ESC Congress 2017 In Review

Official peer-reviewed highlights

Focus on
Interventions & Peripheral Circulation

In This Issue

ESC Clinical Practice Guidelines 2017 - Diagnosis and Treatment of Peripheral Arterial Diseases

The management of peripheral arterial diseases continues to evolve as new devices, diagnostics, and treatments are tested out in well-conducted clinical trials. The growing evidence emanating from recent trials has been incorporated in the updated 2017 ESC Clinical Practice Guidelines.

Also

- Management of Patients with PADs and Cardiac Disease
- Clinical Trial Highlights
- TAVI/TAVR Summit

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ESC European Society of Cardiology

Dear Colleagues,

We are delighted to present this special issue of *ESC Congress 2017 in Review,* focused on peripheral arterial diseases, which are increasingly prevalent in clinical practice and may be challenging to manage. The peer-reviewed highlights in this issue are based on presentations at the European Society of Cardiology (ESC) Congress 2017 held in Barcelona, Spain.

Within this issue, you will find a closer look at the newly published 2017 ESC Clinical Practice Guidelines on the diagnosis and treatment of peripheral arterial diseases, which cover arterial disease in every location except for the coronary and intracranial arteries as well as the aorta.

The Hot Line trials and late-breaking registry results presented in this issue include the COMPASS study which demonstrated that the combination of rivaroxaban 2.5 mg BID plus aspirin was superior to rivaroxaban 5 mg BID or aspirin alone in reducing the primary outcome of major adverse cardiac events, as well as the key outcome for PAD, major adverse limb events (defined as severe limb ischaemia leading to an intervention and major amputation due to vascular insufficiency above the forefoot).

We hope that the articles and practical perspectives presented in *ESC Congress 2017 in Review - Focus on Interventions and Peripheral Circulation* will provide you with new insights. Please be advised that in order to access ESC Congress content (videos, slides, abstracts, and reports) all year long, visit us online at any time at www.escardio.org/365.

We hope to see you in Munich for ESC Congress 2018. For more information, please visit www.escardio.org/ESC2018.

Professor Stephan Achenbach, FESC
ESC Congress Programme Committee Chair 2016-2018

Dear Practitioner,

We are pleased to share with you this special issue of *ESC Congress in Review 2017* with a focus on interventions and peripheral circulation from presentations at the European Society of Cardiology (ESC) Congress held in Barcelona, Spain.

The featured article concentrates on the newly released 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases. Changes from the 2011 guidelines include the use of a "vascular team" for multidisciplinary management, risk stratification for asymptomatic carotid disease, and a focus on lower extremity disease.

A number of highly anticipated and potentially practice-changing clinical trials were presented at ESC Congress 2017, including the results from the COMPASS study and a combined analysis of FAME 1 and 2. COMPASS extended the results from ATLAS TIMI-51, demonstrating that the combination of low-dose rivaroxaban (2.5 mg BID) plus aspirin was superior to aspirin alone for prevention of cardiovascular (CV) death, stroke, or myocardial infarction in patients with stable coronary artery disease (CAD) or peripheral arterial disease (PAD). In patients with PAD, the combination not only significantly reduced the primary outcome of major adverse cardiac events (MACE), but also significantly reduced the key outcome for PAD, major adverse limb events (MALE). The key composite of MACE or MALE or major amputation occurred in 6.3%, 7.6%, and 9.0% of patients receiving combination therapy, rivaroxaban alone, or aspirin alone, respectively. This represents an important advance for the treatment of patients with PAD.

The study, a subanalysis of FAME 1 and 2, that investigated whether the difference between fractional flow reserve (FFR) at baseline and post-percutaneous coronary intervention (PCI) impacts the 2 year vessel-oriented clinical events (VOCE) rate (vessel-related CV death, vessel-related revascularisation, and vessel-related myocardial infarction) found that a larger improvement in FFR was associated with a lower event rate, suggesting that reduction in ischaemic potential is an independent predictor of VOCE at 2 years.

In addition to the results from clinical trials and registry updates, you will also find information on selected areas of CV medicine including a dedicated look at the 2017 ESC Clinical Practice Guidelines focused update on dual antiplatelet therapy and at the management in patients with PAD who also have concomitant cardiac diseases, including CAD, atrial fibrillation, and heart failure.

We hope that you find the articles and practical perspectives that are contained in this special edition of *ESC Congress 2017 in Review – Focus on Interventions and Peripheral Circulation* helpful in integrating this new information into your clinical practice.

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ESC European Society of Cardiology

2017 ESC Clinical Practice Guidelines on Diagnosis and Treatment of Peripheral Arterial Diseases

Written by **Phil Vinall**

Reviewing and updating guidelines is an important part of the European Society of Cardiology's (ESC) mission. New and/or updated recommendations are typically presented at the Society's annual meeting. The following is an overview of the 2017 ESC Clinical Practice Guidelines on the Diagnosis and Treatment of Peripheral Artery Diseases (PADs), developed in collaboration with the European Society for Vascular Surgery (ESVS), and presented on 28 August.

Diagnosis and Treatment of PADs

Victor Aboyans, MD, PhD, Dupuytren University, Limoges, France, noted that the guidelines cover arterial disease at every location except for the aortic, coronary, and intracranial arteries. There is also a special section on multisite artery disease and a new chapter on cardiac conditions frequently found in patients with PADs.

General Prevention and Antithrombotic Therapies

Proper management for patients with PADs requires attention to both general cardiovascular (CV) risk prevention and specific locally related symptoms. Lucia Mazzolai, MD, PhD. Lausanne University Hospital, Lausanne, Switzerland, discussed general prevention. Key steps include a thorough clinical history, physical examination, and laboratory testing. The Ankle-Brachial Index (ABI) is not only important for diagnosis of lower extremity artery disease (LEAD), but it also can be used for CV risk stratification and serves as a general marker of CV disease risk. Best medical therapy for patients with PADs should include both pharmacologic and non-pharmacologic measures (Table 1).

Table 1. Guidelines for General Prevention of Cardiovascular Disease in Patients With PAD

Recommendations	Class	Level
Healthy diet and physical activity (all patients with PADs)	I	C
Smoking cessation (all patients with PADs)	I	B
Control BP at < 140/90 mm Hg (patients with PADs + hypertension)	I	A
Consider ACEIs or ARBs as first line therapy (patients with PADs + hypertension)	IIa	B
Statins (all patients with PADs)	I	A
Reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by ≥ 50% if baseline values are 1.8-3.5 mmol/L (70 – 135 mg/dL) (all patients with PADs)	I	C

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BP, blood pressure.

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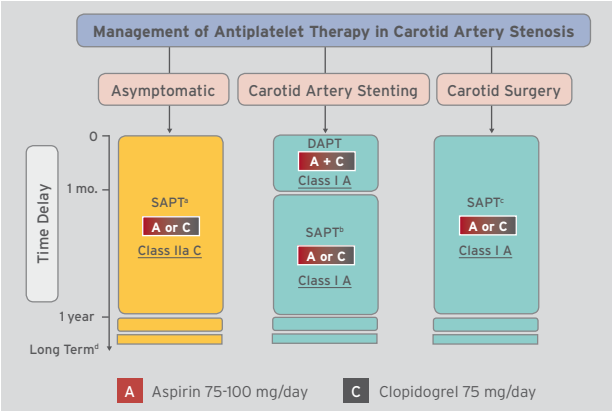
Antithrombotic Therapy

Jean-Phillippe Collet, MD, Paris-Sorbonne Université, Paris, France, noted that long-term single antiplatelet therapy (SAPT) is recommended for patients with symptomatic carotid artery stenosis (Class I Level A) and DAPT is recommended for ≥ 1 month after carotid stenting (I A). For asymptomatic patients with a > 50% stenosis, long-term SAPT (usually low-dose aspirin) should be considered when there is a low risk of bleeding (IIa C; Figure 1).

In patients with LEAD who do not require anticoagulation, the use of antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic disease (III A).

Figure 1. Antiplatelet Therapy in Patients With Carotid Artery Stenosis



a At the exception of patient at very high bleeding risk.
b DAPT may be used if another indication supersedes that of carotid artery stenting such as acute coronary syndrome or percutaneous coronary intervention of less than 1 year.
c In case of recent minor stroke or TIA. A loading dose of aspirin (300 mg) and/or clopidogrel (300/600 mg) is recommended at the acute phase of stroke/TIA or during CAS.
d Stands for as long as it is well tolerated.

ACS, acute coronary syndrome; ASA, aspirin; CAS, carotid artery stenting; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; TIA, transient ischaemic attack.

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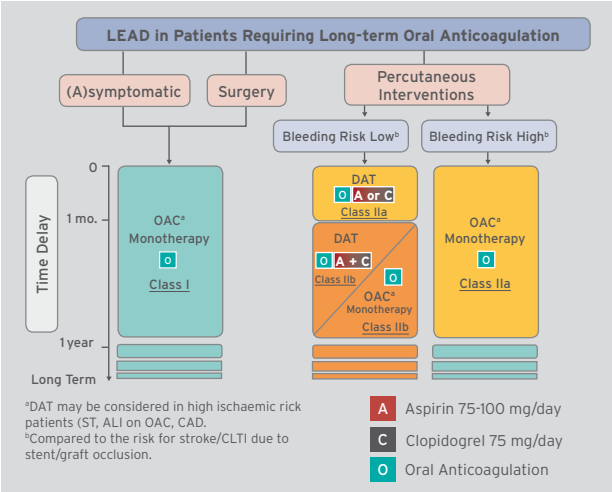
Symptomatic patients should receive long-term SAPT (I A). Patients who have undergone percutaneous coronary intervention (PCI) should receive short-term DAPT then long-term SAPT (both IIa C) while those who have received carotid surgery should be treated with long-term SAPT or a vitamin K antagonist (VKA; both IIb B). The recommendations for LEAD patients who require anticoagulation are shown in Figure 2.

