical therapy significantly improved 1-year major adverse outcomes.[8,9] These three Taiwan ACS registries have demonstrated the gaps between guideline recommendations and clinical practice in the management of ACS in Taiwan.

The quality of ACS care, including primary PCI for STEMI and pharmacological therapies for ACS, has improved in Taiwan. PCI is the major revascularization strategy for ACS in Taiwan. In the United States, the median D2B in 2010 was 64 min and 91% of patients had D2B < 90 min in primary PCI.[21]

Another weak point of our ACS care is the underuse of DES which is now a standard treatment during PCI. DES was used in only about 21-30% of cases in the Taiwan ACS Full Spectrum registry and in 40-60% of Taiwan ACS Stent registry patients. New generation DES has a lower incidence of stent thrombosis and target vessel revascularization compared to bare metal stent in ACS patients.[22,23] ACEI/ARB and beta blocker were only prescribed in about 70% of STEMI patients and 60% of NSTE-ACS patients in the Taiwan ACS Stent registry and the Taiwan ACS-DM registry, ACEI/ARB, beta blockers, and statins were prescribed in 65.7%, 64.8% and 77%,
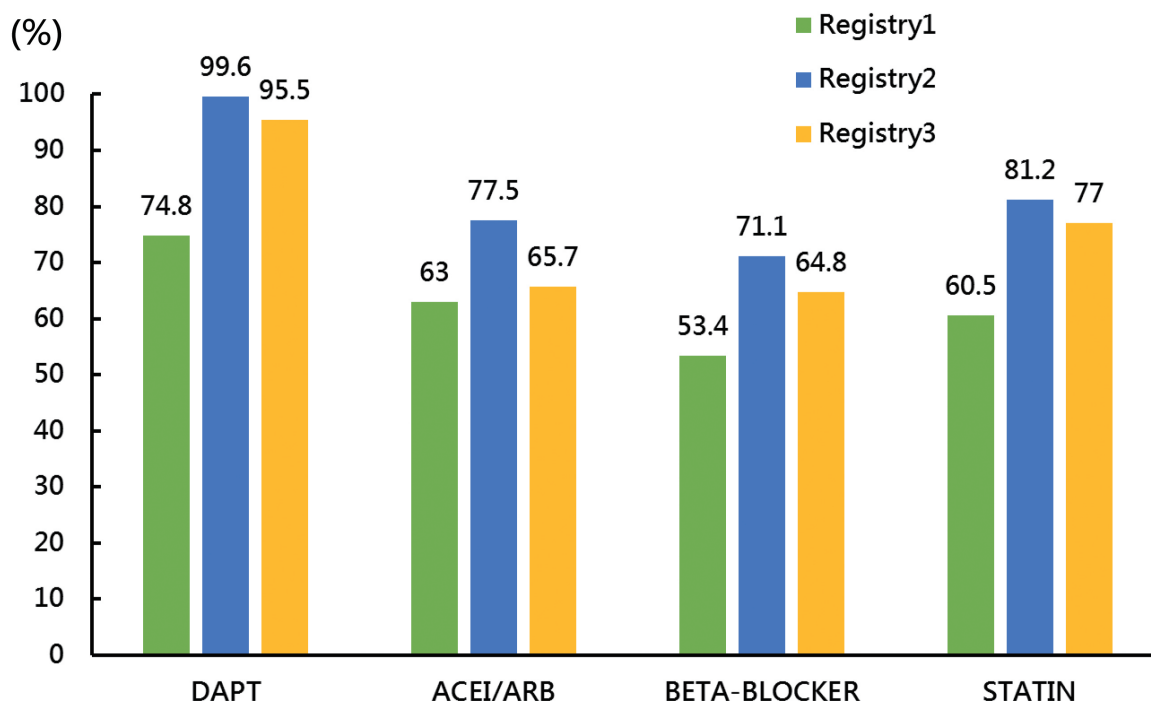

Figure 2. Rate of secondary preventive medicine used, including dual antiplatelet (DAPT), angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), beta-blocker and statin in three Taiwan ACS registries following patient discharge.

respectively. The prescription rates of these drugs in Asian-American acute MI patients were usually more than 90%.[24] Adherence to therapy guidelines was also high for beta-blockers, ACEI/ARB, and statin use in patients with STEMI and NSTEMI as reported in the Get with the Guidelines-Coronary Artery Disease registry.[25] Prescription rates of these drugs should be increased to further improve patients' prognosis in Taiwan.

Conclusions

Much improvement in clinical guideline adherence has been observed in the Taiwan ACS registry after local guideline establishment. However, there remains a gap in renin-angiotensin system blockade, beta-blocker and statin use between real-world and guideline directed therapy. Concerted efforts are needed to continue this positive trend.

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Antiplatelet Therapy for Non ST-segment Elevation Acute Coronary Syndrome: Highlight of the 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the Management of Non ST-segment Elevation Acute Coronary Syndrome

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Abstract

Antiplatelet therapy is the cornerstone in the management of non ST-segment elevation acute coronary syndrome (NSTE-ACS). The 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the Management of NSTE-ACS was recently published. This guideline suggests that administration of dual antiplatelet therapy with aspirin and P2Y12 inhibitor is necessary for NSTE-ACS to reduce recurrent ischemic events. Regarding the choice of P2Y12 inhibitor, ticagrelor is indicated for NSTE-ACS patients treated with either invasive or medical treatment; while prasugrel is only recommended in patients undergoing percutaneous coronary intervention (PCI). For patients with high bleeding risk features, clopidogrel or decreased dose of prasugrel might be considered to reduce the bleeding risk. Glycoprotein IIb/IIIa inhibitor is only recommended as adjunctive therapy during PCI for large thrombus burden or as bailout for thrombotic complications. We hope the implementation of this guideline's recommendations can lead to the improvement of clinical outcomes for NSTE-ACS patients in Taiwan.

Keywords: acute coronary syndrome, antiplatelet therapy, guideline

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Introduction

The onset of acute coronary syndrome (ACS) is closely linked to vulnerable coronary plaque rupture, which induces a cascade of platelet adhesion, activation, and aggregation, and subsequently leads to the formation of occlusive thrombus in the coronary artery.[1] Antiplatelet therapy is recognized as a cornerstone of treatment for ACS. In past decades, dual antiplatelet therapy (DAPT) has been proven to improve the clinical outcomes in ACS patients. In the Taiwan ACute CORonary Syndrome Descriptive (T-ACCORD) registry, 1331 non-ST segment elevation acute coronary syndrome (NSTE-ACS) patients were enrolled from 27 hospitals in Taiwan. DAPT for more than 9 months was associated with a higher survival rate in this observational study.[2] The Taiwan ACS Full Spectrum Registry recruited 3131 ACS patients, of whom 46.8% were NSTE-ACS subjects. It demonstrated that DAPT for less than 9 months was associated with an increased risk of composite ischemic outcome.[3] Compared with clopidogrel, new generation P2Y12 in-hibitors including prasugrel and ticagrelor have been shown to further reduce ischemic events in ACS patients. Since these new drugs are more potent in platelet inhibition, the trade-off between ischemic and bleeding risk becomes a challenge in ACS management. The 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the management of NSTE-ACS was recently published.[4] The purpose of this article is to highlight the recommendations for antiplatelet therapy proposed in the guidelines. We sought to summarize these recommendations and provide a brief overview of the most important scientific background evidence.

Aspirin

Aspirin has been well studied before in both randomized control trials[5-8] and meta-analysis[9,10]

to reduce recurrent myocardial infarction (MI) or mortality in NSTE-ACS patients. Aspirin should be prescribed in all ACS patients unless there are contraindications. In Taiwan, for rapid absorption, 300 mg aspirin with non-enteric coated chewable form is recommended as the initial loading dose. Aspirin 100 mg/day is suggested as the long-term maintenance dose. The recommendation for aspirin in this guideline is:

- **For patients with NSTE-ACS, aspirin should be given at an initial oral loading dose of 300 mg (in aspirin-naive patients) and a maintenance dose of 100 mg/day if there are no contraindications.**

P2Y12 inhibitor

1. Clopidogrel

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study showed that DAPT with clopidogrel and aspirin reduced major cardiovascular (CV) events compared with aspirin monotherapy in NSTE-ACS patients.[8] This benefit was consistently demonstrated in ACS patients undergoing percutaneous coronary intervention (PCI).[11] Two large multicenter registries in Taiwan showed DAPT with aspirin and clopidogrel longer than 9 months was associated with better clinical outcomes.[2,3] Higher clopidogrel loading dose of 600 mg was associated with higher and faster platelet inhibition than with 300 mg loading dose in patients undergoing elective PCI.[12,13] The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Symptoms (CURRENT–OASIS 7) trial demonstrated that high clopidogrel loading dose (600 mg) was associated with similar rate of primary outcome (CV death, MI, or stroke) and higher risk of major bleeding compared with 300 mg loading dose. But in the subgroup of patients who received PCI, clopidogrel 600 mg loading was associated with significant risk reductions in both primary outcome and stent thrombosis.[14] A meta-analysis showed the 600 mg

clopidogrel loading regimen was associated with lower major CV events and similar major bleeding risk compared with the 300 mg loading regimen in patients undergoing PCI.[15] Hence, based on this evidence, a loading dose of 300 mg to 600 mg is recommended in patients with NSTE-ACS in Taiwan. One of the drawbacks of clopidogrel is its drug response variability due to genetic polymorphisms. This may cause clopidogrel resistance and increase the CV risk in some patients.[16,17] As an inactive prodrug, clopidogrel requires a 2-step metabolism to become an active metabolite. This results in a slower onset of action because of the time needed to reach sufficient therapeutic drug level.[18] Therefore, new generation P2Y12 inhibitors including prasugrel and ticagrelor have been developed to overcome unmet clinical needs.

2. Prasugrel

Prasugrel (60 mg loading and 10 mg/day maintenance dose) achieves a faster and greater platelet inhibition than clopidogrel in patients receiving PCI.[19] The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 trial randomized ACS patients with scheduled PCI to be treated with either prasugrel or clopidogrel. Overall, prasugrel reduced more ischemic events compared with clopidogrel, but also increased the risk of major bleeding. Post hoc analyses revealed patients weighing less than 60 kg and patients 75 years of age or older had no net benefit from prasugrel. Patients with previous stroke or transient ischemic attack (TIA) had net harm from prasugrel due to a trend toward more major bleeding (p = 0.06).[20] The results were consistent among the NSTE-ACS subgroup analysis showing reduced primary endpoint but increased major bleeding with prasugrel. However, after excluding patients with previous stroke/TIA, weight less than 60 kg, and aged 75 or older, prasugrel was shown to be superior to clopidogrel regarding the primary endpoint and without significant increase

of major bleeding in NSTE-ACS patients.[21] As a consequence, prasugrel is not recommended in patients with prior history of stroke/TIA and should be used with caution in patients with low body weight or old age. In NSTE-ACS patients who only received medical control, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study showed that the ischemic and bleeding events were similar between prasugrel and clopidogrel groups.[22] In addition, the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) study demonstrated that the pretreatment with prasugrel before coronary angiography in NSTE-ACS patients not only had no benefit in reducing ischemic events, but further increased major bleeding complications.[23] Prasugrel should only be prescribed when PCI is indicated after coronary angiography.

In Japan, prasugrel is used with lower loading and maintenance dose (20/3.75 mg) to avoid bleeding events. The lower dose regimen was tested in the PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI (PRASFIT-ACS) study.[24] After excluding patients with prior ischemic stroke/TIA, the lower dose prasugrel was associated with a trend of 23% reduction in adverse CV events and similar major bleeding risk compared with clopidogrel in Japanese ACS patients undergoing PCI.

3. Ticagrelor

Ticagrelor is an active drug and does not require hepatic metabolism for activation. The maximal platelet inhibition can be achieved more extensively and rapidly than with clopidogrel. In addition, ticagrelor reversibly binds to P2Y12 receptors, resulting in a faster platelet inhibition offset after drug discontinuation when compared with clopidogrel.[25] The major CV outcome trial of ticagrelor was the Platelet Inhibition and Patient

Outcomes (PLATO) study, which tested the efficacy and safety of ticagrelor (180 mg loading and 90 mg twice daily maintenance dose) in ACS patients. Compared with clopidogrel, ticagrelor significantly reduced the combined risk of CV death, MI, or stroke. However, ticagrelor was associated with a significantly higher rate of major bleeding not related to coronary artery bypass grafting (CABG).[26] The benefits of ticagrelor versus clopidogrel in the overall PLATO trial were consistent with patients initially treated with invasive or non-invasive strategies.[27,28] The subgroup analysis of the PLATO study for NSTE-ACS patients showed similar results as the overall PLATO populations.[29]

The data from small sized randomized control trials and observational studies in Asia revealed controversial and conflicting results for ticagrelor. The PHILO study included 801 Asian ACS patients (Japanese, n = 721; Taiwanese, n = 35; South Korean, n = 44; unknown ethnicity, n = 1) that were scheduled to receive PCI.[30] It demonstrated that ticagrelor was not superior to clopidogrel regarding the primary efficacy endpoint but carried a trend to higher bleeding risk. The small sample size, low event rate, and imbalance in clinical characteristics in this study may have contributed to the discrepancy in results between the PLATO and PHILO studies. In Taiwan, there were two retrospective observation studies comparing ticagrelor and clopidogrel in ACS patients. Both studies showed that patients treated with ticagrelor were associated with lower ischemic events and similar major bleeding risks when compared to clopidogrel-treated patients.[31, 32]

Based on currently available evidence, ticagrelor should be the first-line P2Y12 inhibitor for NSTE-ACS patients in Taiwan regardless of the initial treatment strategies (invasive or ischemia-guided). But if concerns about bleeding prevail over ischemia, clopidogrel or reduced dose of prasugrel (only for patients receiving PCI) are reasonable alternative choices. The common bleeding risk features include old age, low body weight, anemia, chronic kidney disease,

concomitant use of oral anticoagulant, prior intracranial hemorrhage, or other major bleeding history. The selection of P2Y12 inhibitors and the trade-off between ischemic and bleeding risk should be individualized to get the greatest net clinical benefit for NSTE-ACS patients in Taiwan.