Figure 2. Antithrombotic Therapy in Patients With LEAD Requiring Oral Anticoagulation



ALI, acute limb ischaemia; CAD, coronary artery disease; CLTI, chronic limb-threatening ischaemia; DAT, dual antithrombic therapy; OAC, oral anticoagulation; ST, stent thrombosis.

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Table 2. Revascularisation in Patients With Renal Artery Disease

Recommendations	Class	Level
Routine revascularisation is not recommended in RAS secondary to atherosclerosis	III	A
Balloon angioplasty, with or without stenting, may be considered in selected patients with RAS and unexplained recurrent CHF or flash pulmonary oedema	IIb	C
In patients with hypertension and/or signs of renal impairment related to renal FMD, balloon angioplasty with bailout stenting should be considered	IIa	B
When there is an indication for revascularisation, surgical revascularisation should be considered for patients with complex anatomy of the renal arteries, after a failed endovascular procedure, or during open aortic surgery	IIa	B

CHF, congestive heart failure; FMD, fibromuscular dysplasia; RAS, renal artery stenosis.

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Patients With Renal Artery Disease (RAD) or Extracranial Carotid Disease

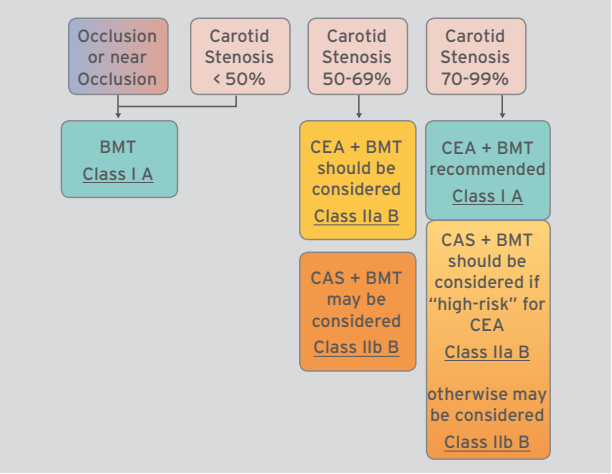
Charalambos Vlachopoulos, MD, University of Athens Medical School. Athens, Greece, reviewed the new recommendations for patients with RAD.

In the case of RAD and hypertension associated with unilateral renal artery stenosis (RAS) the recommendation is for ACEIs/ARBs (I B). These therapies may also be considered for bilateral severe RAS and in the case of stenosis in a single functioning kidney, if well tolerated and under close monitoring (IIb B). For hypertension associated with RAD, the recommendation is for calcium channel blockers, β-blockers, and diuretics (I C). The recommendations for revascularisation are shown in Table 2.

Jean-Baptiste Ricco, MD, PhD, University of Poitiers, Poitiers, France, presented the guidelines for the management of patients with extracranial carotid disease (ECD).

Optimal medical treatment reduces the risk of stroke in asymptomatic patients with ECD but some risk remains. In "average surgical risk" patients with an asymptomatic 60% to 99% stenosis whose clinical characteristics may put them at an increased risk of late ipsilateral stroke, carotid artery stenting (CAS) may be an alternative to carotid endarterectomy provided documented perioperative stroke/death rates are < 3% and the patient's life expectancy is > 5 years (IIb B). Recommendations for revascularisation in patients with symptomatic ECD are shown in Figure 3. The guidelines also provide specific recommendations for screening and treating patients undergoing coronary artery bypass graft (CABG).

Figure 3. Revascularisation in Patients With Symptomatic ECD



BMT, best medical therapy; CAS, carotid artery stenting; CEA, carotid endarterectomy.

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Mesenteric Artery Disease

Sebastian Debus, MD, University Heart Center Hamburg-Eppendorf, Hamburg, Germany, noted that the 2017 guidelines have been expanded to cover both acute and chronic mesenteric ischaemia (CMI) and arterial and venous ischaemia. Duplex ultrasound is recommended as first line examination for suspected CMI (I C), once diagnosed, those with symptomatic CMI should undergo revascularisation (I C). A novel recommendation is on the use of d-dimers to rule out acute mesenteric ischaemia when the levels are normal (IIa B)

Upper Extremity Artery Disease (UEAD)

Atherosclerotic UEAD affects mostly proximal arteries. It can be detected by inter-arm blood pressure difference (> 15 mm Hg) and is associated with increased CVD risk and mortality. Marianne Brodmann, MD, University of Graz, Graz, Austria, discussed some of the new guidelines for UAED. For patients with symptomatic subclavian artery stenosis/occlusion revascularisation (stenting or surgery) should be considered (IIa C) based on the lesion characteristics and the patient's risk. Revascularisation should also be considered for some patients with asymptomatic proximal stenosis undergoing CABG, post-graft, or in patients who also have ipsilateral arteriovenous fistula for dialysis (IIa C) or in the case of bilateral stenosis to be able to accurately monitor blood pressure (IIb C).

Lower Extremity Artery Disease (LEAD)

Prof Brodmann also covered the ESC recommendations for LEAD. Although the Fontaine and Rutherford classification systems for LEAD should still be used, the 2017 Guidelines introduced the concept of 'masked LEAD' to account for asymptomatic patients who are only asymptomatic because another condition limits their ability to or prevents them from walking. Prof Brodmann reiterated the value of the ABI but noted that in the case of incompressible ankle arteries or ABI > 1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis, or pulse volume recording are indicated (I C). Imaging recommendations for patients with LEAD are shown in Table 3. The recommendations for the management of patients with intermittent claudication are detailed in Table 4.

Multisite Artery Disease (MSAD)

MSAD is common in patients with atherosclerotic involvement in 1 vascular bed, ranging from 10% to 15% in patients with CAD to 60% to 70% in patients with severe carotid stenosis or LEAD. Patients with MSAD have a 1.5- to 2-fold increase in the risk of major cardiac events both in-hospital and at 1 and 3 years, versus single-site disease [Steg PG et al. *JAMA*. 2007; Alberts MJ et al. *Eur Heart J*. 2009; Subherwal S et al. *Circ Cardiovasc Qual Outcomes*. 2012; Wilson WM et al. *Am J Cardiol*. 2011]. The guidelines for MSAD were presented by Marco De Carlo, MD, PhD, Pisa University Hospital, Pisa, Italy. In patients with any presentation of PADs, clinical assessment of symptoms and physical signs of other localisations and/or CAD is necessary, and in case of clinical suspicion, further tests may be planned. The indications for screening for associated atherosclerotic disease in additional vascular territories are shown in Figure 4.

Table 3. Imaging in Patients With LEAD

Recommendations	Class	Level
DUS is indicated as first-line imaging method to confirm LEAD lesions	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterisation of LEAD lesions and guidance for optimal revascularisation strategy	I	C
Data from an anatomical imaging test should always be analysed in conjunction with symptoms and haemodynamic tests prior to treatment decision	I	C
DUS screening for AAA should be considered	IIa	C

AAA, abdominal aortic aneurysm; CTA, computed tomography angiography; DUS, duplex ultrasound; LEAD, lower extremity artery disease; MRA, magnetic resonance angiography.

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Table 4. Recommendations for the Management of Patients With Intermittent Claudication

Recommendations	Class	Level
On top of general prevention, statins are indicated to improve walking distance	I	A
In patients with intermittent claudication:		
• supervised exercise training is recommended	I	A
• unsupervised exercise training is recommended when supervised exercise training is not feasible or available	I	C
When daily life activities are compromised despite exercise therapy, revascularisation should be considered	IIa	C
When daily life activity is severely compromised, revascularisation should be considered, in association with exercise therapy	IIa	B

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Figure 4. Screening of Associated Atherosclerotic Disease in Additional Vascular Territories

Leading Disease \ Screened Disease	CAD	LEAD	Carotid	Renal
CAD				
Scheduled for CABG		IIa	I / IIb	U
Not scheduled for CABG		IIb	NR	U
LEAD				
Scheduled for surgery	I		NR	U
Not scheduled for surgery	NR		NR	U
Carotid stenosis				
Scheduled for CEA/CAS	IIb	NR		U
Not scheduled for CEA/CAS	NR	NR		U

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CAS, carotid artery stenting; CEA, carotid endarterectomy; LEAD, lower extremity artery disease; NR, no recommendation; U, uncertain.

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Cardiac Conditions in PADs

Michal Tendera, MD, Medical University of Silesia, Katowice, Poland, discussed cardiac conditions frequently associated with PADs (heart failure [HF], AF, and valvular heart disease [VHD]). Patients can present with either the PADs or the cardiac condition.