The recommendation for the use of P2Y12 inhibitors in this guideline is:

- **Ticagrelor (180 mg loading dose then 90 mg twice daily) or clopidogrel (300-600mg loading dose, 75 mg daily dose) are recommended in NSTE-ACS patients treated with either invasive or medical treatment unless contraindicated and ticagrelor is preferred to clopidogrel. (COR I, LOE B)**
- **Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended only in NSTE-ACS patients undergoing PCI without contraindication. (COR I, LOE B)**
- **Clopidogrel rather than ticagrelor or prasugrel may be considered in patients with increased bleeding risk features. (COR IIa, LOE C)**
- **Reduced dose of prasugrel (20 mg loading dose, 3.75 mg daily dose) may be considered in NSTE-ACS patients undergoing PCI if there are increased bleeding risk features. (COR IIb, LOE B)**
- **Pretreatment with prasugrel before diagnostic angiography is not recommended for NSTE-ACS patients. (COR III, LOE B)**

Glycoprotein IIb/IIIa receptor inhibitors

Glycoprotein (GP) IIb/IIIa inhibitor has been shown to reduce ischemic events in NSTE-ACS patients undergoing PCI.[33-35] A meta-analysis indicated that GP IIb/IIIa inhibitor was associated with a significant reduction of death or non-fatal MI at 30 days in NSTE-ACS patients. The

benefits were more prominent in patients receiving PCI than in patients who received medical treatment only.[36] The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial compared NSTE-ACS patients receiving invasive treatment with three antithrombotic regimens: bivalirudin alone, unfractionated heparin or enoxaparin plus a GP IIb/IIIa inhibitor, or bivalirudin plus a GP IIb/IIIa inhibitor. Compared with heparin plus GP IIb/IIIa inhibitor, bivalirudin was associated with significantly reduced risk of major bleeding and similar ischemic endpoints.[37] Routine upstream use of GP IIb/IIIa inhibitor before invasive treatment could not reduce ischemic events, but increased the risk of major bleeding.[38,39] There have not been prospective studies about the efficacy and safety of combination therapy with GP IIb/IIIa inhibitor and new generation P2Y12 inhibitors such as prasugrel or ticagrelor. DAPT with potent P2Y12 inhibitor is the current standard therapy in NSTE-ACS patients. GP IIb/IIIa inhibitor is now only indicated provisionally during PCI for coronary thrombotic lesions or thrombotic complications bailout after PCI.

The recommendation for the use of GP IIb/IIIa inhibitors in this guideline is:

- **Use of GP IIb/IIIa inhibitors in patients with NSTE-ACS as adjunctive therapy during PCI may be indicated for large thrombus burden or as bailout for thrombotic complications. (COR IIa, LOE B)**
- **Routine use of GP IIb/IIIa inhibitors in patients with NSTE-ACS is not recommended before coronary angiography. (COR III, LOE A)**

Conclusions

Overall, the 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the management of NSTE-ACS provide several recommendations for antiplatelet therapy in NSTE-ACS patients. Based on current evidence, DAPT with aspirin and new generation P2Y12 inhibitor is preferred for further ischemic risk reduction and better clinical outcomes. However, the most appropriate regimen should still be individualized to balance the ischemic and bleeding risks in NSTE-ACS patients in Taiwan.

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Review of Percutaneous Left Atrial Appendage Closure for Non-valvular Atrial Fibrillation in Taiwan

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and approximately one fifth of ischemic strokes are caused by AF. Stroke prevention among patients with non-valvular AF (NVAF) and a CHA_2DS_2-VASc score ≥ 2 is indicatedwithoral anticoagulants, as recommended in clinical guidelines. However, some patients cannot be treated with anticoagulants, for a variety of reasons or multiple comorbidities. Left atrial appendage (LAA) closure has evolved as an effective strategy for stroke prevention among NVAF patients for whom oral anticoagulants are indicated, but cannot be tolerated in clinical practice. Currently, there is robust evidence based on randomized clinical trials with one percutaneous LAA closure device, and some registry data with other devices, regarding the safety and efficacy of this therapy. However, concerns have been raised about optimal patient selection, management of peri-procedural complications including device-related thrombus and residual leaks. In this review, we summarize and evaluate recently available evidence regarding percutaneous LAA closure in Taiwan with the aim of assisting health professionals in selecting the best management strategies.

Keywords: NVAF, ischemic stroke, atrial fibrillation, oral anticoagulation, CHA_2DS_2-VASc, LAA closure, LAA occluder

Introduction

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, and its incidence is increasing.[1-3] Theprevalence rate of AF in most Asian countries is around 1% in the adult population, lower than that in white people (about 2%).[4] AF is associated with a significant risk of ischemic stroke, congestive heart failure, and overall mortality and presents an important health care challenge for cardiovascular and general clinicians. Approximately one fifth of ischemic strokes are caused by AF and oral anticoagulants (OAC), along with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) markedly reduce ischemic stroke and mortality in patients with non-valvular AF (NVAF) and a CHA_2DS_2-VASc score (congestive heart failure,

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hypertension, age ≥75 years, diabetes, stroke/ transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category [female]) ≥ 2.[1,3,5,6] Other pharmacological interventions such as rhythm control and rate control improve AF-related symptoms and may preserve cardiac function, but have not demonstrated a reduction in long-term morbidity or mortality.[1,3] However, some patients cannot be treated with OAC for a variety of reasons, including absolute or relative contraindications due to high bleeding risk, patient noncompliance, drug interactions or multiple comorbidities even with a CHA$_2$DS$_2$-VASc score ≥ 2. The left atrial appendage (LAA) is the most common source of thrombus in AF patients with ischemic stroke, whereby echocardiography and autopsy studies have shown that more than 90% of thrombi in patients with NVAF and 57% of thrombi in patients with valvular AF originated from the LAA.[7-10] Specific LAA morphology, concomitant trabeculations, pectinate muscle morphology, inflammation, atrial remodeling, and a hypercoagulable state contribute to thrombogenicity.[11,12] Observational studies have demonstrated inconsistent results of surgical LAA excision or occlusion.[13] Percutaneous LAA closure with self-expanding devices which are trans-septally implanted in the LAA, have emerged as safe and effective alternatives for prevention of stroke and systemic embolism (SE) in NVAF patients indicated for OAC.[14,15] In Taiwan, currently available percutaneous LAA closure devices include Watchman (Boston Scientific,

Marlborough, MA, USA), Amplatzer Cardiac Plug (ACP, Abbott Vascular, Santa Clara, CA, USA) and Amulet (Abbott Vascular, Abbott Park, IL, USA) (Picture 1). In this paper, we summarize and evaluate recently available evidence (Table 1 and 2) regarding percutaneous LAA closure with the aim of assisting health professionals in selecting the best management strategies.

Watchman

The Watchman nitinol cage percutaneous LAA closure device is the most widely studied and has been approved by the Food and Drug Administration (FDA) in the United States since 2015 and reimbursed by Taiwan's National Health Insurance since 2016. The Watchman device consists of a self-expanding nitinol frame covered with a permeable polyethylene terephthalate (PET) membrane and includes 10 active fixation anchors. A fabric membrane filter made of PET covers the atrial surface of the device, preventing thrombi from escaping into the left atrial chamber and promoting endothelialization during the healing process.[16,17] This device is deployed transseptally using a dedicated 14 Fr sheath and a 12 Fr delivery catheter, usually under transesophageal echocardiography (TEE) and fluoroscopic guidance, but it can also be placed using intracardiac echocardiography. The PROTECT-AF study (Watchman Left Atrial Appendage Closure Device for Embolic Protection in Patients with Atrial Fibrillation) enrolled 707 patients with

(A)　　　　　　　　　(B)　　　　　　　　　(C)
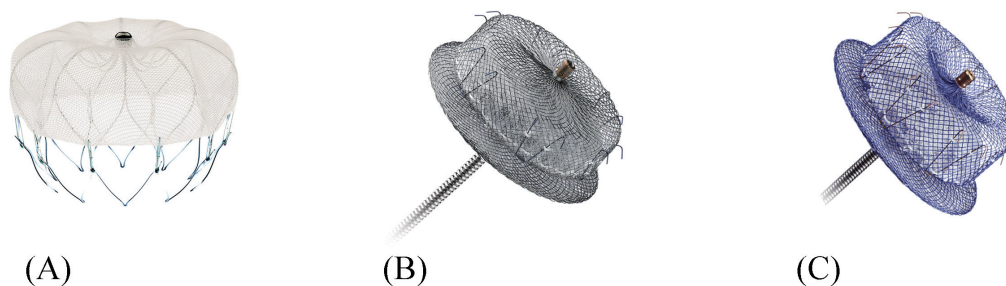
Picture 1. Currently available devices for percutaneous left atrial appendage (LAA) closure in Taiwan. (A) Watchman (B) Amplatzer Cardiac Plug (C) Amulet.

Table 1. Major studies on percutaneous LAA closure devices: Watchman.

Characteristics	PROTECT-AF	PREVAIL	CAP registry	CAP2 registry	EWOLUTION	Post-FDA Approval
Study types	Randomized trial	Randomized trial	Prospective registry	Prospective registry	Prospective registry	Prospective registry
Enrolled patients	800	461	566	579	1021	3822
Randomized	463/244	269/138				
Implantation success rate (%)	91	95.1	95	94.8	98.5	95.6
$CHADS_2$ score	2.2 ± 1.2	2.6 ± 1.0	2.4 ± 1.2	2.7 ± 1.1	NA	NA
CHA_2DS_2-Vasc score	3.5 ± 1.6	4.0 ± 1.2	3.9 ± 1.5	4.5 ± 1.3	4.5 ± 1.6	NA
HAS-BLED score ≥3 (%)	19.9	29.7	36.2	28.3	40.0	NA
Anticoagulation	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	27% treated with OAC, 60% DAPT, 7% single APT, 6% without any therapy	NA
Ischemic stroke (%)	2.2/1.6	1.9/0.7	NA	NA	1.1	NA
Hemorrhagic stroke (%)	0.1/1.6	0.4/0	NA	NA	NA	NA
Major bleeding (%)	3.5/4.1	0.4/NA	0.7	NA	2.6	NA
Pericardial effusion/tamponade (%)	4.8/0	0.4/0	2.2	2.4	0.5	1.3
Device embolization (%)	0.6/0	0.7/0	0	0	0.2	0.2
Procedure related stroke (%)	1/0	0.4/0	0	NA	NA	0.1
Device-related thrombus	NA	NA	NA	NA	3.7	NA

APT = antiplatelet therapy; CAP = Continued Access to PROTECT AF; CAP2 = Continued Access to PREVAIL ; DAPT = dual antiplatelet therapy; FDA = Food and Drug Administration; LAA = left atrial appendage; NA = not available; OAC = oral anticoagulation; PROTECT-AF = The WATCHMAN LAA Closure Device for Embolic PROTECTion in Patients with Atrial Fibrillation; PREVAIL = Randomized Trial of LAA Closure vs. Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation; EWOLUTION = Design of a Registry to Evaluate Real-World Clinical Outcomes in Patients With AF and High Stroke Risk-Treated With the WATCHMAN Left Atrial Appendage Closure Technology
n/n=percutaneous LAA closure device/warfarin arms.

Table 2. Major studies on percutaneous LAA closure devices: Amplatzer Cardiac Plug and Amulet.

Characteristics	Tzikas et al.[26]	Landmesser et al.[28]
Study types	Retrospective registry, ACP	Prospective registry, Amulet
Enrolled patients	1047	1088
Implantation success rate (%)	97.3	99.0
CHA_2DS_2-Vasc score	4.5 ± 1.6	4.2 ± 1.6
HAS-BLED score	3.1 ± 1.2	3.3 ± 1.1
Antithrombotic therapy at discharge	No use: 8.3% Single APT: 34.7% DAPT: 15.7% OAC (alone or with APT): 25.2%	No use: 2% Single APT: 23% DAPT: 54.3% OAC (alone or with APT): 18.9%
Procedure-related stroke (%)	0.9	0.2
Procedure-related death (%)	0.8	0.2
Procedure-related Major bleeding (%)	1.2	2.4
One year all-cause mortality (%)	4.2	NA
One year major bleeding rate (%)	2.1	NA
Pericardial effusion/tamponade (%)	1.2	1.2
Device embolization (%)	0.7	0.1
Major vascular complication (%)	0.4	0.9
Device-related thrombus	0.3	1.5

ACP = Amplatzer Cardiac Plug; APT = antiplatelet therapy; DAPT = dual antiplatelet therapy; LAA = left atrial appendage; NA = not available; OAC = oral anticoagulation.

NVAF and a $CHADS_2$ risk score of 1 or more (ie, at least one of the following: previous stroke or TIA, congestive heart failure, diabetesmellitus, hypertension, or were 75 years or older) randomized to either the Watchman device (n = 463) or continued warfarin (n = 244) in a 2:1 ratio.[14] After device implantation, warfarin was continued for 45 days, but discontinued if a TEE showed a small peri-deviceleak (residual jet <5 mm), followed by clopidogrel for 4.5 months and life-long aspirin. Successful device implantation was recorded in 88% of subjects, where as TEE criteria for warfarin discontinuation were met in 86% and 92% at 45 days and 6 months, respectively. Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and SE with a one-sided probability

criterion of non-inferiority for the intervention of at least 97.5%, by use of a two-fold non-inferiority margin. Serious adverse events (SAEs) that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolization. After 1065 patient-years (PY) of follow-up, the primary efficacy event rate was 3.0 per 100 PY (95% credible interval [CrI] 1.9-4.5) in the intervention group and 4.9 per 100 PY (2.8-7.1) in the control group (rate ratio [RR] 0.62, 95% CrI 0.35-1.25). Primary safety events were more frequent in the intervention group than in the control group (7.4 per 100 PY, 95% CrI 5.5-9.7, vs 4.4 per 100 PY, 95% CrI 2.5-6.7; RR 1.69, 1.01-3.19). The PROTECT-AF study concluded that the efficacy of the Watchman device was non-inferior to that of warfarin therapy with a higher

rate of adverse safety events in the intervention group than in the control group, whereby events in the intervention group were mainly a result of peri-procedural complications. Most adverse events were related to the implant procedure, which included major bleeding, pericardial effusion, and stroke in 3.5%, 4.8%, and 1.1%, respectively. After 1588 PY of follow-up (mean 2.3 ± 1.1 years), the primary efficacy event rates were 3.0% and 4.3% per 100 PY in the Watchman and warfarin groups, respectively (relative risk 0.71; 95% confidence interval [CI], 0.44%–1.30% per year), which met the criteria for non-inferiority. There were more primary safety events in the Watchman group (5.5% per year; 95% CI, 4.2%–7.1% per year) than in the control group (3.6% per year; 95% CI, 2.2%–5.3% per year; relative risk 1.53; 95% CI, 0.95–2.70).[18] The influence of experience on the safety of percutaneous LAA closure using the Watchman device has been analyzed in another study which included patients in the PROTECT-AF trial (542 patients) and those from a subsequent non-randomized CAP (Continued Access to PROTECT AF) registry of patients undergoing Watchman implantation (460 patients).[19] The safety end point included bleeding- and procedure-related events (pericardial effusion, stroke, device embolization). There was a significant decline in the rate of procedure- or device-related safety events within 7 days of the procedure across the 2 studies, with 7.7% and 3.7% of patients, respectively, experiencing events (p = 0.007), and between the first and second halves of PROTECT-AF and CAP, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events (p = 0.006). The rate of serious pericardial effusion within 7 days of implantation, which had made up >50% of the safety events in the PROTECT-AF trial, was lower in the CAP Registry (5.0% versus 2.2%, respectively; p = 0.019). There was a similar experience-related improvement in procedure-related stroke (0.9% versus 0%, respectively; p = 0.039). Finally, the functional impact of these safety events, as defined by significant disability

or death, was statistically superior in the Watchman group compared with the warfarin group in the PROTECT-AF trial. This remained true whether significance was defined as a change in the modified Rankin score of ≥ 1, ≥ 2, or ≥ 3 (1.8 versus 4.3 events per 100 PY; relative risk, 0.43; 95% CI, 0.24-0.82; 1.5 versus 3.7 events per 100 PY; relative risk, 0.41; 95% CI, 0.22-0.82; and 1.4 versus 3.3 events per 100 P; relative risk, 0.43; 95% CI, 0.22-0.88, respectively). Therefore, it was concluded that there is a significant improvement in the safety of the Watchman LAA closure with increased operator experience, as with all interventional procedures. The PREVAIL study (Randomized Trial of LAA Closure vs. Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation) was conducted to answer someof the safety concerns raised by the FDA on the basis of the PROTECT-AF study.[20] The PREVAIL study included patients with NVAF who had a $CHADS_2$ score ≥ 2 or 1 and another risk factor, randomly assigned (in a 2:1 ratio) to undergo percutaneous LAA closure and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138). At 18 months, the rate of the first co-primary efficacy endpoint including stroke, SE, and cardiovascular/unexplained death was 0.064 in the device group versus 0.063 in the control group (RR 1.07, 95% CrI: 0.57-1.89) and did not achieve the pre-specified criteria for non-inferiority (upper boundary of 95% CrI ≥ 1.75). The rate for the second co-primary efficacy endpoint (stroke or SE >7 days' post-randomization) was 0.0253 versus 0.0200 (risk difference 0.0053, 95% CrI: -0.0190-0.0273), achieving non-inferiority. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT-AF, satisfying the pre-specified safety performance goal. Even using a broader, more inclusive definition of adverse effects, these still were lower in the PREVAIL trial than in the PROTECT-AF (4.2% vs. 8.7%; p = 0.004). Pericardial effusions requiring surgical repair decreased from 1.6% to