About one-third of patients with LEAD have HF [Kelly R et al. *J Am Coll Cardiol*. 2002]. In patients presenting with PADs, the evaluation of left ventricular function may be valuable for risk stratification and to establish the best management strategy. Recommendations for those presenting with HF are shown in Table 5.

Table 5. Patients Presenting With Heart Failure

Recommendations	Class	Level
Full vascular assessment is indicated in all patients considered for heart transplantation or cardiac assist device implantation	I	C
In patients with symptomatic PADs, screening for HF with TTE and/or natriuretic peptides assessment should be considered	IIa	C
Screening for LEAD may be considered in patients with HF	IIb	C
Testing for RAD may be considered in patients with flash pulmonary oedema	IIb	C

HF, heart failure; LEAD, lower extremity artery disease; PADs, peripheral artery diseases; RAD, renal artery disease; TTE, transthoracic echocardiogram.

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LEAD is associated with an increased risk of AF and also tends to be more severe in these patients. In patients with AF, the ABI is a valid method to detect LEAD. Oral anticoagulation is recommended for patients with LEAD and AF with a CHA_2DS_2-VASc score ≥ 2 (I A) and should be considered for all other patients (IIa B).

PADs are common in patients with VHD, especially elderly patients with symptomatic aortic stenosis; thus, screening for LEAD and UEAD is indicated for patients undergoing transaortic valve implantation or other structural interventions requiring an arterial approach (I C). All of the data for patients with PADs indicate the need for collaboration among specialists emphasising the importance of the "Vascular Team".

Ileana Desormais, MD, PhD, Dupuytren University Hospital, Limoges, France, closed the session with a discussion of some of the gaps in the evidence. She noted that 49% of the recommendations in the new ESC Guidelines for PADs are Level of Evidence C (consensus, and/or small, retrospective studies or registries) meaning that only 51% of current practice in PADs is evidence based. There is a significant gap in our knowledge of the epidemiology of PADs, especially in European patients and women. European registries are needed for patients with LEAD and a validated and improved classification system needs to be developed for chronic limb-threatening ischaemia. Other gaps exist for CAD and on the benefits of revascularisation, but studies are ongoing to address some of these issues (Table 6).

Table 6. Evidence Gaps in PADs

Knowledge Gap	Trial?	Est. Completion
Carotid Artery Disease		
Benefits of new antithrombotic drugs/DAPT duration	No	
Revascularisation in asymptomatic carotid artery stenosis	PRECISE-MRI ACTRIS CREST-2	2019 2022 2020
Timing of carotid revascularisation in the acute phase of stroke after intra-cerebral thrombolysis/thrombectomy	No	
Benefits of Revascularisation (Clinical Benefit/Optimal Mode)		
Symptomatic subclavian artery stenosis/occlusion	No	
Renal artery stenting for flash oedema	No	
Stents, balloons, drug-eluting stents for LEAD superficial femoral artery/below-the-knee interventions in patients with CLTI.	ASPIRE PAD BASIL-2 BESTCLI VOYAGER	2018 2018 2019 2019 2019

DAPT, dual antiplatelet therapy; CLTI, chronic limb-threatening ischaemia; LEAD, lower extremity artery disease.

Rivaroxaban Plus Aspirin Superior to Aspirin Alone in Patients With Stable Cardiovascular Disease: Results From the COMPASS Trial

Written by **Maria Vinall**

Primary results from the COMPASS trial [Eikelboom JW et al. *N Engl J Med*. 2017] presented by John W. Eikelboom, MD, McMaster University, Hamilton, Ontario, Canada, showed that rivaroxaban plus aspirin improves outcomes in patients with stable cardiovascular (CV) disease.

COMPASS was a multicentre, randomised, prospective, double-blind, 3-arm superiority trial. Patients (27,395) from 602 centres in 33 countries were randomised (1:1:1) to 2.5 mg BID rivaroxaban plus 100 mg QD aspirin, or 5 mg BID rivaroxaban alone, or 100 mg QD aspirin alone. The primary study endpoint was a composite of CV death, stroke, or myocardial infarction (MI). Safety and net clinical benefit was derived from a modified ISTH major bleeding score and included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalisation.

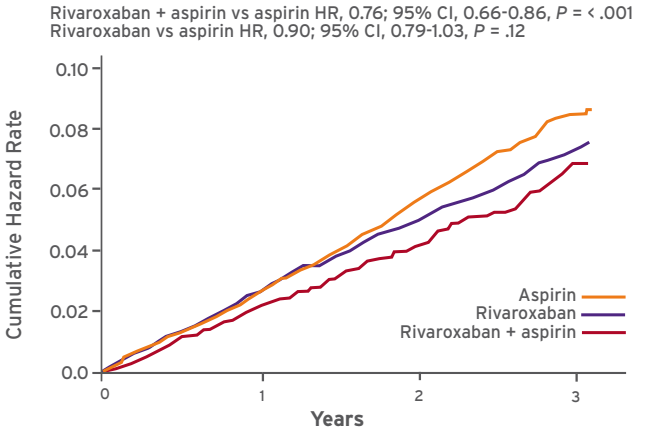
At baseline, 91% of participants had a history of coronary artery disease and 27% a history of peripheral artery disease (PAD). There was high use of evidence-based therapies: 90% of patients were on lipid-lowering agents; 71% on an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; and 70% on β-blockers. Participants (22% women) were a mean age of 68 years with a mean blood pressure of 136/78 mm Hg and mean total cholesterol of 4.2 mmol/L. The Data and Safety Monitoring Board recommended discontinuation of the rivaroxaban/aspirin arms of the study for clear benefit of rivaroxaban.

There was a significant 24% reduction in the primary endpoint among participants randomised to combination therapy compared with aspirin alone (HR, 0.76; 95% CI, 0.66 to 0.86; $P < .001$); rivaroxaban alone was not significantly better than aspirin alone (HR, 0.90; 95% CI, 0.79 to 1.03; $P = .12$; Figure 1). For the individual components of the primary endpoint, the reduction was significant in the combination-therapy group for CV death (RRR 22%; $P = .02$) and stroke (RRR 42%; $P < .001$) but not for MI (RRR 14%; $P = .14$).

Significantly more major bleeding occurred in the 2 rivaroxaban arms compared with aspirin alone. The rivaroxaban 2.5 mg plus aspirin arm increased major bleeding by 70% (3.1% vs 1.9%; HR, 1.70; 95% CI, 1.40 to 2.05; $P < .001$) while major bleeding in the rivaroxaban-alone arm was increased by 51% (HR, 1.51; 95% CI, 1.25 to 1.84; $P < .001$). Rates of fatal bleeding or symptomatic intracranial haemorrhage were low and were not significantly increased with rivaroxaban plus aspirin versus aspirin (HR, 1.23; $P = .40$); there was a trend toward an increase with rivaroxaban 5 mg alone compared with aspirin (HR, 1.59; $P = .05$). Both rivaroxaban arms increased bleeding leading to transfusion versus aspirin alone (HR, 1.97; $P < .001$ for rivaroxaban 2.5 mg; HR, 1.50; $P = .03$ for rivaroxaban 5 mg).

With respect to the 7,470 patients with PAD, Sonia Anand, MD, McMaster University, Hamilton, Ontario, Canada, reported that the combination of rivaroxaban

Figure 1. Primary Composite Outcome: Cardiovascular Death, Stroke, or Myocardial Infarction



From *The New England Journal of Medicine*, Eikelboom JW et al, Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease, EPub 28 August 2017.

2.5 mg BID plus aspirin was superior to aspirin alone in reducing the primary outcome of MACE, as well as the key outcome for PAD, major adverse limb events (MALE; defined as severe limb ischaemia leading to an intervention and major amputation due to vascular insufficiency above the forefoot).

For eligibility purposes, PAD was defined as previous aortofemoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularisation of the iliac, or infra-inguinal arteries; previous limb or foot amputation for arterial disease; history of intermittent claudication of 1 or more of the following: ankle/brachial blood pressure ratio < 0.90; significant peripheral artery stenosis (≥ 50%); previous carotid revascularisation or asymptomatic carotid artery stenosis (≥ 50%) [Bosch J et al. *Can J Cardiol*. 2017].

A MACE event occurred in 5.1% of patients receiving rivaroxaban 2.5 mg plus aspirin (HR, 0.72; 95% CI, 0.57 to 0.90; *P* = .005) and 6.0% receiving rivaroxaban 5 mg alone (HR, 0.86; 95% CI 0.69 to 1.08; *P* = .19) compared with 6.9% of patients receiving aspirin alone.

MALE events were significantly reduced with both combination therapy (HR, 0.54; 95% CI, 0.35 to 0.84; *P* = .005) and rivaroxaban alone (HR, 0.63; 95% CI, 0.41 to 0.96; *P* = .03) compared with aspirin alone. Major amputation was low (< 1%) in all groups, but significantly lower for rivaroxaban plus aspirin (HR, 0.30; 95% CI, 0.11 to 0.80; *P* = .01) compared with aspirin alone.

The key composite of MACE or MALE or major amputation occurred in 6.3%, 7.6%, and 9.0% of patients receiving combination therapy, rivaroxaban alone, or aspirin alone, respectively. There was a 31% reduction in MACE or MALE with rivaroxaban plus aspirin compared with aspirin alone (HR, 0.69; 95% CI, 0.56 to 0.85; *P* = .0003), while the difference was not significant for rivaroxaban alone compared with aspirin alone (RRR: 14%; *P* = NS).

There was a significant increase in major bleeding (*P* = .009) among patients receiving rivaroxaban but no significant increase in fatal or critical organ bleeding. There was a significant net clinical benefit from combination therapy in this population of patients (HR, 0.72; 95% CI, 0.59 to 0.87; *P* = .0008).

In concluding, Dr Anand noted that rivaroxaban 2.5 mg BID plus aspirin is significantly superior to aspirin alone in reducing MACE or MALE or major amputation. There is an increase in major bleeding with the combination, but no significant increase in fatal or critical organ bleeding.

Content Ed Net
MEDICOM

The editors would like to thank the many members of the ESC Congress 2017 presenting faculty who generously gave their time to ensure the accuracy and quality of the articles in this publication

Leaflet Thrombosis Following TAVR Is Associated With Serious Adverse Events

Written by **Toni Rizzo**

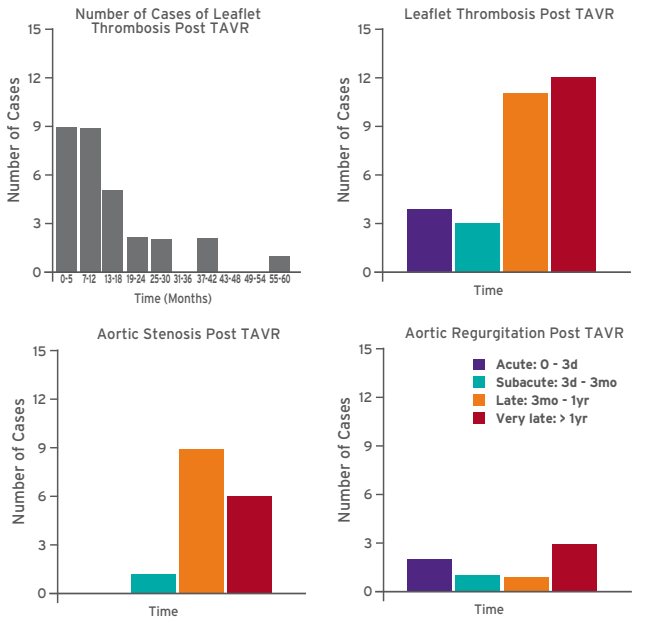
Leaflet thrombosis is a complication of transcatheter aortic valve replacement (TAVR) that can lead to transcatheter valve failure, but the clinical consequences of leaflet thrombosis are not clear. The purpose of this study, presented by Ankur Kalra, MD, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA, was to determine whether leaflet thrombosis has clinical significance beyond peri-TAVR stroke and transient ischaemic attack (TIA).

The Manufacturer and User Facility Device Experience (MAUDE) database was searched for the identifier code, "NPT," designated by the US Food and Drug Administration to identify TAVR-related adverse events (AEs) occurring between the dates January 2012 and October 2015. Selected entries were searched further for the terms, "leaflet," "central aortic regurgitation (AR)," and "aortic stenosis." All reports that did not have the term "leaflet" were excluded. Cases of structural valve dysfunction (SVD) due to procedure-related factors or not classified were also excluded. Presentation of leaflet thrombosis, mode of diagnosis, and timing of onset after TAVR were recorded.

A total of 5,691 TAVR-related AEs were reported in the database. There were 546 AEs based on the prespecified search terms and 156 AEs of SVD due to leaflet restriction (n = 129) or leaflet malcoaptation (n = 27). SVD caused by leaflet thrombosis was documented in 30 cases, 20 with the Edwards-Sapien valve and 10 with the CoreValve (Figure 1). Of these, 60% occurred in the first year following TAVR and 40% occurred within 13 to 60 months. SVD presented as aortic stenosis in 53.3% of patients, regurgitation in 23.3% of patients, or both in 13.3% of patients. Aortic stenosis occurred within 15.5 ± 12.2 months and regurgitation occurred within 10.1 ± 10.9 months of TAVR. Three of the 30 patients had a stroke or TIA.

Leaflet thrombosis was treated with escalation of antiplatelet or anticoagulant therapy in 26.7% of patients, valve-in-valve TAVR in 10.0% of patients, or surgery in 46.7% of patients. Other interventions included diuretics (n = 1), thrombus aspiration (n = 1), and balloon aortic valvuloplasty (n = 2). Two patients received no intervention. Outcomes after leaflet thrombosis were stroke or TIA in 10.0% of patients, cardiogenic shock in 6.7% of patients, and death in 30.0% of patients.

Figure 1. Cases and Timing of Leaflet Thrombosis, Aortic Stenosis, and Aortic Regurgitation



TAVR, transaortic valve replacement.

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Limitations of the study included ascertainment bias and lack of independent verification of reports obtained from the database. Additionally, time lapse and interim management decisions between AE occurrence and final interventions were not available. The authors noted that a different diagnosis other than leaflet thrombosis, such as infective endocarditis, may have been considered in the patients who had surgery. Further, incomplete capture of all events because of lack of standard definitions during the study period might have resulted in missed diagnoses and underreporting by manufacturers. The search terms also did not include the term "stroke/TIA."

In summary, this study demonstrated that leaflet thrombosis is a serious AE following TAVR. Most cases occurred in the first year following TAVR. Leaflet thrombosis was associated with the serious clinical manifestations of stroke, cardiogenic stroke, and death. The authors concluded that early diagnosis of leaflet thrombosis may be crucial for planning appropriate management and optimising clinical outcomes for patients.

CABG Better Than PCI in Patients With Type 1 Diabetes

Written by **Nicola Parry**

Martin J. Holzmann, MD, PhD, Karolinska University Hospital, Stockholm, Sweden, presented results from an observational cohort study in patients with type 1 diabetes mellitus (T1DM) with multivessel disease, demonstrating that the long-term risks of cardiac death, myocardial infarction (MI), and repeat revascularisation were significantly higher in patients who underwent percutaneous coronary intervention (PCI) than in those who underwent coronary artery bypass grafting (CABG) [Nyström T et al. *J Am Coll Cardiol.* 2017].

Based on data from randomised controlled trials (RCTs) current guidelines recommend CABG as the preferred strategy of revascularisation compared with PCI in patients with diabetes and multivessel disease. Data from a recent meta-analysis of these studies showed a 33% relative risk reduction for all-cause mortality at 5 years in patients with diabetes and multivessel disease who underwent CABG compared with PCI [Verma S et al. *Lancet Diabetes Endocrinol*. 2013].

Although none of those RCTs involved subgroup analyses based on diabetes type, Dr Holzmann noted that T1DM patients are more likely to die after CABG than those with type 2 diabetes (T2DM). Indeed, after CABG, he stressed that T2DM patients have a similar prognosis to that of patients without diabetes who undergo CABG. And because most patients with diabetes have T2DM, the findings from these studies may not be generalisable to those with T1DM.

Dr Holzmann and colleagues therefore aimed to determine whether T1DM patients with multivessel disease might benefit from CABG instead of PCI.

Using data from the SWEDEHEART registry and other Swedish national registries, the researchers conducted an observational cohort study that included 2,546 patients with T1DM and multivessel (≥2 vessels) disease who underwent revascularisation (n = 1,863 for PCI, n = 683 for CABG) between 1995 and 2013 in Sweden.

The primary outcome was all-cause mortality. Secondary outcomes were cardiac-specific mortality, MI, heart failure, stroke, and repeat revascularisation.

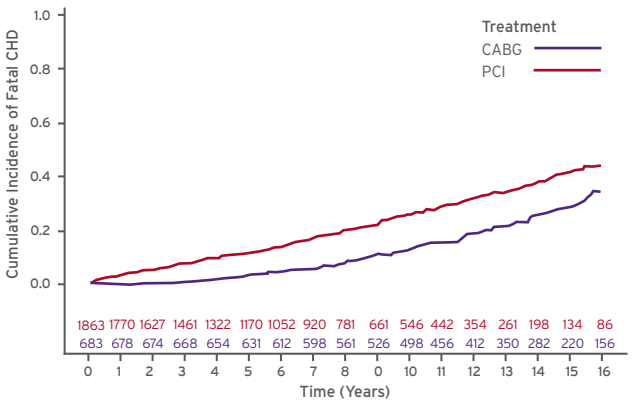
Researchers found a sharp decline in the proportion of patients undergoing CABG compared with PCI during the study period. From 1995 to 2000, 58% of patients underwent CABG, but this decreased to 21% from 2001 to 2006, and to only 5% from 2007 to 2013.

Patients who underwent CABG were younger than those who underwent PCI (57 vs 61 years). They were less likely to be female (37% vs 41%), to have experienced acute MI within 14 days (14% vs 37%), and to have experienced a previous episode of stroke (7% vs 10%). However, they were more likely to have disease in 3 vessels.

Through a mean follow-up of 10.6 years, there were no significant differences between the groups in the risk of all-cause mortality (adjusted HR, 1.14; 95% CI, 0.99 to 1.32).

However, compared with CABG patients, PCI patients had a 45% higher risk of cardiac-specific death (adjusted HR, 1.45; 95% CI, 1.21 to 1.74; Figure 1) and a 47% higher risk of MI (adjusted HR, 1.47; 95% CI, 1.23 to 1.78). PCI patients also had a 5-fold greater risk of repeat vascularisation (adjusted HR, 5.64; 95% CI, 4.67 to 6.82).