0.4% (p = 0.027), and those requiring pericardiocentesis decreased from 2.9% to 1.5% (p = 0.36), although the number of events was small. The PREVAIL trail concluded that percutaneous LAA closure using the Watchman device was non-inferior to warfarin for ischemic stroke prevention or SE > 7 days' post-procedure. Although non-inferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms and procedural safety was significantly improved. The trial also provided additional data that the Watchman device is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy. Despite not meeting the first co-primary efficacy endpoint, the FDA Circulatory System Advisory Panel reviewed the data from both of thesetrials (PROTECT-AF and PREVAIL) in entirety, judged the device to be safe, and approved the percutaneous LAA closure device, Watchman, for routine clinical practice in 2015. The EWOLUTION (Design of a Registry to Evaluate Real-World Clinical Outcomes in Patients With AF and High Stroke Risk-Treated With the WATCHMAN Left Atrial Appendage Closure Technology) registry provides large-scale post-marketing data from more than one thousand participants regarding procedural success and complications, and long-term patient outcomes, including bleeding and incidence of stroke/TIA.[21,22] The EWOLUTION registry enrolled subjects at high risk of stroke (average $CHADS_2$ score: 2.8 ± 1.3, CHA_2DS_2-VASc score: 4.5 ± 1.6) and moderate-to-high risk of bleeding (average HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history orpredisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly]: 2.3 ± 1.2). 45.4% of patients had a history of TIA, ischemic stroke, or haemorrhagic stroke; 62% of patients were judged unsuitable for NOAC by physicians. The Watchman device was successfully deployed in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of implanted patients. The overall 30-day mortality rate was 0.7%. The most common SAE occurring within 30 days of the procedure was major bleeding requiring transfusion. Incidence of SAEs within 30 days was significantly lower for subjects judged to be ineligible for OAC compared with those eligible for OAC (6.5 vs. 10.2%, p = 0.042). This 30-day data showed that percutaneous LAA closure with the WATCHMAN device has a high success rate with low peri-procedural risk, even in a population with a higher risk of stroke and bleeding, and multiple co-morbidities. Improvement in implantation techniques has led to a reduction of peri-procedural complications previously limiting the net clinical benefit of the procedure. Longer 1-year data of the EWOLUTION registry showed that the Watchman implant succeeded in 1005 patients (98.5%), without leaks >5 mm in 1002 patients (99.7%) with at least 1 TEE follow-up in 875 patients (87%). Antiplatelet therapy was used in 784 (83%), while VKAs were used in only 75 (8%). 1-year mortality rate was 9.8%, reflecting the advanced age and co-morbidities in this enrolled population.[23] Device-related thrombus was observed in 28 patients at routine TEE (3.7%) and was not correlated with the drug regimen (p = 0.14). Ischemic stroke rate was 1.1% (relative risk 84% vs estimated historical data); the major bleeding rate was 2.6% and was predominantly (2.3%) non-procedure/device related. Percutaneous LAA closure with the Watchman device has a high implant and sealing success rate.1-year data of the EWOLUTION registry showed that stroke risk reduction appears to be safe and effective with an ischemic stroke rate as low as 1.1%, even though 73% of patients had a contraindicationto and were not using OAC. 5-year outcomes after percutaneous LAA closure from the PREVAIL and PROTECT-AF trials enrolled 1,114 patients for 4,343 PY and demonstrated that the Watchman provides stroke prevention in NVAF comparable to warfarin (all-stroke/SE; hazard ratio [HR]: 0.961; p = 0.87), with additional reductions in hemorrhagic stroke, disabling/fatalstroke,

cardiovascular/unexplained death, all-cause death, and post-procedure bleeding (HR: 0.20; p = 0.0022; HR: 0.45; p = 0.03; HR: 0.59; p = 0.027; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003, respectively).[24] Four real-world registries or meta-analysis demonstrated safety and feasibility with post-procedural dual antiplatelet therapy (DAPT), without using OAC. The ASAP (ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology), a multicenter, prospective, nonrandomized study, enrolled 150 patients with NVAF and CHADS$_2$ score ≥ 1, who were considered ineligible for warfarin, where by history of hemorrhagic/bleeding tendencies (93%) was the most common reason.[25] The primary efficacy endpoint included combined events of ischemic stroke, hemorrhagic stroke, SE, and cardiovascular/unexplained death. The ASAP study demonstrated an ischemic stroke rate of 1.7%/year with a 77% relativerisk reduction of stroke, adjusted for a predicted stroke risk of 7.3% for the CHADS$_2$ score and successfully confirmed that management with aspirin and 6 months of clopidogrel was safe and feasible after the Watchman percutaneous LAA closure. 1-year data from the EWOLUTION registry further shows that 60% of patients were treated with DAPT, 7% with single antiplatelet, 11% with a NOAC, and 16% with VKA. During follow-up, discontinuation of clopidogrel and OAC occurred, resulting in 84% of patients receiving antiplatelet therapy (55% single and 28% DAPT) and 9% taking no medications. The average time to discontinue DAPT was 6 months, but a large proportionof patients (25%) used a short DAPT regimen (≤ 3 months). The annual rate of ischemic stroke was 1.1%, which translates into an 84% risk reduction, as compared with the calculated stroke rate of 7.2% without the use of OAC for similar CHA$_2$DS$_2$-VASc scores. There were no differences in death, stroke, or bleeding rates observed between patients with or without a contraindication for anticoagulation, and there was no relation to the type of OAC used.[21,23] Follow-up TEE revealed adequate sealing (no residual jet >5

mm) in 99% of patients. Device-related thrombus was present in 3.7% of patients but was not correlated with the drug regimen. Preliminary results at 2-year follow-up from the EWOLUTION registry were presented at the European Society of Cardiology (ESC) Congress 2018 and showed consistent findings as compared with the 1-year follow-up data but the manuscript is not yet available. Summarized data of the Watchman device is listed in Table 1.

ACP

ACP is the first-generation device specifically developed for percutaneous LAA closure and comprises a self-expanding double-disc nitinol platform with a proximal disc, distal lobe, and six pairs of distal wires for stabilization (Figure 1). There have been no randomized controlled trials (RCTs) comparing the ACP device with OAC, and only observational studies are available. Tzikas et al. reported the largest multicenter experience withthe CAP device, including 1,047 patients with NVAF treated in 22 centers.[26] Overall, procedural success was 97.3% and peri-procedural major adverse events were 4.97%. The annual rate of SE was 2.3% (31/1349 PY), which is a 59% risk reduction adjusted for a predicted stroke risk of 5.6%/year for the CHA$_2$DS$_2$-VASc score. The annual rate of major bleeding was 2.1% (28/1349 PY), which is a 61% risk reduction adjusted for a predicted bleeding risk of 5.34%/year. During follow-up, aspirin monotherapy increased from 31% to 63.7%, whereas VKA decreased from 16% to 1.6%, showing that the ACP device could be a useful strategy inpatients who are not eligible for OAC and who can besafely managed with DAPT. The ACP device is currently not FDA-approved in the United States but is available in Europe. 4-year follow up data using the ACP device in 134 NVAF patients with long-term OAC contraindication from cumulative experience of 2 Italian centers revealed similar reduced annual rates of SE and major bleeding (2.5% and 1.3%) respectively.[27]

Amulet

The Amulet device is the second generation of ACP with improvements in the implantation apparatus to promote ease of deployment, safety, and efficacy. A global prospective registry of a large cohort of NVAF patients (n = 1088) at high risk for ischemic stroke as well as bleeding, implanted with the Amulet device demonstrated a high implantation successrate (99.0%) and major adverse events during implantation and subsequent hospitalization were 3.2%.[28] Patients were discharged on a single antiplatelet agent (23.0%), DAPT (54.3%) or an OAC (18.9%). TEE follow-up showed adequate (<3 mm jet) occlusion of the LAA in 98.2% of patients and device-related thrombus in 1.5% of patients. This large real-world prospective registry of percutaneous LAA closure using the Amulet device confirms a high implant success rate, a low peri-procedural complication rate, good closure rates and low rates of device-associated thrombus in a population with a high risk of stroke and bleeding. However, there are no RCTs comparing the Amulet device with OAC. In the United States, the ongoing Amulet–IDE (AMPLATZER Amulet LAA Occluder Trial) clinicaltrial (NCT02879448) is currently being randomized to evaluate safety and efficacy for stroke prevention in patients with NVAF. The Amulet device is currently not FDA-approved in the United States but is available in Europe. Comparative studies have shown similar results obtained with the ACP and Amulet devices in terms of safety, implantation success and appropriate closure of the LAA.[29,30] The Amulet device is associated with shorter fluoroscopy times and radiation dosages, reduced use of contrast-dye, lower recapture rates, and less peri-device leaks as compared to the ACP device.[31]

Which patients with NVAF should be considered for percutaneous LAA closure?

Patients with NVAF and CHA_2DS_2-VASc scores ≥ 2 are indicated to receive NOACs or VKAs for stroke prevention. However, there is adiscrepancy in real-world practice, where eligible patients are deemed ineligible for OAC due to absolute or relative contraindications or high bleeding risk. NOACs use in such patients ineligible for OAC remains limited and has shown a higher risk of recurrent major bleeding, especially gastrointestinal bleeding. In theory, these patients arepotentially suitable for percutaneous LAA closure.However, RCTs of the Watchman device were conducted in patients eligible for warfarin. The EWOLUTION registry supported the benefit of the Watchman device in patients deemed ineligible for OAC, and a significant proportion of patients were treated with DAPT, with substantial reductions in stroke and major bleeding. NVAF patients with high HAS-BLED scores may benefit from percutaneous LAA closure, as studies have consistently shown a significant reduction in risk of major bleeding which could translateinto a survival benefit. Also, NVAF patients with high CHA_2DS_2-VASc scores and without any bleeding contraindications still have ischemic stroke despite OAC use, as demonstrated in the RCTs of currently available NOACs and such patients might potentially benefit from combination therapy with percutaneous LAA closure and OAC. However, there are currently no data to support such a strategy in thesehigh-risk patients.

Post-procedural antithrombotic therapy

The major challenge associated with percutaneous LAA closure is managing post-procedural antithrombotic therapy and bleeding risk. Recent studies have revealed that the incidence of device-related thrombus with the percutaneous LAA closure is around 4%. If athrombus is confirmed on follow-up TEE, patients should continue OAC, and follow-up TEE in 3 to 6 months is recommended.As current understanding of coagulation and bleeding mechanisms at a molecular and cellular level

continues to develop, future targeted therapies may change theclinical practice dramatically.

Post-procedural leaks

The incidence of reported leaks hasranged from 0% to 63%, depending on the type of LAA device and the frequency and modality of monitoring. Using competent imaging modalities and adequate device sizing are keys to reduce peri-device leaks. Currently, continued surveillance with TEE and temporary initiation of anticoagulation are recommended.

Conclusions

AF is a major cause of ischemic stroke. 90% of embolic thrombi in patients with NVAF originate from the LAA. Percutaneous LAA closure is an effective interventional alternative to prevent ischemic stroke in patients with high risk of bleeding or prior bleeding history.

Disclosure

The authors report no conflicts of interest in this work.

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Review of Intravascular Optical Coherence Tomography in Clinical Practice of Coronary Interventions

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Abstract

Optical coherence tomography (OCT) is an imaging modality that provides high resolution of intravascular tissue microstructure for coronary intervention. OCT is now widely applied to clinical scenarios of coronary artery disease, including the assessment of plaque and thrombi characteristics, lesion preparation strategy, stent optimization, and for decreasing complications post stent deployment. Accumulating data support the clinical role of OCT in assisting intervention decision-making. In this study, we comprehensively review the published data and provide a practical approach to OCT-guided percutaneous coronary intervention in coronary intervention practice.

Keywords: optical coherence tomography, coronary artery disease, intracoronary imaging

INTRODUCTION

Optical coherence tomography (OCT) is a method of obtaining tomographic images based on the coherence of near infrared light. Two Japanese researchers, Naohiro Tanno and James G. Fujimoto, developed OCT around 1990. In vitro observation of the retina and coronary artery was first performed in 1991.[1,2] OCT and intravascular ultrasound (IVUS) are two commonly used intravascular imaging modalities. Acknowledging that IVUS was developed earlier in the late 1980s, published data on OCT in coronary intervention is much less than that on IVUS. In the past, time-domain OCT (TD-OCT) required balloon occlusion and a complex procedure to obtain the image. Since the development of new generation OCT systems implementing frequency-domain OCT (FD-OCT) imaging methods, the previous limitations of time-domain OCT have been overcome.[3] FD-OCT has now been increasingly used in biomedical research and clinical practice for over two decades.

Although FD-OCT has markedly improved intracoronary image resolution as compared to IVUS, there are clear differences between OCT and IVUS. OCT has advantages in resolution, surface detail, automatic and fast-pullback system, while IVUS is better in penetration, media-to-media sizing and is a simultaneous real-time system.[4] For intervention cardiologists, the question of which image modality is better may

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be too simple; what matters is whether IVUS or OCT is more suitable and which one provides more significant assistance for decision-making in our cases. In this study, we review the definitive data of intravascular OCT in clinical applications, including image interpretation, diagnosis, lesion preparation, stent optimization, and the assessment of complications post stent deployment.

Image Interpretation of OCT

The coronary artery appears on OCT as a concentric three-layered structure, including (1) Internal elastic lamina: inner high-signal and 20-mm in thickness; (2) Medial layer: middle low-signal dark band; and (3) External elastic lamina: outer high-signal band (Figure 1A).[5] An atherosclerotic lesion on OCT appears as a segmental intimal thickening or loss of the normal arterial structure.

Atherosclerotic plaques can further be differentiated into three major kinds of plaques by OCT, including (1) Fibrous plaque: homogenous, brighter, lower attenuation signal (Figure 1B); (2) Calcified plaque: heterogeneous, darker, sharp edge, low attenuation signal (Figure 1C); and (3) Lipid-rich plaque: homogenous, darker, diffuse borders and high attenuation signal (Figure 1D).[6] Since the resolution of OCT (10–20 μm) is 10-times higher than that of IVUS (100–150
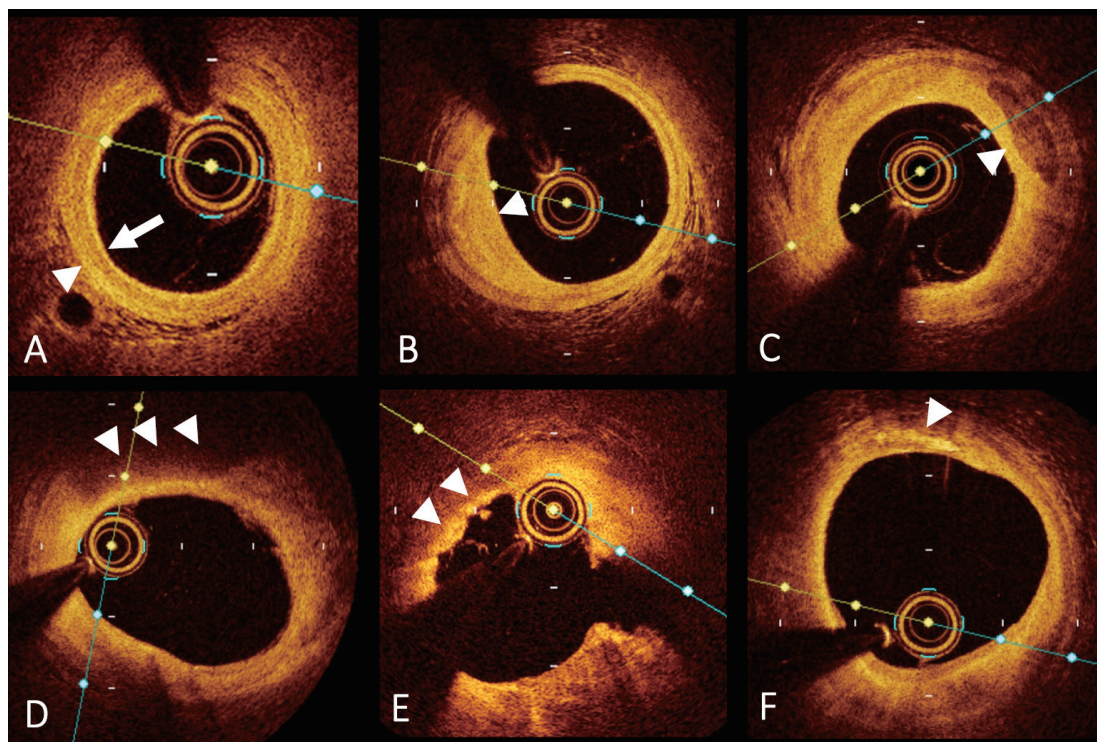

Figure 1. Normal coronary structure and different characteristics of plaques on OCT.
(A) 3-concentric layered structure of coronary artery. Internal elastic lamina *(white arrow)* is the inner layer with high-signal; External elastic lamina *(white arrow head)* is the outer layer with high signal; the middle low-signal dark band is the media layer. (B) Fibrous plaque *(white arrow head)* has homogenous, brighter, lower attenuation signal. (C) Calcified plaque *(white arrow head)* has heterogeneous, darker, sharp edge, low attenuation signal. (D) Lipid-rich plaque *(white arrow head)* has homogenous, darker, diffuse borders and high attenuation signal. (E) Macrophages *(white arrow head)* are punctate high-signal spots accumulated at the edge of necrotic core. (F) Cholesterol crystals *(white arrow head)* are very high-signal, high-scattering, linear structure associated with a lipid pool.

μm), macrophages and cholesterol crystals can be detected by OCT. Macrophages (Figure 1E) are punctate high-signal spots which sometimes accumulate at the border of the fibrous cap and necrotic core. Cholesterol crystals (Figure 1F) are very high-signal, high-scattering, linear structures associated with a lipid pool.[6]

Thin-cap fibroatheromas (TCFAs), defined as fibroatheroma with thin fibrous cap of < 65 μm, are the vulnerable plaque prone to rupture and highly implicated in acute coronary syndrome in autopsy studies.[7-9] OCT now makes it possible to measure the fibrous cap thickness exactly with an online image.[10] Patients with ACS have a higher

proportion of OCT-TCFAs, which have thinner fibrous caps than those in non-ACS patients.[11,12] In patients with ACS, OCT-TCFAs are more commonly found in the proximal segments of the culprit vessel.[10,13] There is not yet enough evidence for an exact cutoff-value on OCT for the thickness of the fibrous cap or the lipid pool arc, to directly reflect clinical events. Further OCT studies are required to investigate the natural development of these vulnerable plaques in patients with ACS.

In acute coronary syndrome, OCT can also differentiate red or white thrombus as follows: (1) Red thrombi (Figure 2A) are identified by their low birefringence, and high attenuation protrusions
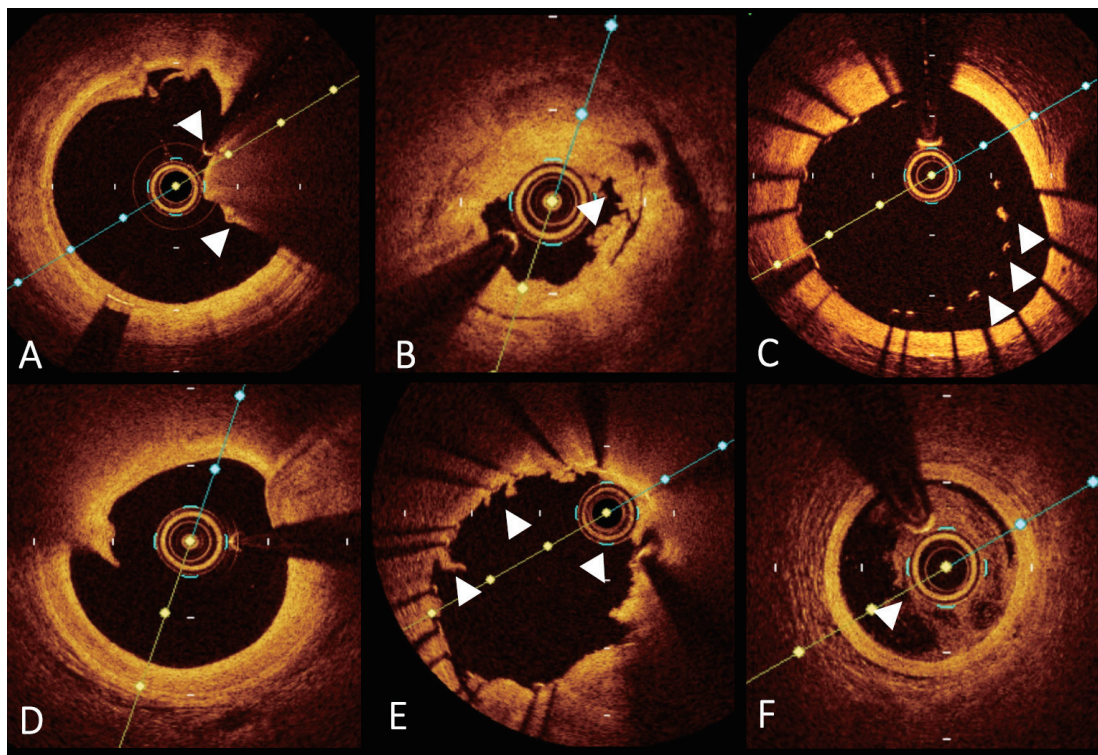

Figure 2. Assessment of intravascular thrombosis and complications post stent deployment assessment by OCT.
(A) Red thrombus *(white arrow head)* is acute and red blood cells rich, which has low birefringence, high attenuation signal on OCT. (B) White thrombus *(white arrow head)* is relative chronic and platelet rich, which has high birefringence, low attenuation signal on OCT. (C) Stent malapposition means stent struts *(white arrow head)* are not attached to the Internal elastic lamina of vessel wall. (D) OCT can detect edge dissection *(white arrow head)* in good sensitivity. (E) Tissue protrusion *(white arrow head)* can be easily detected by OCT. (F) Red blood cells *(white arrow head)* in the vessel inner lumen will interfere image interpretation of OCT.

inside the lumen of the artery. These are relatively acute and contain a high proportion of red blood cells. (2) White thrombi (Figure 2B) are of high birefringence and low attenuation. They are relatively chronic and platelet-rich. While there is no significant difference in peak intensity of OCT signal, the 1/2 attenuation width of the signal intensity curve is significantly different between red and white thrombi. The cut-off value of 250 μm can differentiate white from red thrombi with a sensitivity of 90% and specificity of 88%. Optical coherence tomography may allow us not only to estimate plaque morphology but also to distinguish red from white thrombi.[14]

OCT GUIDANCE of PCI

Lesion Preparation

Lesion preparation is the most important step to avoid stent under-expansion and to decrease peri-procedure complications. As interventional cardiologists treat more and more complex lesions today, intravascular image assistance is more commonly used in complex procedures. Different types of plaques detected by OCT may lead to different strategies for lesion preparation.[15] As mentioned before, a large lipid burden and TCFA are more vulnerable, and have a stronger relationship with peri-procedural myocardial infarction (MI).[16,17] Therefore, undersized balloon inflation or direct stenting can reduce the infarction rate in these lipid-rich plaques. This inference was proven in the ILUMIEN I study. Rates of clinically significant peri-procedural MI were found to be different when procedural changes were made based on pre- and post-PCI OCT (P = 0.029). The overall rate of in-hospital MI was 6.9% by Academic Research Consortium and 6.4% by Universal MI definitions.[18]

Calcium has always been the worst enemy of the interventionist. Calcium impedes stent crossability, expansion, embedment, and coverage.[19,20] Among these, stent expansion is the single most important parameter related to clinical outcomes.[21] Aggressive non-compliant

balloon pre-dilatation, a cutting / scoring balloon, or atherectomy device should be considered in calcified or undilatable plaques. OCT and IVUS both have high sensitivity for detecting the calcification arc. OCT can more precisely determine the calcium thickness and depth than IVUS.[22,23] Non-compliant balloon inflation can be first considered in wide arc, low thickness, or deep calcium plaque on OCT (with cutoff values of < 227-degree calcium arc and <0.67 mm in thickness, respectively) to induce calcium fracture.[23] Instead, rotational atherectomy should be chosen directly in superficial circumferential calcification (> 227-degree calcium arc). If the stenotic lesion is still undilatable after non-compliant balloon or if the calcium thickness is too high, cutting or scoring balloons can make the incisions at the edges between calcified and non-calcified components to improve vessel compliance under controlled dissection.[23] Prospective studies are needed to determine whether OCT-guided lesion preparation for calcified plaque would improve clinical outcomes or not.[18]

Stent Optimization

Stent optimization is determined by vessel size measurement, stent selection, landing zones and post-dilatation. FD-OCT can measure the vessel size automatically by the clear border between the lumen and vessel wall. While vessel linear dimensions are overestimated by IVUS by about 10% in the phantom model, FD-OCT measurement is closer to the actual size.[24]

Unlike IVUS, there is still no well-established method for stent sizing with OCT. The low-depth penetration of light through lipid-rich plaque results in an inability of OCT to visualize the external elastic lamina (EEL) at the lesion site in some cases. Most previous OCT studies have thus used luminal dimensions for selection of stent size, not the external elastic lamina.[18,25] In the ILUMIEN II study, the post hoc retrospective analysis between the ILUMIEN I and ADAPT-DES study, optical coherence tomographic

guidance resulted in similar stent expansion but a smaller final minimal stent area (MSA) compared with IVUS guidance.[26] In the OPINION trial, OCT also led to smaller stent diameter (2.92 ± 0.39 mm^2 vs. 2.99 ± 0.39 mm^2; $p < 0.005$) and post-procedural MSA (5.17 mm^2 [IQR: 4.06 to 6.29] vs. 5.63 mm^2 [IQR: 4.76 to 7.52]; $p = 0.088$) than did IVUS.[25] The ILUMIEN III study conducted a novel EEL-based OCT-guided sizing strategy to overcome the shortage: it measured the proximal and distal reference mean EEL diameters and used the smaller of these diameters rounded down to the nearest 0.25 mm to determine stent diameter. If necessary, high pressure or larger non-compliant balloon inflations can be used to achieve at least acceptable stent expansion (a MSA of at least 90% in both the proximal and distal halves of the stent relative to the closest reference segment). Under this strategy, Post-PCI MSA achieved after OCT-guided PCI was non-inferior to that achieved with IVUS-guided PCI. Both OCT and IVUS resulted in better post-PCI MSA compared to angiography guidance. OCT guidance led to less major stent malapposition than both IVUS guidance and angiography guidance.[27] Thus, whether OCT guidance of stent implantation can achieve similar luminal dimensions as IVUS guidance or not remains unclear. This may depend on the different strategy of inner lumen-based or EEL-based OCT-guided stent sizing. Further large studies are needed to investigate whether OCT guidance results in better clinical outcomes than does IVUS guidance or angiography guidance.

Safe landing zone is difficult to decide or easy to miss on long diffuse plaque by angiography alone. High resolution intravascular image by OCT can prevent stent landing in eccentric calcium or lipid-rich plaques, which is useful to prevent edge dissections or longitudinal geographic miss. The fast pullback OCT acquisition system makes precise stent length measurements because it is less susceptible to heart movements. Integration of real time angiographic co-registration (ACR) with OCT is feasible now. This OCT-ACR integrated system may reduce human errors in corresponding OCT findings to the angiogram. In the Doctor fusion study, the OCT-ACR system reduced the number of implanted stents through improved sizing and positioning.[28] Future studies are needed to compare or combine the OCT guided anatomic lesion length with the FFR guided "physiological" lesion length to optimize the stent selection. Real time OCT-ACR integrated system can also quickly identify under-expanded stent struts automatically. This function can avoid unnecessary post-dilatation and over-dilatation of stent struts, thus decreasing peri-procedural complications.[29]

Post Stent Deployment

Intravascular images are widely used after stent deployment for early detection and prevention of clinical events. Stent malapposition, stent edge dissection and tissue protrusion can be visualized in detail by OCT. The relationship of these findings to subsequent adverse events and how they should be managed remains uncertain.[30] The ongoing ILUMIEN IV study will help determine whether correction of post-deployment findings will translate to fewer stent-related adverse events.

Stent malapposition (Figure 2C), which is most frequently observed at stent edges, may be related to stent/vessel size or contour mismatch.[31] Some cases of stent malapposition can be resolved by time with re-endothelialization. While multiple factors will affect endothelium healing after stenting (i.e., stent design, strut thickness, types of polymer, underlying plaque morphology), there is no consensus on the maximum distance between stent struts and vessel lumen that can be associated with endothelialization or adverse events.[32,33]

Intravascular OCT has a very high sensitivity for stent edge dissections (Figure 2D) and operators should not over-react to it. Most of the "minor" edge dissections without flow limitation can be healed without clinical events.[34] In the CLI-OPCI II study, "major" stent edge dissections detected by OCT > 200 μm were independent predictors of MACE (composite of all-cause

death, MI, and target lesion revascularization, Hazard ratio 2.54, p = 0.004).[35] Operators should be prepared to treat this degree of edge dissection or if complicated with intramural hematoma to avoid vessel collapse.