Figure 1. Cardiac-Specific Death in T1DM Patients Undergoing CABG vs PCI



Reprinted from Nyström T, Sartipy U, Franzén S, et al. PCI Versus CABG in Patients With Type 1 Diabetes and Multivessel Disease. *J Am College of Cardiol*. Aug 2017. DOI: 10.1016/j.jacc.2017.07.744, with permission from the American College of Cardiology.

There were no differences in the long-term risks of stroke or HF between the 2 groups.

The results of this study indicate that among patients with T1DM and multivessel coronary artery disease, CABG, not PCI, should be the preferred strategy for revascularisation.

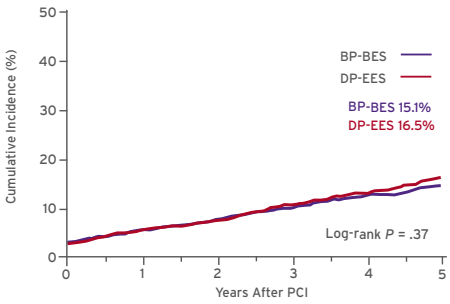
No Difference in 5-Year Clinical Outcomes With Biodegradable vs Durable Polymer Drug-Eluting Stents

Written by **Toni Rizzo**

A meta-analysis reported similar efficacy and safety outcomes during 26 months of follow-up after implantation of a biodegradable polymer biolimus-eluting stent (BP-BES) compared with a durable polymer everolimus-eluting stent (DP-EES) [El-Hayek G et al. *JACC Cardiovasc Interv*. 2017]. A follow-up beyond 1 year may be required to evaluate the efficacy and safety of a BP-BES because of the stent-related adverse events occurring before biodegradable polymer degradation. The aim of this follow-up extension of the NEXT trial [NCT01303640], presented by Masahiro Natsuaki, MD, Saga University, Saga, Japan, was to evaluate the 5-year clinical outcomes of the BP-BES compared with the second-generation DP-EES.

The NEXT trial randomised patients scheduled for percutaneous coronary intervention to implantation with the Nobori BP-BES (n = 1,617) or the Xience V/Promus DP-EES (n = 1,618). Follow-up was scheduled at 1, 2, and 3 years, with extension study follow-up at 5 and 10 years. The primary analysis was for noninferiority of BP-BES compared with DP-ESS for the safety endpoint of death or myocardial infarction (MI) and the efficacy endpoint of target lesion revascularisation (TLR). A total of 3,235 patients were included in the 3-year follow-up analysis, 2,568 patients entered the extended follow-up study, and complete 5-year follow-up was achieved in 2,408 patients.

Figure 1. Death or Myocardial Infarction



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
BP-BES group							
N of patients with at least 1 event		39	77	104	131	161	190
N of patients at risk	1283	1243	1203	1170	1134	1058	1009
Cumulative incidence		3.0%	6.0%	8.1%	10.0%	12.7%	15.1%
DP-EES group							
N of patients with at least 1 event		39	71	100	137	171	208
N of patients at risk	1285	146	1213	1179	1135	1054	991
Cumulative incidence		3.0%	5.5%	7.8%	10.7%	13.5%	16.5%

BP-BES, biopolymer biolimus-eluting stent; DP-EES, durable polymer everolimus-eluting stent; PCI, percutaneous coronary intervention.

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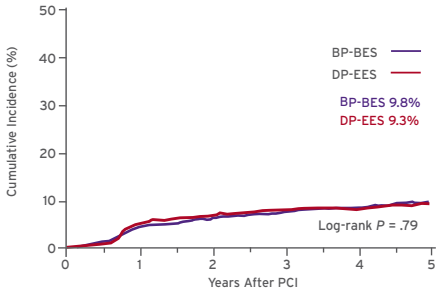
Baseline and procedural characteristics were similar between the 2 groups. At the 5-year follow-up, there were no significant differences between the 2 groups in either of the primary endpoints. The primary safety endpoint of death or MI had occurred in 15.1% of patients in the BP-BES group compared with 16.5% of patients in the DP-EES group (log-rank *P* = .37; Figure 1).

At 5 years, 9.8% of patients in the BP-BES group had undergone TLR compared with 9.3% of patients in the DP-EES group (log-rank *P* = .79; Figure 2).

Figure 2. Target-Lesion Revascularisation



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
BP-BES group							
N of patients with at least 1 event		2	55	78	95	106	118
N of patients at risk	1283	1279	1192	1138	1083	1004	947
Cumulative incidence		0.2%	4.4%	6.2%	7.7%	8.6%	9.8%
DP-EES group							
N of patients with at least 1 event		2	63	84	97	102	114
N of patients at risk	1285	1281	1191	1141	1089	1017	951
Cumulative incidence		0.2%	5.0%	6.7%	7.8%	8.2%	9.3%

BP-BES, biopolymer biolimus-eluting stent; DP-EES, durable polymer everolimus-eluting stent; PCI, percutaneous coronary intervention.

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Clinical outcomes at 5 years were not significantly different between the BP-BES and DP-EES groups, including death (11.7% vs 12.6%; *P* = .51), cardiac death (4.4% vs 3.9%; *P* = .54), MI (5.2% vs 4.8%; *P* = .72); stent thrombosis (0.49% vs 0.34%; *P* = .52); stroke (4.8% vs 5.7%; *P* = .38); target vessel revascularisation (TVR; 14.2% vs 12.4%; *P* = .22), and TIMI major or minor bleeding (6.5% vs 6.4%; *P* = .99).

A landmark analysis conducted from years 1 to 5 found no significant difference in the cumulative incidence of death or MI (BP-BES 9.7% vs DP-EES 11.6%; log-rank *P* = .13) or TLR (BP-BES 5.6% vs DP-EES 4.5%; log-rank *P* = .25) between groups. The cumulative incidence of TVR was significantly higher in the BP-BES (8.1%) than the DP-EES group (5.9%; *P* = .04). There were no significant differences in the other clinical outcomes between the groups in the landmark analysis.

In summary, the safety and efficacy outcomes of the BP-BES were similar to those of the DP-EES through 5 years after stent implantation. The authors concluded that a very long-term follow-up of 10 years may be necessary to show the potential benefits of the BP-BES over the DP-EES.

Improvement in FFR After PCI Predicts Lower Event Rate at 2 Years

Written by **Toni Rizzo**

After percutaneous coronary intervention (PCI), fractional flow reserve (FFR) is often < 1.0 due to residual diffuse disease, suboptimal stent deployment, or underestimated second stenosis. In a recent study of patients undergoing PCI [Piroth Z et al. *Circ Cardiovasc Interv*. 2017], two-thirds of post-PCI FFR values of the treated lesion remain < 0.92, the lowest limit of normal. The incidence of future cardiovascular events was lowest in the patients who had a post-PCI FFR ≥ 0.92. The objectives of this study, presented by Stephane Fournier, MD, OLV Hospital, Aalst, Belgium, was to investigate whether the change in FFR (ΔFFR) was associated with vessel-oriented clinical events (VOCE) at 2 years.

The study was a subanalysis of the FAME 1 and FAME 2 studies. In the FAME studies, a total of 1499 lesions with pre-PCI FFR ≤ 0.80 were treated with PCI. All of the treated lesions with available post-PCI FFR values (n = 838) were included in the subanalysis. The primary endpoint was VOCE at 2 years, defined as the composite of vessel-related cardiovascular death, vessel-related unplanned hospitalisation with urgent revascularisation, and vessel-related myocardial infarction (MI).

The post-PCI ΔFFR frequency distribution included 277 lesions in the lower tertile (ΔFFR ≤ 0.18), 282 lesions in the middle tertile (ΔFFR > 0.19 and ≤ 0.31), and 278 lesions in the upper tertile (ΔFFR > 0.31). Previous PCI was present in 29.6% of patients in the lower tertile, 22.3% of the middle tertile, and 15.5% of the upper tertile (*P* < .001). The pre-PCI FFR was 0.76 in the lower tertile, 0.69 in the middle tertile, and 0.50 in the upper tertile (*P* < .001). The post-PCI FFR was 0.87 in the lower tertile, 0.91 in the middle tertile, and 0.92 in the upper tertile (*P* < .001).

Factors that predicted ΔFFR included male gender (HR, -0.016; 95% CI, -0.027 to -0.006; *P* = .003), diabetes (HR, -0.012; 95% CI, -0.022 to -0.002; *P* = .024), previous PCI (HR, -0.020; 95% CI, -0.030 to -0.010; *P* < .001), and pre-PCI FFR (HR, -0.958; 95% CI, -0.988 to -0.928; *P* <.001).

The primary endpoint of VOCE occurred in 9.0% of the lower tertile compared with 4.7% of the upper tertile (adjusted *P* = .010; Table 1). There were no significant differences between the lower versus upper tertiles in the individual components of death and MI. Target vessel revascularisation was more common in the lower versus upper tertile (7.2% vs 2.5%; *P* = .002).