Tissue protrusion (Figure 2E) detected by IVUS is reported to be associated with poor short-term outcomes, including no-reflow phenomenon, peri-procedural MI, and stent thrombosis.[36] High resolution OCT can identify tissue protrusions with unprecedented precision.[37] Tissue protrusion can be categorized into 3 groups, including (1) smooth protrusion: minimal vessel injury, (2) disrupted fibrous tissue protrusion: mild vessel injury, and (3) irregular protrusion: moderate to severe vessel injury with a high likelihood of medial disruption and lipid core penetration. Only irregular protrusion was an independent predictor of device-oriented clinical events and target lesion revascularization in a large cohort study.[38]

NOW and FUTURE

Special Considerations
Bioresorbable Vascular Scaffold

Bioresorbable vascular scaffold (BVS) is a newly emerging stent technique in recent decades. However, improper implantation of current-generation BVSs is associated with a higher risk of scaffold thrombosis. These improper implantations include malapposition, underexpansion, and incorrect sizing.[39] For the best possible results with BVS, PSP technique is highly recommended: Predilatation adequately, Sizing scaffold correctly, and Post-dilation to avoid underexpansion.[40] Hence, the use of an intravascular imaging tool, and especially OCT, should be mandatory in BVS implantation. As mentioned, the automatic measurement and high-resolution OCT image can provide significant assistance for lesion preparation and stent optimization. Additionally, only OCT can grant clear visualization of the vascular scaffold structure to evaluate scaffold fracture, endothelium healing, scaffold bioresorbing process, edge

dissection, and malapposition in post-implantation assessment.[41]

Bifurcation Lesion

Bifurcation lesions are one of the major complex coronary interventions, related to higher rates of in-stent restenosis and stent thrombosis.[42] While provisional single-stenting is now the most recommended strategy, two-stent strategy is still required for some complex bifurcation lesions.[43] Understanding the bifurcation anatomy, including carina angle, vessel size discrepancy and plaque location, is a significant step in determining the intervention strategy. Online 3-dimensional reconstruction of the intravascular image by OCT is very helpful for the intervention cardiologist to understand the bifurcation structure.[44,45] Automatic stent strut detection systems are also effective in evaluating the points of wire re-crossing through the main stent struts, the size and shape of side branch openings, and the stent design integrity.[46] These are the key factors to optimize the kissing balloon technique in bifurcation stenting, which lead to favorable outcomes.

Limitations of OCT

OCT facilitates the precise visualization of vessel anatomy and plaque morphology. Its ability to determine plaque vulnerability (i.e., thin-cap fibrotic atheroma, high-attenuation plaque, and macrophage accumulation) is helpful in deciding a PCI strategy in high-risk patients.[47] However, OCT has some limitations including low tissue penetration, blood clearance and uncertain physiological significance.

The low tissue penetration (1 to 2 mm) of current OCT systems is a major limitation. Assessment of plaque volume or visualization of plaques in the deep layers of the vessel wall may not always be feasible by OCT, especially when there is a large plaque burden. As mentioned, lipid-rich plaque and red thrombus can cause signal attenuation which can obscure the EEL of the vessel wall.[48]

Since OCT image acquisition requires

contrast to achieve blood clearance, poor blood clearance by the contrast will result in a poor OCT image (Figure 2F), which is difficult to interpret. Although it may be feasible to use non-contrast flush media to clear blood, renal function deterioration should be monitored in patients with advanced chronic kidney disease. Because of the blood clearance issue and low tissue penetration, OCT is not recommended in aorto-ostial lesions, large left main body and distal small vessels.[49]

In the ILUMEIN I study, pre-procedural OCT evaluation of the MLA with a cut-off value of 1.6 to 1.9 mm^2 is modest, correlated with FFR and impacts physicians' PCI decision-making strategy.[18] Although OCT-derived MLA has high positive physiological predictive value (80 to 92%) with FFR, the decision whether to perform PCI based on OCT-derived MLA alone is not recommended due to lower negative predictive value for physiological significance (66 to 89%).[50,51] These limitations should be taken into account to avoid misleading interpretation and unnecessary procedure.

Future Directions

OCT is a relatively new imaging modality, with fewer data on its use in PCI compared with IVUS.[24,49,52] Large-registry data in percutaneous coronary intervention (PCI) have raised questions regarding the clinical significance of the detailed findings on high-resolution imaging by OCT, highlighting the paucity of data from prospective clinical trials.[30] In the future, OCT will also be able to accumulate a tremendous amount of evidence and have more quantitative metrics like IVUS. We believe that intravascular OCT should position itself as a peri-procedural tool to take full advantage of its superior plaque characterization, ACS applications, stent planning, and volumetric lumen segmentation for stent optimization. Real time angiographic co-registration with OCT has made precise "anatomical" evaluation more feasible for stent optimization. In the future, OCT may be combined with simultaneous "physiological" assessment to optimize the

treatment strategy. Whether optical coherence tomography guidance for PCI results in improved clinical outcomes compared with angiographic guidance alone will be addressed in the large-scale multicenter randomized ILUMIEN IV trial.

CONCLUSION

OCT provides a detailed coronary intravascular image of anatomical findings and potential pathological changes. It has unrealized potential for applications in the diagnosis and treatment of coronary artery disease. Systematic efforts to educate the interventional cardiology community about the appropriate use of OCT and the demonstration of improved clinical outcomes from randomized trials are required to further integrate this novel modality into clinical practice.

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Case Report: Massive Nasopharyngeal Bleeding during Endovascular Salvage for Subacute Stent Thrombosis in a Post-Radiation Patient

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Abstract

Carotid artery stenting (CAS) has been established as an alternative to endarterectomy (CEA) in radiotherapy-induced carotid stenosis, as prior cervical radiation increased surgical risk. Subacute stent thrombosis, although rare, may occur and result in catastrophic complication. We report a middle-aged patient, with radiotherapy-related symptomatic carotid stenosis, who succumbed to massive nasopharyngeal bleeding following endovascular salvage for subacute (3 weeks after carotid artery stenting) stent thrombosis. After symptomatic carotid stenosis was diagnosed, the patient received endovascular therapy successfully, however, subacute stent thrombosis developed. Further endovascular neurovascular salvage was performed with success, but the procedure was complicated by massive nasopharyngeal bleeding, hypotension, large cerebral infarction and death. Potential causes of subacute stent thrombosis might be the characteristics of the lesion and antiplatelet agent resistance. Massive nasopharyngeal bleeding might result from post-irradiation fragility of the vascular wall and balloon dilatation associated internal carotid artery rupture, potentiated by intra-arterial lytic therapy for neurovascular salvage. Bleeding events might be fatal after thrombolytic agent during endovascular salvage.

Keywords: radiotherapy, carotid stenosis, endovascular procedures, carotid artery thrombosis, hemorrhage

Introduction

Cervical radiotherapy plays an important role in head and neck cancer treatment. However, radiation causes progressive intimal hyperplasia and accelerates atherosclerosis in the affected area. Patients with high-degree carotid artery stenosis are at high risk for cerebral infarction.

Carotid artery stenting (CAS) has been established as an alternative to endarterectomy (CEA), as prior cervical radiation increased surgical risk.[1] Unfortunately, subacute stent thrombosis, although rare, may occur and result in catastrophic complication.

We hereafter report a patient, with radiotherapy-related symptomatic carotid stenosis,

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who succumbed to massive nasopharyngeal bleeding following endovascular salvage for subacute (3 weeks after carotid artery stenting) stent thrombosis. The treatment courses and relevant literatures are reviewed.

Case Report

A middle-aged patient had a history of nonkeratinizing nasopharyngeal carcinoma (cT1N1M0, stage I) and he was treated by concurrent chemo-radiotherapy (CCRT) with radiotherapy dose at 70 Gy in 35 fractions in 2001 without recurrence. He underwent carotid artery stenosis evaluation in 2013 due to newly developed gait instability and slurred speech. He had presented with progressive left nasal obstruction and epistaxis 3 months prior his carotid artery lesions were identified. A growing left nasal cavity tumor which caused epistaxis was found by otolaryngologist. Magnetic resonance imaging (MRI) revealed a left nasal cavity lesion (36 x 32 mm) extending to the anterior ethmoid sinus without intracranial extradural extension. Left ethmoid sinusitis and left sphenoid sinus mucocele and hemorrhages were also noted. We performed tumor biopsy which revealed high-grade neuroendocrine carcinoma, T4aN2cM0 (minimal extension to cranial fossa, pterygoid plate), stage

IVB. He was then treated with CCRT and the regimen was cisplatin. Total radiation dose was 60 Gy with a fraction dose of 2 Gy. He tolerated the treatment well with only mild left periorbital swelling, odynophagia, taste impairment, and leukopenia. His left nasal obstruction and epistaxis both resolved completely.

Two months after CCRT, he reported persistent oral cavity pain, headache, tinnitus, impaired hearing, and swallowing difficulty. Frequent choking resulted in several times aspiration pneumonia, and subsequent work-up revealed limited tongue motion and delayed/incomplete swallowing reflex. Progressive dizziness, impaired hearing, slurred speech, left vocal palsy with dysphonia, and gait instability were also noted. Follow-up MRI revealed no evidence of tumor recurrence, but carotid duplex ultrasonography showed left internal carotid artery (ICA) occlusion with reversed ophthalmic artery. Brain perfusion computed tomography (CT) confirmed the left ICA total occlusion (Figure 1A), and also documented significant right ICA stenosis at petrous segment (Figure 1B). Slightly prolonged mean transit time was noted in right middle cerebral artery territory (Figure 1C). Diagnostic angiography revealed 80% right ICA stenosis at upper cervical and petrous junction (Figure 2A). Left ICA total occlusion was also
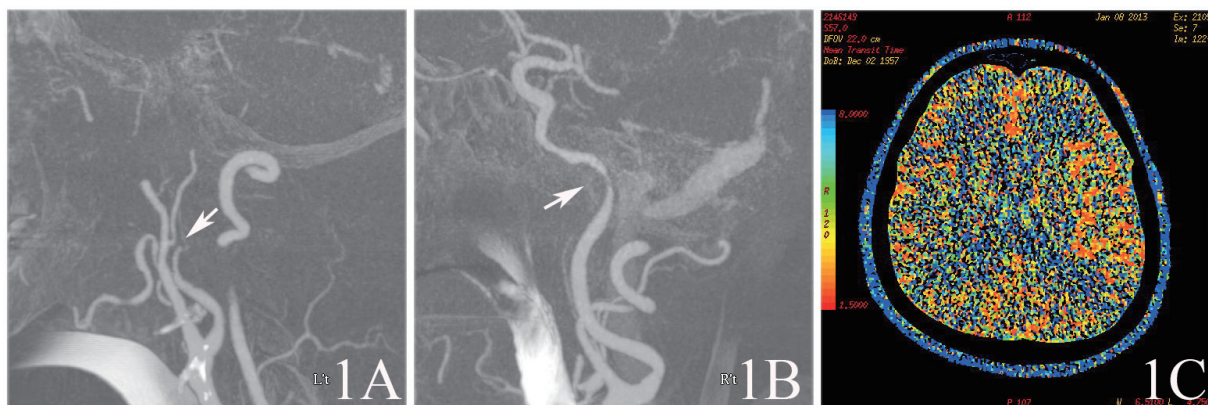

Figure 1. Pre-procedural computer tomography. Perfusion CT reveals left cervical ICA occlusion (arrow)(1A); Significant right internal carotid artery stenosis at petrous segment (arrow) (1B); Slightly prolonged mean transit time at right middle cerebral artery (MCA) territory (1C).

documented (Figure 2B), with distal reconstitution at the ophthalmic segment (Figure 2C). After detailed discussions about the treatment options with the patient, his family and our team members, we decided to perform endovascular intervention via the right femoral route. Heparin was given to achieve activated clotting time above 250 seconds, and right ICA stenting (PRECISE stent 7 x 40 mm, Cordis, California) was done uneventfully with embolic protection device (Figure 2D & 2E). We prescribed dual antiplatelet agents and he was discharged with stable condition.

Three weeks after endovascular procedure, sudden-onset left side weakness occurred, and he was sent to the emergency department immediately where brain CT revealed a long segmental thrombus, from right ICA origin to the cavernous portion (Figure 3A), causing total occlusion. The circle of Willis was intact (Figure 3B), but bilateral hemispheric hypoperfusion was noted. Subacute stent thrombosis was impressed, and emergent neurovascular salvage was performed. Cerebral angiography was done within 4 hours from symptom-onset time, showing right ICA stent thrombosis (Figure 4A) and distal ICA reconstitution via reversed ophthalmic artery (Figure 4B). As clot retrieval device was not available in Taiwan at that time, we performed thrombus aspiration with 7F Thrombuster II (Kaneka, Osaka, Japan), followed by angioplasty using Ikatzuchi balloon catheter (Kaneka) (angioplasty 4C). However, adequate
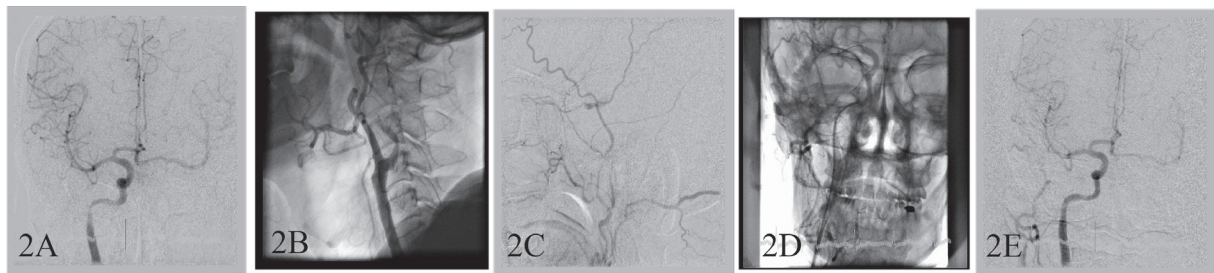

Figure 2. Endovascular therapy for right internal carotid artery stenosis. Cerebral angiography reveals right petrous ICA stenosis (2A), and left cervical ICA occlusion (2B) with distal reconstitution at ophthalmic segment (2C); Cordis PRECISE Stent 7 x 40 mm was deployed to cover the petrous ICA stenosis (2D); Final angiography reveals no residual stenosis (2E).
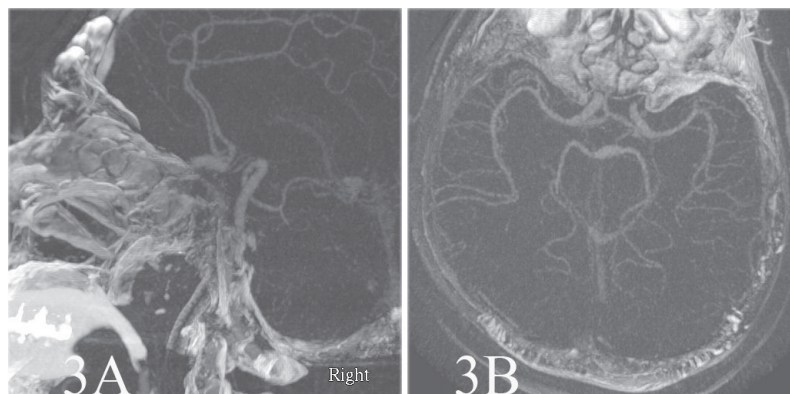