Table 1. VOCE in the Lower vs Upper Tertiles of Change in FFR

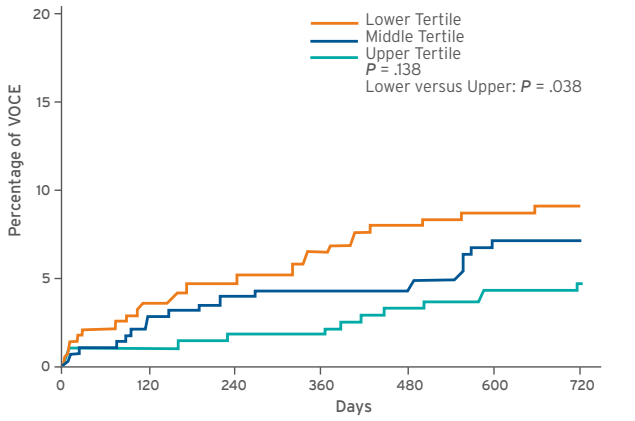
Tertiles	Lower	Upper	*P*-value (unadjusted)	*P*-value (adjusted*)
VOCE (n ; %)	25 (9.0)	13 (4.7)	**.043**	**.010**
Death (n ; %)	4 (1.4)	4 (1.4)	.966	.689
MI (n ; %)	5 (1.8)	4 (1.4)	.733	.318
TVR (n ; %)	20 (7.2)	7 (2.5)	**.010**	**.002**

*Adjusted for post-PCI FFR, pre-PCI FFR < 0.70, smoker status, previous PCI, and family history.

FFR, fractional flow reserve; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularisation; VOCE, vessel-oriented clinical events.

The time-to-events curve of VOCE showed that the lower the ΔFFR, the higher the percentage of VOCE. The difference was only significant between the lower and upper tertiles (*P* = .038; Figure 1).

Figure 1. Time to Events Curve of VOCE



Reproduced with permission from S Fournier, MD.

Comparison of the area under the curve versus pre-PCI stenosis severity showed that the lower the pre-PCI FFR (the tighter the stenosis), the larger the predictive value of ΔFFR as compared with post-PCI FFR.

Dr Fournier concluded that the higher the post-PCI FFR value, the lower the event rate; however, the likelihood ratio for event occurrence is weak. A larger improvement in FFR was associated with a lower event rate, suggesting that reduction in ischaemic potential is an independent predictor of VOCE at 2 years.

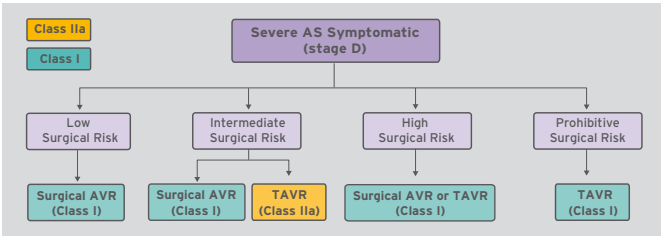
TAVI/TAVR Summit

Written by **Phil Vinall**

The 2014 AHA/ACC Guidelines for the Management of Patients with Valvular Heart Failure [Nishimura RA et al. *Circulation*. 2014] specified that the following factors should be considered when selecting patients for transcatheter aortic valve replacement (TAVR): Society of Thoracic Surgeons (STS) risk score, frailty, major organ system compromise not to be improved post surgery, and the presence and level of procedure-specific impediment. Using these criteria, patients were defined as being at low, intermediate, high, or extreme/inoperable risk. A focused update was issued recently that includes changes to some of the indications for TAVR based on risk data accumulated from the many clinical trials conducted since 2014 (Figure 1) [Nishimura RA et al. *Circulation*. 2017]. Martin B. Leon, MD, Columbia University Medical Center, New York City, New York, USA, reviewed some of these changes in the Aortic Valve Interventions Symposium on 26 August 2017.

In the high surgical-risk group, there are small differences favouring TAVR over surgery at all mortality outcomes [Smith CR. *N Engl J Med*. 2011]. In intermediate- or moderate-risk patients, the outcomes of death and disabling stroke are similar for TAVR and surgical aortic-valve replacement [Leon MB et al. *N Engl J Med*. 2016]. Key findings from recent studies show there are fewer vascular complications with surgery, but TAVR offers improved rates for mortality, strokes, severe bleeding, new onset atrial fibrillation (AF), and quality of life. For lower-risk patients, treatment choice should be based on whether the known value of less-invasive TAVR versus open surgery outweighs the unknown long-term durability of TAVR. In Dr Leon's opinion, surgical risk is important but clinical (eg, age, frailty, the presence of chronic obstructive pulmonary disease, liver or kidney disease, dementia) and anatomic (eg, heavily calcified aorta, concomitant disease, risk of coronary artery occlusion or rupture) factors must also be considered.

Figure 1. 2017 AHA/ACC TAVR Guidelines



AS, aortic stenosis; AVR, aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Reprinted from Nishimura RA et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e1159-e1195. Copyright ©2017. With permission from the American Heart Association.

Eberhard Grube, MD, Heart Center Bonn, Germany, and Stanford University, School of Medicine, Palo Alto, California, USA, presented unusual complications he encountered during a transcatheter aortic valve implantation (TAVI) procedure. The first involved an undetected ventricular septal defect that led to sudden drop in blood pressure, an increase in wedge pressure, and a decrease in oxygen saturation. The defect was only detected by colour echo. The procedure continued after the defect was patched, but the patient died 10 days later. Lesson learned? Be prepared. Have all the equipment in different sizes and amounts; know the differential diagnosis of hypotension after valvuloplasty; realise that TAVI complications might occur even at remote sites. In the second case, Dr Grube encountered difficulty during catheter placement due to aorta and wire kinking. Three different catheters were needed before success was achieved. Lesson learned? Have various TAVR devices on the shelf.

Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) are the mainstays for diagnosis/quantification and therapy induction, as well as evaluation of complications and success during follow-up. Michel Zuber, MD, Heart Team, University Hospital, Zurich, Switzerland, believes standard TOE guidance in general anaesthesia during TAVI/TAVR will be replaced by a minimalistic approach with sedation without TOE, with equivalent safety and efficacy outcomes in very experienced centres. TTE will then be important for the diagnosis/treatment of intra-procedural emergencies. TOE will continue to be necessary to confirm valve size and for continuous monitoring in patients with renal dysfunction without preintervential computed tomography (CT).

However, guidelines recommend TOE for intraprocedural confirmation of the landing zone morphology and measurements, positioning of the valve, and post-procedural evaluation of complications [Hahn RT et al. *JACC Cardiovasc Imaging*. 2015]; while general practice data supports its value as a protective factor.

On the other hand, a comparison of transfemoral TAVR using sedation/TTE versus intubation/TOE showed TTE with sedation was associated with similar safety and efficacy outcomes as the standard TOE procedure in very experienced centres, but sedation/TTE resulted in shorter hospital stays and intervention times, and significantly lower cost [Babaliaros V et al. *JACC Cardiovasc Interv*. 2014]. Although TAVI may be performed under

angiographic guidance without TOE [Attizzani GE et al. *Am J Cardiol*. 2015] there is no immediate detection of complications without echo [Kronzon I et al. *JACC Cardiovasc Imaging*. 2015].

Joseph F. Maalouf MD, Mayo Clinic, Rochester, Minnesota, USA, shared his checklist of the items to examine before performing a TAVI/TAVR.

Confirming a tri-leaflet atrioventricular morphology and aortic valve annular sizing are at the top of his list. Determining the aortic valve annular dimensions with echocardiography is critical for heart valve placement. CT is the method of choice for measuring aortic valve annular diameter, annular area and perimeter for most patients. Valve undersizing can lead to paravalvular regurgitation and valve embolisation; while oversizing can cause under expansion of the transcatheter valve, annular rupture, conduction disturbances, and reduced valve durability. An optimal approach to ensure a good seal and minimal paravalvular leaking and stable seating of the valve is controlled oversizing [Hahn RT et al. *JACC Cardiovasc Imaging*. 2015].

Next on the checklist is comprehensive evaluation of the entire aortic valve complex landing zone, including the sinus of Valsalva height and diameter; height of the coronary ostia and in particular the left main coronary ostium above the annulus; and the sinotubular junction diameter. Third on the checklist is assessing the extent/asymmetry of the annular/root and outflow tract calcification. Fourth, check for the presence/degree of aortic, mitral, and tricuspid regurgitation, and left/right ventricular function, then for sigmoid septum/basal septal hypertrophy/left ventricular outflow tract obstruction and exclude intracardiac mass/thrombus and pericardial effusion. Finally check access issues such as transapical access and thoracic aorta atheroma.

Samir Kapadia, MD, Cleveland Clinic, Cleveland, Ohio, USA discussed strategies for anticoagulation post-TAVI/TAVR to prevent thrombosis while considering bleeding risk (Table 1).