Figure 3. CT examination before endovascular neurovascular salvage. CT angiography reveals stent placement at cervical to proximal petrous segment of right ICA with long segmental thrombus and total occlusion of right ICA, from its origin to cavernous segment (3A); The circle of Willis is patent (3B).
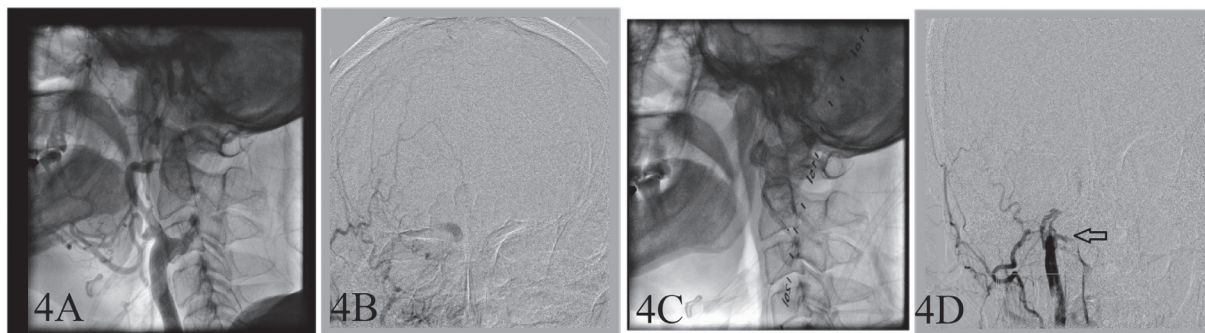
Figure 4. Neurovascular salvage for right carotid subacute stent thrombosis. Cerebral angiography shows total occlusion of right cervical ICA (4A); with distal reconstitution via reversed ophthalmic artery (4B); Dilatation with Ikatzuchi 2.5 x 15 mm balloon after thrombus aspiration (4C); Massive bleeding from distal cervical ICA (Black arrow) to nasopharynx after thrombolysis (4D).

antegrade flow was not established due to the extremely large thrombus burden. Intra-arterial thrombolysis was then given via microcatheter using recombinant tissue-type plasminogen activator (Actilyse, Boehringer Ingelheim, Germany). Distal flow increased to Thrombolysis in Cerebral Infarction (TICI) perfusion scale grade 2 after a total dose of 10 mg. Unfortunately, massive bleeding developed into oral and nasal cavities after thrombolysis, requiring endotracheal intubation and cardiopulmonary resuscitation. The bleeder was visualized by angiography, from upper cervical ICA into right nasopharynx (Figure 4D). Profound shock ensued despite vigorous fluid and component transfusion. The patient's consciousness also deteriorated. Local gauze packing with vasoconstrictor and foley balloon catheter tamponade were applied to the right side nasal cavity, but the bleeding continued. Brain CT revealed large infarction with mass effect at the right hemisphere, with multiple small foci of hemorrhagic transformation. The patient remained comatose and passed away five days later despite intensive management and hemodynamic support.

Discussion

The middle-aged patient we reported had a history of nonkeratinizing nasopharyngeal carcinoma and newly diagnosed left nasal high-grade neuroendocrine carcinoma. Symptomatic carotid artery stenosis was found after the second CCRT and he underwent subsequent endovascular therapy successfully. However, subacute stent thrombosis developed three weeks after carotid artery stenting. We performed endovascular neurovascular salvage immediately, but unfortunately, the procedure was complicated by massive nasopharyngeal bleeding, hypotension, large cerebral infarction and death. Several points merit discussion as follows.

The Relationship Between Radiation and Plaque Vulnerability/Vessel Fragility

The vulnerability of radiation-induced carotid stenosis (RICS) plaque has been a controversial issue. In current literatures, the researchers used several methods, including histologic analysis and image studies, to evaluate vulnerability in RICS plaque. The histologic analysis of Fokkema et al. revealed the tendency of RICS plaque to be stable. By contrast, several reports using carotid ultrasonography and magnetic resonance imaging but lacking histologic analysis have suggested a high incidence of vulnerable plaque in RICS patients.[2,3]

Radiation not only affects plaques but also causes vessel injury.[4,5] The effects include intimal proliferation, necrosis of the media, and fibrosis of the adventitia. We should always be cautious

when treating this kind of lesions, because interventional procedures themselves may cause further damage in an unfavorable vessel anatomy. In our opinion, the reasons for the patient's ICA bleeding might have been the radiation related vessel fragility and balloon dilatation-associated artery rupture.

Endovascular revascularization or endarterectomy

This patient received a total dose of 70 Gy radiotherapy for nasopharyngeal carcinoma in 2001, and another total dose of 60 Gy radiotherapy for left nasal high-grade neuroendocrine carcinoma in 2013. The development of carotid stenosis may be initiated by radiation therapy. The mechanism of radiation injury to the carotid artery includes direct and indirect components. The direct injury to the arterial wall leads to intimal proliferation, necrosis of the media, and fibrosis of the adventitia. Radiation also damages the vasa vasorum, causing indirect injury to the carotid artery with repetitive intra-plaque hemorrhages.[5] Surgical endarterectomy for radiation-induced carotid stenosis is associated with technical issues of arterial wall fibrosis, tissue plane scarring, potential prosthetic infection, anastomotic dehiscence, and surgically inaccessible distal or proximal lesion location. In addition, radiotherapy often causes bilateral stenosis or occlusion, sometimes rendering endarterectomy impossible.[6-8]

Therefore, carotid stenting has been considered as a reasonable alternative in radiation induced carotid stenosis.[4,8,9] However, due to the plaque vulnerability in radiation-related carotid stenosis, the risk of procedural embolism and subsequent in-stent thrombosis may be a concern.[10-12] In addition, in-stent restenosis rate was found higher in radiation induced carotid stenosis[4] than in non-radiated lesions. A systematic review comparing endarterectomy versus stenting for radiation induced carotid stenosis has shown that both techniques might be feasible, but there were more subsequent cerebrovascular events

and restenosis in patients treated with stenting.[13] These findings probably reflect the progressive nature of radiation injury, despite aggressive control of cardiovascular risk factors.[4] Therefore, the choice of revascularization strategy should be individualized.

Potential causes of subacute cerebral infarction

As illustrated in Figure 1, critical stenosis with large plaque burden was located at the petrous portion of the right ICA, and the left ICA was totally occluded. Stenting was chosen, since endarterectomy would have been extremely difficult and risky. We used distal embolic protection device and performed endovascular intervention cautiously. Luckily the initial stenting procedure was successful without complication. However, the underlying vulnerable plaque might have protruded through the stent struts into the vessel lumen, leading to turbulent flow and thrombi formation. The choice of PRECISE stent, an open-cell stent with large cell size (free cell area: 5.89 mm^2), may have potentiated this effect. However, stent deliverability and vessel conformability would be another concern when deploying a closed-cell design stent to the petrous ICA.

Given that dual antiplatelet therapy plays an important role in carotid artery stenting, another potential cause for subacute stent thrombosis is antiplatelet drug resistance. In one study, regarding the prevalence of drug resistance in a Chinese population with minor stroke receiving dual antiplatelet therapy, 24.4% exhibited aspirin resistance, 35.9% exhibited clopidogrel resistance, and 19.2% displayed concomitant aspirin and clopidogrel resistance.[14] However, the rapid clinical deterioration prohibited further platelet function study on the patient in this case.

Neurovascular salvage

The patient arrived within 4 hours after stroke onset. CT scan and angiography both revealed stent thrombosis causing right ICA

occlusion. Using stent retriever to remove the clot has been shown to be effective in acute ICA occlusion,[15] but the device was unavailable at that time in Taiwan. Thrombus aspiration and balloon dilatation were performed, but the thrombus burden was too much to restore adequate flow. Intra-arterial heparin and recombinant tissue-type plasminogen activator were given according to prior protocol,[16] resulting in TICI 2 flow. Unfortunately, massive nasopharyngeal bleeding ensued, finally resulting in the demise of our patient. There was no evidence of local or intracranial tumor recurrence in his baseline imaging, but we did find extensive post-irradiation changes (mucosal thickening, mucus retention, and increased soft tissue density) in the patient's nasopharynx and paranasal sinuses. According to the radiation therapy record, the total cumulative radiation dose was extremely high and the field of the recent radiation was directed toward the ethmoid/sphenoid areas. Additionally, the interventional procedures themselves may have also caused further damage in an unfavorable vessel anatomy. Severe bleeding after intra-arterial lytic therapy most likely resulted from the radiation and procedure associated fragility of the vascular wall, surrounding soft tissue, and the proximity of the distal cervical ICA to the nasopharyngeal cavity. Despite mechanical tamponade using gauze and balloon compression in the nasal cavity, the hemorrhagic shock still resulted in massive ischemic stroke in this unfortunate patient with bilateral carotid disease.

Covered stents in the carotid circulation are mainly used for repair of aneurysm, pseudoaneurysm, dissection, perforation and arteriovenous fistula.[17,18] Several literatures have also reported the experiences of covered stent usage in carotid blowout syndrome and transsphenoidal surgery associated ICA rupture. We can take covered stent into consideration if bleeding or vessel injury event occurs. However, the designs of covered stents are rigid, with relatively large crossing profiles, making the procedure challenging at the petrous portion of

ICA.

Strategy of revascularization in symptomatic patients with high surgical risk

In the latest American Heart Association/ American Stroke Association (AHA/ASA) guidelines (updated in 2014),[19,20] it is recommended to choose CEA over CAS in symptomatic patients at average or low surgical risk (Class I). But there is no definite recommendation for selection of revascularization in symptomatic patients at high surgical risk. The criteria for being classed as "high risk for CEA" include one or more of: clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, recurrent stenosis after CEA, previous radical neck surgery or radiation therapy to the neck, and age > 80 years. According to this guideline (Class IIa recommendation), it is reasonable to choose CAS over CEA when patients have unfavorable neck anatomy (including post-irradiation changes) for arterial surgery.

Therefore, We have tried to report the varied conditions and difficulties during revascularization with CAS in our high-surgical-risk patient. And more, we hope that this unfortunate clinical course can help further research to clarify the appropriate treatment recommendation in symptomatic and high-surgical-risk group in the future.

Conclusion

We reported a patient who twice received extensive radiotherapy for head and neck malignancies and developed severe symptomatic carotid artery stenosis. Carotid stenting was initially successful, but subacute stent thrombosis occurred three weeks later. Intra-arterial lytic therapy restored TICI 2 flow, but was complicated by massive nasopharyngeal bleeding and led to patient death. Management in patients with radiation induced carotid artery disease should be tailored individually, considering their unique pathology.

Disclosure Statement

All authors have no conflict of interest.

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Case Report: Left Main Coronary Artery Bifurcation Stenting, Rotational Atherectomy and Instantaneous Wave-free Ratio

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Abstract

Rotational atherectomy (RA) is an effective device for plaque modification and successful percutaneous coronary intervention (PCI) can be achieved even with severely calcified lesions.However, there are limited data about the safety, periprocedural risk and prognosis in this setting, especially for nonagenarians. Here we report a 91-year-old man presenting with non-ST elevation myocardial infarction with distal left main and triple vessel disease. RA was used for distal LM, left anterior descending andleft circumflex coronary artery. In addition, instantaneous wave-free ratio, a new adenosine-independent index of coronary stenosis severity, was used to assess in-stent restenosis of the left circumflex coronary artery at follow-up. This elder patient tolerated the procedure well and is completely symptom-free at present.

Keywords: bifurcation, left main, rotational atherectomy, iFFR

Introduction

Coronary artery bypass surgery (CABG) is a difficult option sometimesin high-risk patients with critical left main coronary artery (LMCA) disease. Patients with complex calcified left main (LM) disease may have both a high surgical risk and a high lesion complexity, leading to a therapeutic dilemma.[1-3] Rotational atherectomy (RA) is an effective device for plaque modification and successful percutaneous coronary intervention (PCI) can be achieved even with severely calcified lesions. RA prior to stent implantation is an option for a subset of patients with severely calcified bifurcation lesions. However, patients with LM disease were excluded from the randomized

ROTAXUS trial.[4] Only limited data about RA of the LM bifurcation lesions are available.[1-3] The safety and effectiveness of rotational atherectomy in octogenarians for highly calcified LMCA diseasehas also beenlimited.[5] Here we report a case of RA fordistal LM coronary artery disease with high surgical risk. In addition, instantaneous wave-free ratio (iFR), a new adenosine-independent index of coronary stenosis severityis also discussed.

Case report

Mr. Tan, a 91-year-old man with a prior history of gout, diabetes mellitus, hypertension and dyslipidemia for ten years was found to have

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three-vessel disease: RCA 50-60%, LAD 90-95%, LCX 80-85% and distal LM 95-98% 1 month prior to admission. He had been a heavy smoker but had quit many years before. He has hearing impairment but still can walk and eat on his own. After discussion, the patient and his family refused CABG. He had been prescribed both aspirin 100 mg and clopidogrel 75 mg everyday since the elective coronary angiogram. One month later, he presented to us with acute coronary syndrome without ST-segment elevation

(NSTE- ACS). He felt chest tightness and dyspnea on the day of admission and was brought to our emergency room (ER) for help. He had orthopnea and bilateral lower leg pitting edema. He also had oliguria 2~3 days prior to admission. In the ER, his vital signs were as follows: blood pressure 156/96 mmHg, pulse rate 110 bpm and respiratory rate 26 breaths/min. CXR revealed acute pulmonary edema and cardiomegaly (Figure 1A and B). 12 lead EKG revealed V2~6, I, a VL ST depression (Figure 1C). Troponin I was 2.95 ng/
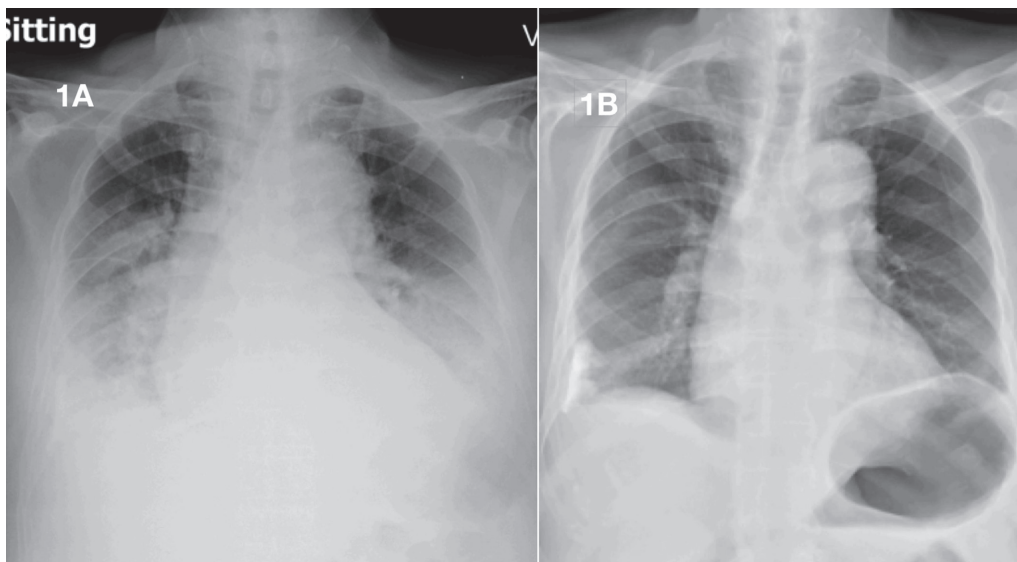
Figure 1A. Acute heart failure with pulmonary edema.
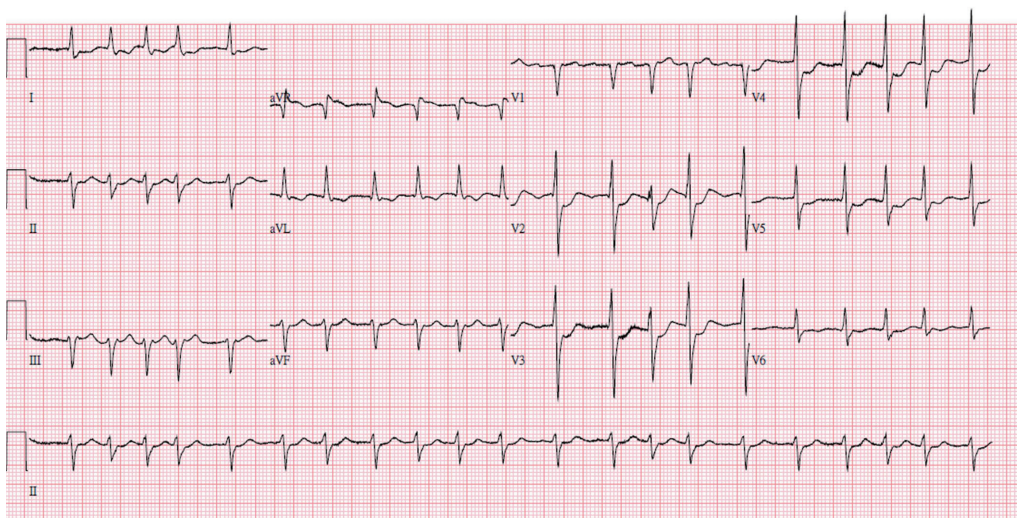**Figure 1B.** Resolved pulmonary edema.