Table 1. Strategies for Anticoagulation Post-TAVI/TAVR

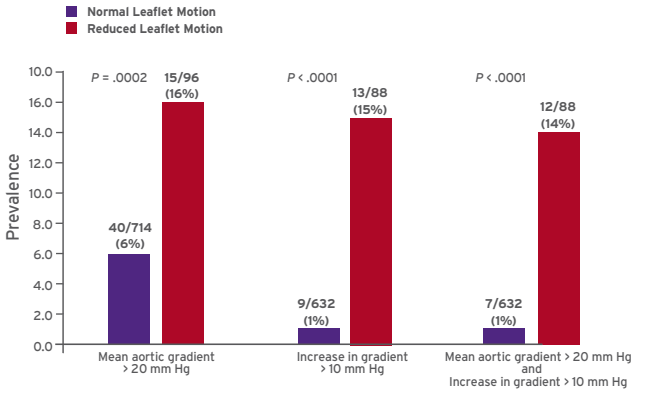
Thrombosis	Bleeding
Patient Factors	
• Low cardiac output • Atrial fibrillation • Small sinuses • Bulky calcifications	• Age • Gender • Renal dysfunction
Device Characteristics	**Pharmacologic Options**
• Annular or supra-annular • Commissural height • "Stent cover" • Radial strength	• ASA • Clopidogrel • Warfarin • NOAC
Procedural Factors	**Other Options**
• Depth of Implantation • Symmetric expansion • Appropriate sizing	• LAA occlusion

ASA, aspirin; LAA, left atrial appendage occlusion; NOAC, non-vitamin K oral anticoagulant.

Post TAVI/TAVR pharmacologic considerations include whether to use single or dual antiplatelet therapy, warfarin or one of the new oral anticoagulants (NOAC), or a combination of antiplatelet and anticoagulation therapy. Given the potential for thrombosis and/or bleeding with anticoagulation, important considerations should include patient characteristics, TAVR device type, the profile of the various pharmacologic agents, and duration of therapy.

Among 890 patients in the RESOLVE and SAVORY Registries subclinical leaflet thrombosis was identified by CT scan in 12% (106/890) of patients with bioprosthetic aortic valves, more commonly in transcatheter 13% (101/752) than in surgical valves 4% (5/138) [Chakravarty T et al. *Lancet*. 2017]. A greater proportion of patients with subclinical leaflet thrombosis had aortic valve gradients > 20 mm Hg and increases in aortic valve gradients > 10 mm Hg than did those with normal leaflet motion (Figure 2). Risk factors for gradient increases include high BMI, valve ≤ 23 mm, valve in valve, and no anticoagulation treatment at discharge [Del Trigo M et al. *J Am Coll Cardiol*. 2016].

Figure 2. Reduced Leaflet Motion and Increased Gradients



Source: Chakravarty T et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383-2392.

The risk of leaflet thickening is associated with regional transcatheter heart valve (THV) stent frame under expansion [Fuchs A et a. *Eurointervention*. 2017]. Post-dilatation of self-expanding THV, as well as a supra-annular valve position seem to reduce the occurrence of this phenomenon. Overexpansion by > 10% of the SAPIEN 3 valve was associated with more thrombus. With the CoreValve Evolut R, the thrombus volume increased linearly with implant depth. A supra-annular neo-sinus may reduce thrombosis risk due to reduced flow stasis [Midha RA et al. *Circulation*. 2017]. Anticoagulation with NOACs or warfarin, but not antiplatelet therapy, reduces leaflet motion and resolves thrombosis, but large randomised studies proving this prospectively are still missing.

Patients on anticoagulants have a 5% higher risk of major bleeding and late bleeding is associated with a

34% greater risk of death [Genereux P et al. *J Am Coll Cardiol*. 2014]. In the ARTE trial, aspirin monotherapy reduced the risk of life-threatening/major bleeding following TAVR with no increase in the risk of stroke or myocardial infarction compared with dual therapy (aspirin plus clopidogrel); however, the size of the trial was small [Rodes-Cabau J et al. *JACC Cardiovasc Interv*. 2017]. Other trials are ongoing.

AF is present in about 30% to 40% of TAVR patients and it confers an increased risk of stroke and bleeding. Treatment choices include LAA occlusion (currently tested in the Watch-TAVR study) and pharmacologic therapy. Until results of reliable randomised studies are available, anticoagulation remains standard therapy in this situation according to current guidelines and available evidence in the absence of contraindications.

Outcomes and Management in Patients With Peripheral Arterial Disease and Cardiac Disease

Written by **Nicola Parry**

Peripheral arterial disease (PAD) and cardiac disease are associated with significant health burdens [Sampson UK et al. *Glob Heart*. 2014; Roth GA et al. *J Am Coll Cardiol*. 2017], and the prevalence of both diseases (polyvascular disease) increases with age. As the population ages the number of patients with these diseases is expected to continue to rise over the coming decades.

In the PAD and Cardiac Disease - A Permanent Cross-Talk symposium on 27 August 2017, several speakers discussed outcomes and management in PAD patients who also have concomitant cardiac diseases, including coronary artery disease (CAD), atrial fibrillation (AF), and heart failure (HF).

Patient Outcomes in PAD Versus MI

Birgitta Sigvant, MD, PhD, Karolinska Institute, Stockholm, Sweden, emphasised that although ischaemic heart disease is the leading cause of death worldwide, PAD is one of the most prevalent cardiovascular (CV) diseases [Roth GA et al. *J Am Coll Cardiol*. 2017; Fowkes FG et al. *Lancet* 2013].

However, the differences in comorbidity, CV outcomes, and mortality have been increasingly appreciated and described in a number of publications. Reporting data from a study that compared these factors among incident myocardial infarction (MI) and PAD patients, Dr Sigvant noted that these 2 patient groups differed at first manifestation of atherosclerotic disease: PAD patients were older (69.3 vs 66.0 years), more likely to be female (45% vs 31%), and had a higher prevalence of conditions such as stroke (10% vs 5%), diabetes (30% vs 22%), and AF (14% vs 7%).

Multiple studies have also shown that PAD patients may be undertreated. Although PAD is associated with high ischaemic risk, patients may be less intensively treated with antiplatelet therapy and statins relative to MI patients (Figure 1; 60% vs 95%).

MI patients had a higher incidence of MI at 6 months than PAD patients (5.5% vs 1.2%); however, the rate of non-CV-related mortality was higher among PAD patients. At 3 months, about 6.6% of MI patients had died of non-CV-related causes, and this was doubled in the PAD population. And at 3 years, about 10% of patients in both groups had died of a CV cause. The cause was related to coronary events in 69% of MI patients and in 43% of PAD patients.

Because PAD patients are less likely to have an MI, risk prevention should extend beyond preventing only coronary ischaemic events, she concluded.

PAD Patients With CAD

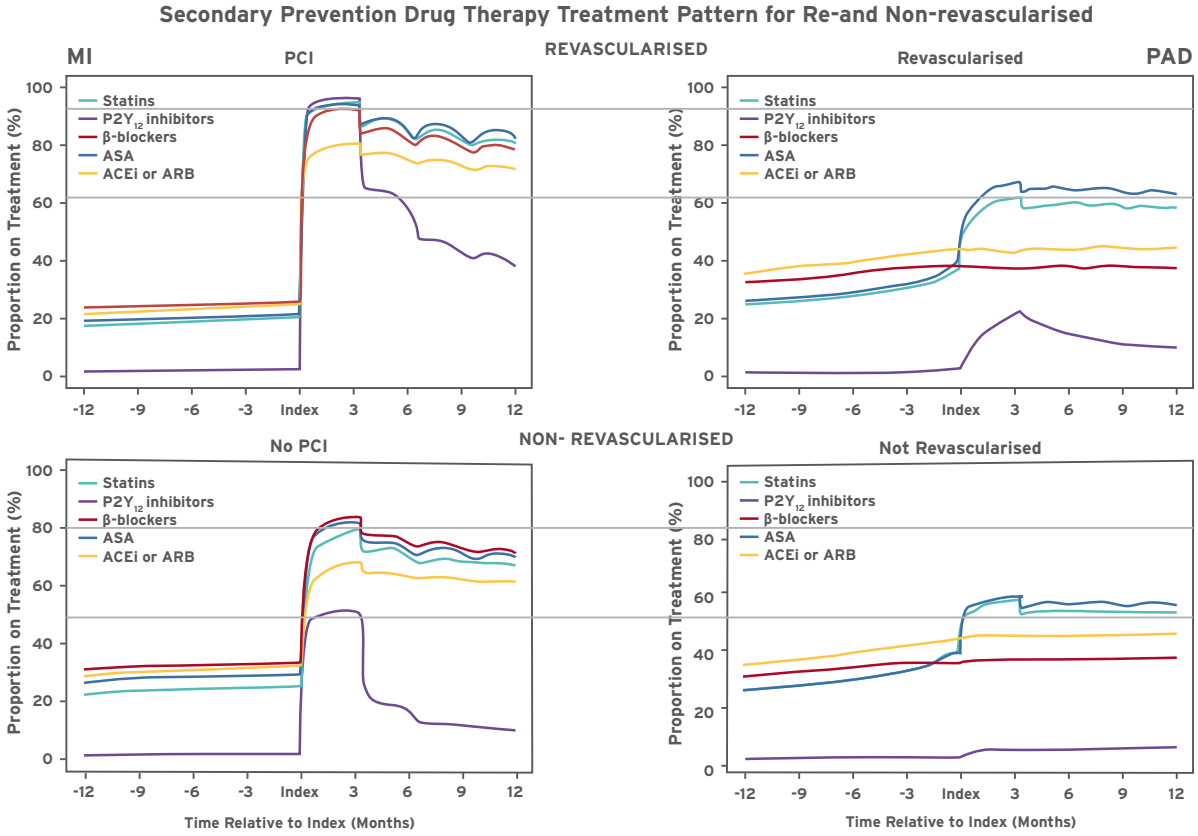
Many PAD patients also have concomitant CAD, said Jeffrey Berger, MD, MS, NYU Langone, New York, New York, USA. And because of their increased risk of incident CV events, intensive secondary prevention strategies are a key treatment focus for patients with both conditions [Bonaca MP et al. *J Am Coll Cardiol*. 2016; Patel A et al. *Eur J Prev Cardiol*. 2015]. He presented data from a subgroup analysis from the EUCLID trial [Berger JS et al. *Am Heart J*. 2016], showing that a history of CAD in patients with symptomatic PAD increases the risk for major adverse cardiac events. After multivariable adjustment, there was a statistically significant increase in the primary outcome (composite of CV death, MI, or ischaemic stroke) in PAD patients with CAD compared with in those without CAD (15.3% vs 8.9%; P = .005). Dr Berger noted that this increase was driven by the endpoint of MI, where patients with concomitant CAD and PAD were more than 2-fold likely to develop an MI than those with PAD alone. However, there was no significant difference between the 2 groups with respect to the rates of ischaemic stroke, CV death, acute limb ischaemia, TIMI major bleeding, or intracranial bleeding.