Figure 1C. ECG shows V2 to V5, I, II, aVL ST depression and aVR ST elevation.

ml and elevated to 3.77 ng/ml after a few hours. NT-proBNP was 19569 pg/mL. He received O_2 therapy with non-rebreathing mask for marked SaO_2 desaturation. Furosemide bolus of 40 mg and nitroglycerin IV infusion were prescribed. He was admitted to ICU with the diagnosis of NSTE-ACS, complicated with acute decompensated heart failure and impending respiratory failure. After receiving treatmenthis condition stabilized and coronary intervention was arranged after informed consent. Coronary angiogram showed tight distal LM bifurcation stenosis with severe calcification (Figure 2A). The LM and LAD were wired first andthe wire was exchanged for Rota-Floppy guidewire with the help of micro-catheter. Rotational atherectomy was first performed in the LAD with a 1.25 burr at 170000 rpm which wasupsized to a 1.75 burr at 160000 rpm. The LCX was then wired with Rota-Floppy guidewire (Figure 2B). A 1.25 mm burr was used to debulk the ostial LCX calcified plaque at 150000 rpm (Figure 2B). DK crush stenting technique was then performed. (Figure 2C, 2D, 2E) After PCI, the patient's condition improved dramatically.
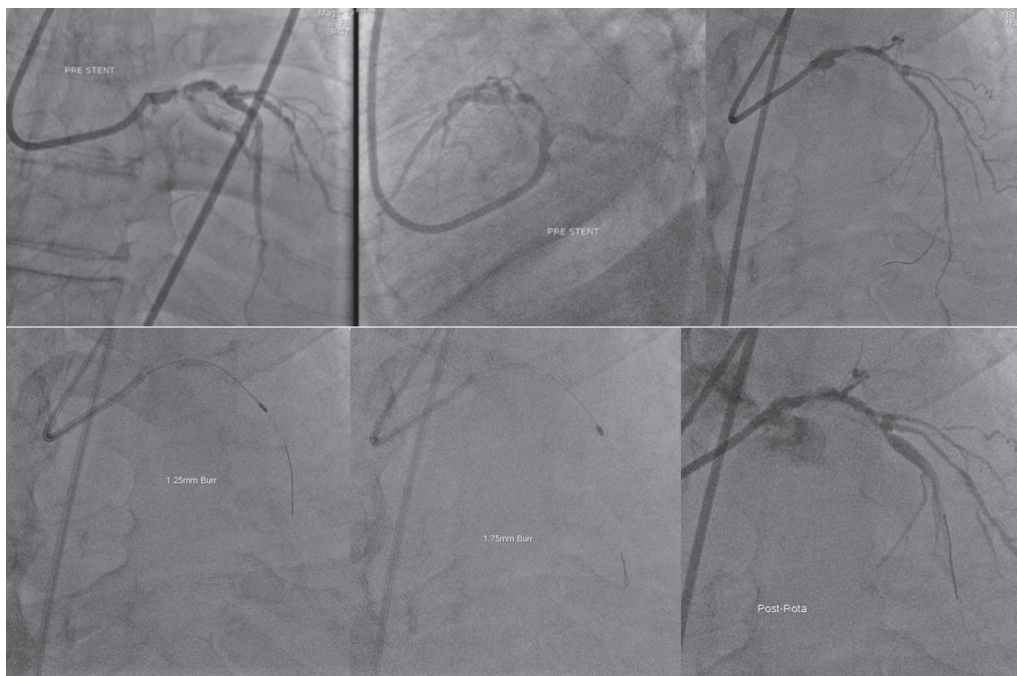

Figure 2A. Distal LM bifurcation angiogram and following1.25 mm burr and 1.75 mm burr to LAD.
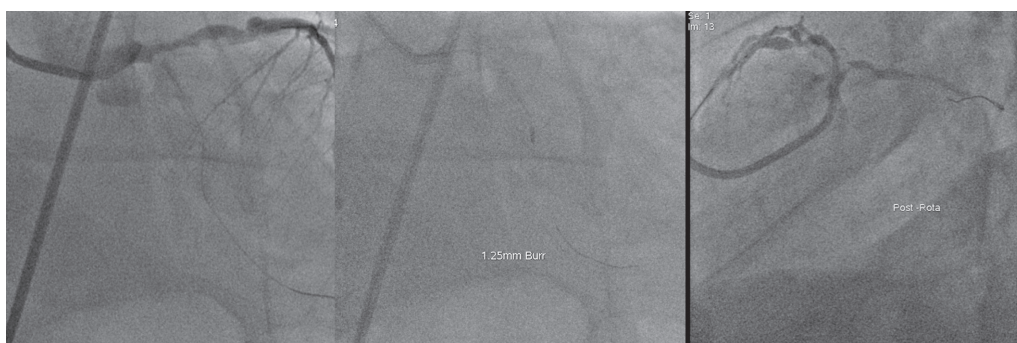

Figure 2B. 1.25 mm burr to LCX.

CXR showed resolution of pulmonary edema. The patient haddyspnea on exertion 4 months later and follow-up angiogram was arranged. It showed in-stent restenosis at the ostial LCX (Figure 3A). The iFR of LAD and LCX were 0.93 and 0.51 (Figure 3B). PCI was performed in the LCX with DEB after proper dilatation of LCX in-stent restenosis. The post-PCI angiogram showed no residual stenosis (Figure 3C). The iFR of LAD and LCX were 0.98 and 1.00, respectively (Figure 3D). The patient is completely symptom free at present.
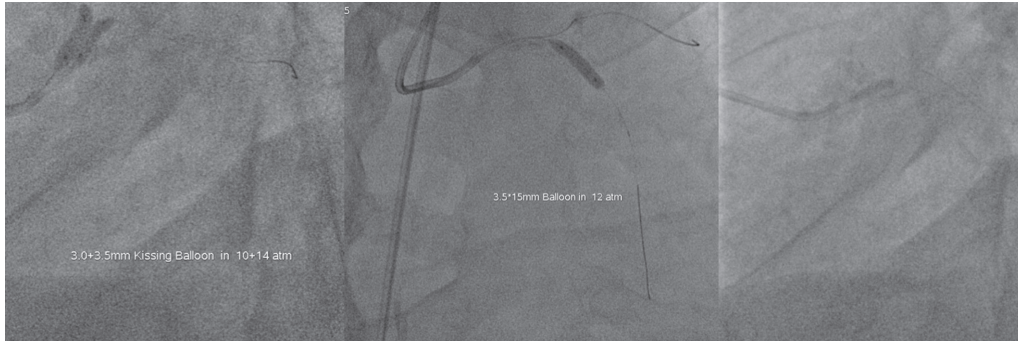
Figure 2C. Kissing balloon dilatation to distal left main bifurcation after rotational atherectomy.
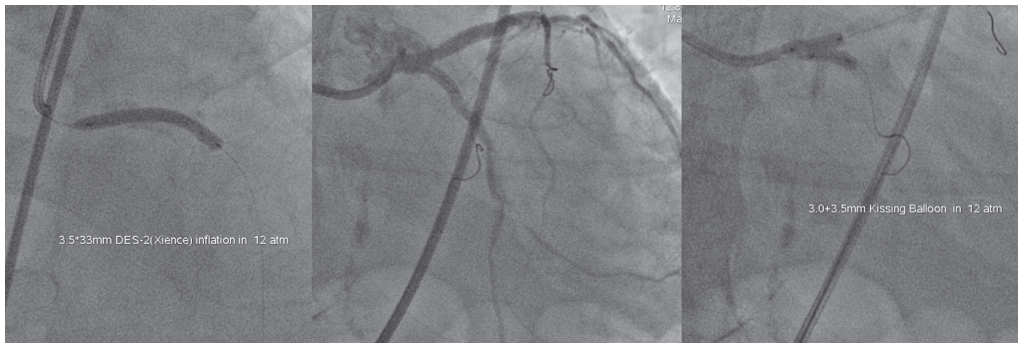

Figure 2D. Second simultaneous kissing balloon for distal LM bifurcation stenting.
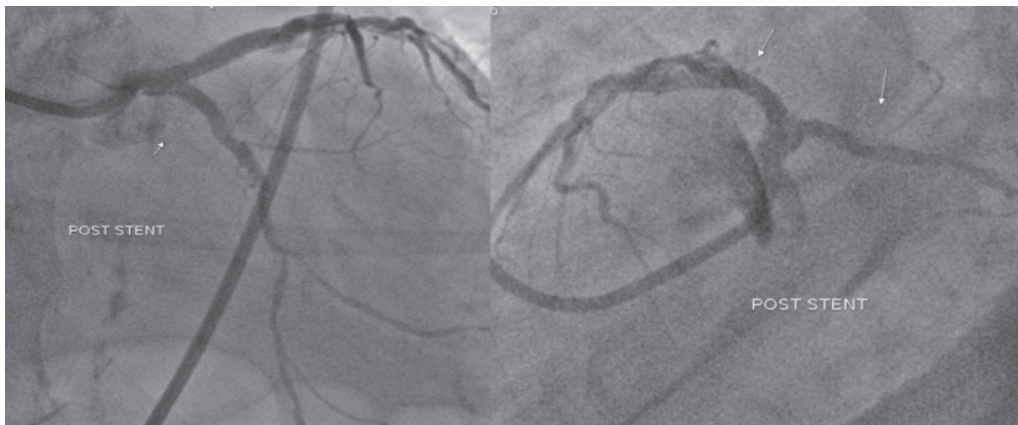

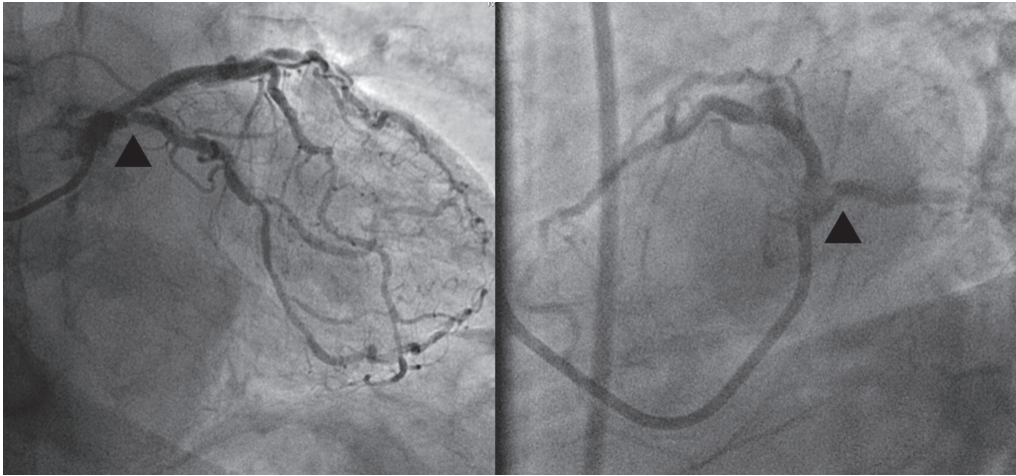**Figure 2E.** Final angiogram after double kissing balloon.

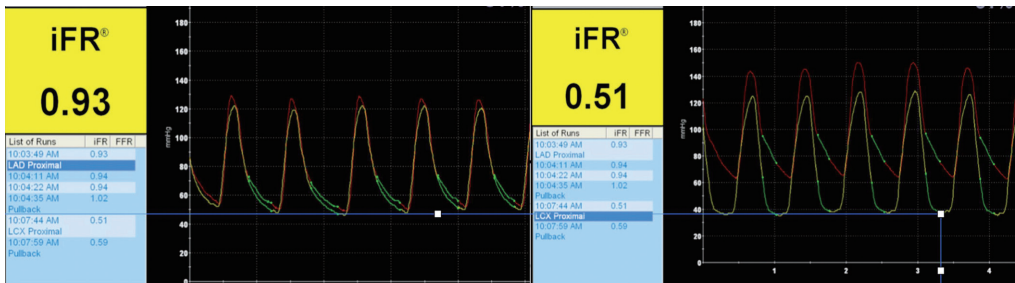**Figure 3A.** Follow-up Angiogram: ostial LCX stenosis and equivocal ostial LAD stenosis.

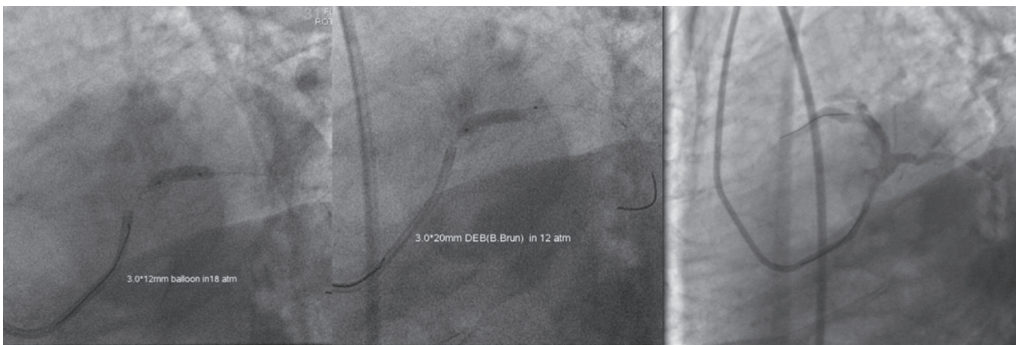**Figure 3B.** pre PCI iFR: LAD 0.93, LCX 0.51.

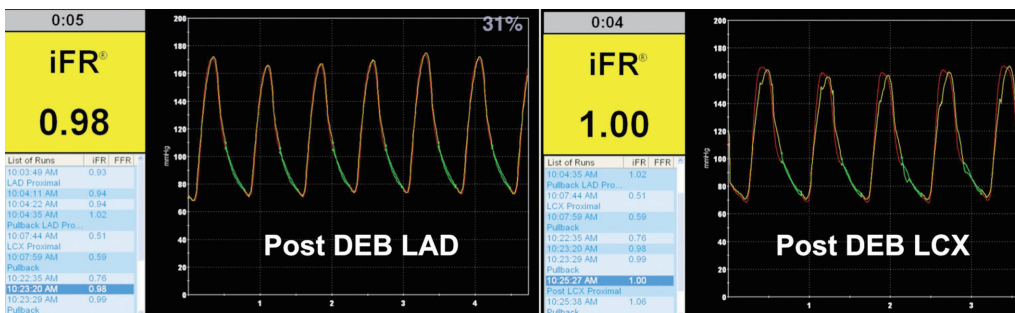**Figure 3C.** DEB to LCX and final angiogram afterward.

Figure 3D. post PCI iFR: LAD 0.98 and LCX 1.0.

Discussion

LMCA bifurcation stenting is an effective revascularization procedure in high-risk patients who are not candidates for bypass surgery.[3] RA is the superior method for debulking left main calcification prior to LMCA bifurcation stenting. However, there are limited data about the safety, periprocedural risk and prognosisin this setting, especially for nonagenarians. In our experience, rotational atherectomy can be of great help in this subset of patients because it can facilitate smooth delivery of stents by plaque modification and shorten procedural time.

The instantaneous wave-free ratio (iFR) is a new adenosine-independent index of coronary stenosis severity. Real-time iFR measurements are easily acquired with excellent diagnostic performance and adenosine infusion is not required. The excellent agreement between iFR and FFR measurements demonstrates the reliability of iFR measurements. iFR for left main coronary disease may enhance diagnostic accuracy and expose fewer patients to adenosine. However, adenosine-free pressure wire derived indices of stenosis severity may be less accurate for LM/pLAD lesions than for other lesion locations.[6] Overall, iFR is a promising method for the assessment of coronary physiology, but still requires prospective clinical endpoint trial evaluation.[7]

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Coronary Subclavian Steal Syndrome in a Post-Coronary Bypass Patient with Flow Reversal from Left Internal Mammary Artery Graft to Distal Subclavian Artery and Upper Limb with Arteriovenous Fistula

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Abstract

Coronary steal syndrome is a rare disease which may result from various types of congenital and acquired diseases and conditions, such as coronary fistula to pulmonary arteries or coronary-ventricular fistulas. Coronary artery bypass surgery (CABG) establishes new arterial or venous grafts to native coronary arteries from other major arteries such as the aorta or subclavian artery, giving rise to opportunities to steal native coronary blood flow via these grafts. Here, we present the case of a post-CABG uremic patient who suffered angina every time he underwent hemodialysis. Coronary subclavian steal syndrome was diagnosed after coronary angiography, which showed blood flow reversal from the left anterior descending artery to the left subclavian artery. Left subclavian artery arteriography showed ostium stenosis. The patient's symptoms were resolved completely after percutaneous transluminal angioplasty (PTA) over the left subclavian artery.

Keywords: coronary steal syndrome, subclavian artery stenosis, left internal mammary artery (LIMA), coronary artery bypass graft (CABG), arterio-venous fistula

Introduction

Coronary subclavian steal syndrome after coronary artery bypass surgery (CABG) is rare.[1] However, important differential diagnosis can be applied in coronary subclavian steal syndrome.

Here, we report a rare case of coronary subclavian steal syndrome in a post CABG patient with flow reversal from left internal mammary artery graft to distal subclavian artery and upper limb with arteriovenous fistula.

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Case Report

A 63-year-old man had a history of type 2 diabetes mellitus, end-stage renal disease and coronary artery disease (CAD). He had previously received percutaneous transluminal coronary angioplasty (PTCA) with stenting over the left anterior descending artery (LAD) middle segment. The CAD continued to progress after several years, so he underwent coronary artery bypass surgery (CABG) around 3 years ago. His left internal mammary artery (LIMA) was anastomosed to the LAD distal segment and 1 saphenous vein graft (SVG) was anastomosed sequentially to the LAD first diagonal branch (LAD-D1) and left circumflex artery (LCX) obtuse marginal branch (OM). The patient visited our cardiovascular clinic due to chest tightness and resting dyspnea when he was undergoing hemodialysis. Recurrence of coronary artery disease such as graft occlusion was highly suspected by his nephrologist, who suggested re-evaluation of his cardiovascular condition. Physical examination revealed regular heart beat without heart murmurs. His arterio-venous graft (AVG) for hemodialysis was created over his left forearm and the thrill was strong. ECG showed sinus rhythm without significant ST-T changes. Chest X-ray showed nothing remarkable. Echocardiography also revealed nothing remarkable, with left ventricle (LV) systolic function preserved in resting condition. Nuclear cardiac stress test showed severe reversible ischemia over the anterior and anteroseptal walls of the LV myocardium (Figure 1). Under the impression of possible CAD recurrence, the
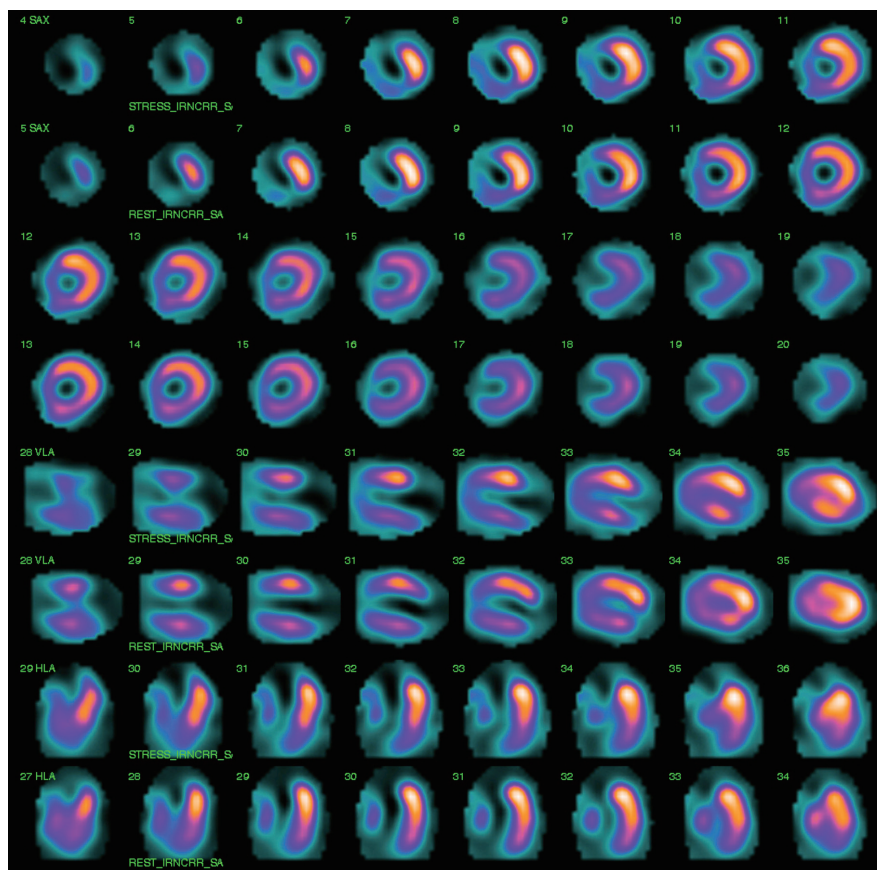

Figure 1. Nuclear cardiac stress test shows reversible ischemia over the anterior and anteroseptal walls of the left ventricular myocardium.

patient later received coronary angiography.

The selective left coronary angiography showed left main (LM) trunk 50% stenosis and distal segment 70% stenosis, LAD ostium 70% stenosis and middle in-stent segment 80% stenosis, and LCX proximal segment 80% stenosis. However, coronary flow reversal was found from LAD to LIMA (Figure 2). The selective right coronary angiography showed non-dominant diffuse atherosclerosis. Selective angiography of SVG showed patency from aorta to LAD-D1 to LCX-OM. Selective angiography of LIMA showed patency but strong competing flow from LAD to left subclavian artery. Since these angiography results couldn't explain the patient's condition, left subclavian arteriography was performed which revealed critical stenosis of the proximal segment (Figure 3). The pressure gradient before and after the stenotic segment exceeded 60 mmHg. Coronary subclavian steal syndrome was diagnosed.

To resolve this problem, percutaneous transluminal angioplasty (PTA) was performed with an Admiral Xtreme PTA balloon catheter, 5 x 80 mm (Medtronic. Minneapolis, MN, USA). Further stenting was performed with an Express

LD stent, 8 x 27 mm (Boston Scientific, Natick, MA, USA). The pressure gradient dropped to less than 5 mmHg after the procedure. Repeat selective left coronary angiography showed there was no more flow reversal. The patient's angina and dyspnea symptoms resolved completely. After six months, follow-upcomputed tomography angiography (CTA) showed stent patency without restenosis.

Discussion

Here we have presented an uncommon cause of angina in a post-CABG patient whose symptoms were related to proximal subclavian artery stenosis, which impaired the normal perfusion from LIMA to LAD. Moreover, in this case, the LIMA "stole" the LAD blood flow to perfuse the left distal subclavian artery and left upper limb, a condition proven by the retrograde flow from LAD to LIMA revealed by the left coronary angiography. Even rarer, an arterio-venous access was created over the patient's left upper limb, which exacerbated the stolen condition when the patient underwent hemodialysis. This could explain why the patient's

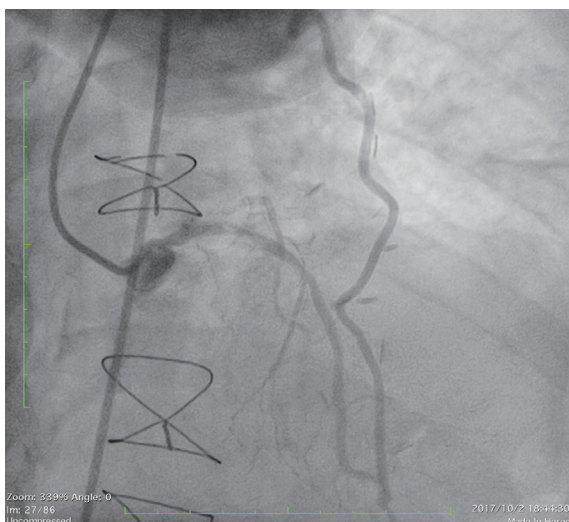**Figure 2.** Selective left coronary angiography reveals flow reversal from LAD to subclavian artery via LIMA graft.
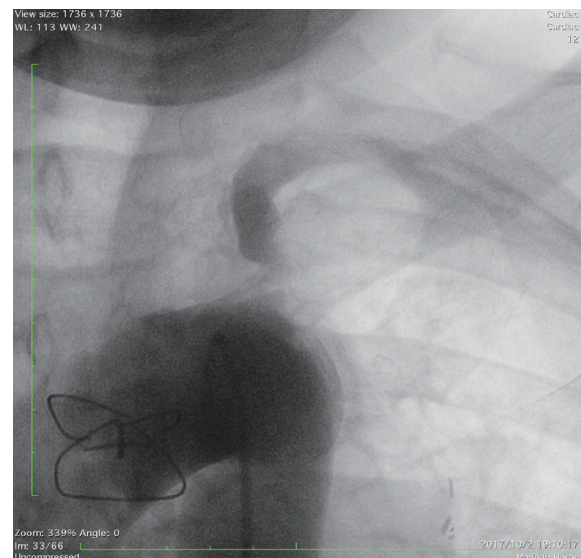

Figure 3. Aortography reveals ostial to proximal segment of left subclavian artery stenosis with pressure gradient > 60 mmHg.

angina always occurred during hemodialysis. There are only a few case reports of such patients, with the first case having been reported in 2002.[1] Crowleyet al. reported a post-CABG patient whose arterio-venous fistula had been created over the left upper limb and also stole the blood flow. Selective left coronary angiography revealed blood flow reversal from LAD to subclavian artery. When they occluded the arteriovenous fistula with manual extrinsic compression pressure the subclavian artery blood pressure increased and the patient's chest pain resolved. When the AV fistula was released, the subclavian artery blood pressure decreased and the patient's angina symptoms recurred. Our case is more complicated because of the presence of proximal subclavian artery stenosis.

Coronary subclavian steal syndrome in post-CABG patientsis uncommon but careful differential diagnosis is needed. In this case, the etiology included native subclavian artery stenosis which may have been missed before the CABG or was newly developed atherosclerosis after the CABG, radiation arteritis,[2] or Takayasu arteritis,[3] etc. This situation should be kept in mind, whereby detailed history review including the CABG surgery record is essential for differential diagnosis, since there are no specific non-invasive diagnostic tools. The blood pressure difference between the upper limbs is not a reliable indicator because of the possibility of segmental stenosis and multiple vessel disease.[4] Computed tomography angiography (CTA) or magnetic resonance angiography (MRA) could provide clues but dynamic coronary angiography is necessary for definite diagnosis. Duplex ultrasonography may be helpful to detect the flow reversal in the ipsilateral vertebral artery, which is a sign of proximal subclavian artery stenosis.

The mainstream therapy for subclavian artery stenosis is endovascular intervention. A trans-femoral or trans-brachial artery approach could both be chosen. Given the many advantages, percutaneous transluminal angioplasty (PTA) over the stenotic segment with scaffolding of peripheral stents is recommended.[5] These advantages include small puncture wound and minimally invasive procedure, only local anesthesia required with no need for general anesthesia, short hospitalization period at lower cost, and high safety. Qureshi et al. showed significant improvement of life quality.[5] Shortcomings of the procedure include restenosis of the intra-stent area and longer learning curve for experts on account of case rarity. The procedure success rate is more than 90% except in circumstances of subclavian artery occlusion. The in-stent restenosis rate was around 12% over a mean follow-up period of 5 years.[6] In unsuccessful PTA cases or subclavian occlusion cases, bypass surgery plays an important role, including carotid-subclavian, carotid-axillary, axillo-axillary, and aorta-subclavian bypass. The bypass surgery risk is acceptable in selected patients.[7] Skilled surgeons and an experienced team are required.

Conclusion

Although rare, left subclavian artery stenosis may induce myocardial ischemia in post-CABG combined uremia patients with left upper extremity arteriovenous fistula while undergoing hemodialysis. Careful history taking and knowledge of any coronary bypass grafts and arterio-venous access may help to identify this rare condition. Percutaneous transluminal angioplasty with or without stenting is the treatment of choice, with low complication rates and good long term prognosis.

Disclosures

None.

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