The study also showed that monotherapy with ticagrelor does not reduce the composite endpoint of CV and acute limb events when compared with clopidogrel (15.4% vs 15.3%; P = .84). And there were no significant differences between the treatment groups with respect to safety endpoints of TIMI major bleeding or TIMI minor bleeding.

PAD Patients With AF

Prof Christine Espinola-Klein, University Medical Center, Mainz, Germany, discussed the frequent co-prevalence of PAD and AF in older patients. And Antonios Vitalis, MD, University of Birmingham, Birmingham, United Kingdom, presented data from the AFFIRM study which investigated the prevalence of PAD in AF patients and associated outcomes [Vitalis A et al. *Eur Heart J*. 2017].

Figure 1. Patients With PAD Are Undertreated



Significantly higher use of guideline-recommended secondary preventive drugs among MI patients invasively treated

ACEi, angiotensin-converting enzyme inhibitor; ASA, acetyl salicylic acid; ARB, angiotensin II receptor blocker; MI, myocardial infarction; PAD, peripheral arterial disease; $P2Y_{12}$, receptor involved in the activation of the glycoprotein IIb/IIIa receptor.

Reproduced with permission from B Sigvant, MD, PhD.

Among 4,060 patients in the AFFIRM study, 282 (6.7%) had a history of PAD. Compared with patients without PAD, those with PAD were slightly older (median age 72 vs 71 years), more likely to be male (65.2% vs 60.4%), and had a worse risk-factor profile including a higher prevalence of hypertension, diabetes, and smoking. They were also more likely to have a previous history of CAD, MI, congestive HF, stroke, or CV intervention.

Patients with PAD also had worse outcomes, having higher rates of death (29.4% vs 15.4%; $P < .01$), CV death (16.0% vs 7.6%; $P < .01$), and stroke or death (31.2% vs 18.1%; $P < .01$).

Multivariate analysis also showed that PAD is an independent predictor for death (HR, 1.41; 95% CI, 1.11 to 1.79; $P < .01$), CV death (HR, 1.45; 95% CI, 1.05 to 2.01; $P = .02$), and stroke or death (HR, 1.31; 95% CI, 1.04 to 1.64; $P = .02$).

Given the high risk associated with PAD in AF patients, Dr Vitalis highlighted the importance of identifying PAD and implementing secondary prevention measures against adverse outcomes.

Patients with AF and PAD are at higher risk for bleeding complications, and Prof Espinola-Klein emphasised that current guidelines recommend oral anticoagulation in those with a CHA_2DS_2-VASc score of ≥ 2 or greater (I A); consideration of oral anticoagulation in all other patients (IIa B); and consideration of oral anticoagulation alone in patients with PAD who have an indication for oral anticoagulation (IIa B) [Aboyans V et al. *Eur Heart J*. 2017].

PAD and Heart Failure

According to Serge Kownator, MD, Cardiology Center, Thionville, France, HF patients with PAD have a worse overall prognosis than those without PAD, and have significantly increased rates of all-cause mortality, CV mortality, and hospitalisation for HF [Wei B et al. *Heart Lung Circ*. 2016].

Because up to one-third of patients with symptomatic PAD have reduced left ventricular ejection fraction (LVEF), Dr Kownator advised that assessment of LVEF function in PAD patients may help clinicians to identify and better manage individuals with unknown CAD, allowing improved risk stratification for future CV events and comprehensive management of CV disease. Because physical limitation in HF can mask symptoms in patients with PAD, the ankle-brachial test may also be helpful in

these individuals.

The recently published ESC guidelines on the diagnosis and treatment of PAD also indicate that clinicians should perform complete vascular evaluation in all patients being considered for heart transplantation or cardiac assist device implantation (I C) [Aboyans V, Ricco JB et al. *Eur Heart J*. 2017]. The guidelines also recommend that clinicians should consider screening for HF with a transthoracic echocardiogram and/or natriuretic peptides assessment in patients with symptomatic PAD (IIa C). Clinicians should also consider screening for PAD in patients with HF (IIb C), and should test for renal artery disease in patients with flash pulmonary oedema (IIb C).

Updated Guidelines Focus on Dual Antiplatelet Therapy in Coronary Artery Disease

Written by **Brian Hoyle**

The European Society of Cardiology (ESC) guideline update on dual antiplatelet therapy (DAPT) in patients with coronary artery disease (CAD) reflects the burgeoning use of aspirin in combination with $P2Y_{12}$ antagonists. Advances have been made with drugs (prasugrel, ticagrelor) that have more predictable antiplatelet effect and the completion of studies that have focused on the optimal duration of DAPT. New drug-eluting stents have lowered concerns of stent thrombosis allowing shorter DAPT duration and recent trials have demonstrated that patients treated with prolonged DAPT have lower long-term risk of ischaemic events. This focused update , presented at the ESC Guidelines 2017 - Focused Update on Dual Antiplatelet Therapy session on 27 August, was designed to provide clinicians with guidance on the use of dual anti-platelet therapy.

Risk Stratification Tools

This update introduced the DAPT and the PRECISE DAPT scoring systems [Costa F et al. *Lancet*. 2017; Yeh RW et al. *JAMA*. 2016] to provide an assessment of the risk of ischaemic and bleeding events to help clinicians guide clinical decision making (IIa A). These scores allow providers to quantify both the risk of ischaemic and bleeding events (Figure 1).

$P2Y_{12}$ Choice, Time of Initiation, and Duration

Acute Coronary Syndrome (ACS)

The TRITON-TIMI 38 [Wiviott SD et al. *N Engl J Med*. 2007] and PLATO trials [Wallentin L et al. *N Engl J Med*. 2009], demonstrated the superiority of prasugrel and ticagrelor over clopidogrel in the treatment of patients with ACS. The focused update recommends the use of ticagrelor or prasugrel over clopidogrel in patients with ACS (Table 1).

Table 1. Recommendations for DAPT in ACS

Recommendations	Class	Level
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pretreated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications.	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose. 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterisation unless there is a high risk of life-threatening bleeding or other contraindications.	I	B

ACS, acute coronary syndrome; NSTE, non-ST elevation; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

The guidelines also address the issue of pretreatment with $P2Y_{12}$ inhibitors. In the ACCOAST trial, pretreatment with prasugrel did not reduce cardiovascular (CV) events and increased the 30-day risk of TIMI major bleeding in patients with non-STEMI [Montalescot G et al. *N Engl J Med*. 2013]. The ATLANTIC trial randomised patients with STEMI to either pre-hospital or in-hospital loading with ticagrelor. Pretreatment with ticagrelor did not increase the resolution of ST-segment elevation before PCI when compared with in-hospital loading. However, the rates of definite stent thrombosis were lower in the patients randomised to pre-hospital ticagrelor (P = .02 at 30 days). Rates of major bleeding events were similar in the 2 groups [Montalescot G et al. *N Engl J Med*. 2014]. The updated guidelines have several new recommendations concerning $P2Y_{12}$ choice and pretreatment including a recommendation for the pretreatment of patients with STEMI who are undergoing PCI and pretreatment with ticagrelor in those patients with NSTEMI undergoing invasive management (Table 2).

Table 2. Pretreatment Recommendations Concerning DAPT Type and Duration in ACS Patients

Recommendations	Class	Level
Pretreatment with a $P2Y_{12}$ inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI.	I	A NEW
In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg BID), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C NEW
In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel.	III	B

NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

The DAPT trial randomised patients who were, still on DAPT 12 months after placement of a DES, and had not suffered an ischaemic or bleeding event, to either continued thienopyridine therapy or placebo. Aspirin was maintained throughout the study period in both groups.

Patients randomised to long-term DAPT had lower rates of stent thrombosis (0.4% vs 1.4%; *P* < .001) and CV events (4.3% vs 5.9%; *P* < .001). The reduction in ischaemic events was counterbalanced by an increase in GUSTO moderate/severe bleeding (2.5% vs 1.6%; *P* < .001) and an increase in total mortality. Similarly, in the PEGASUS-TIMI 54 trial [Bonaca MP et al. *N Engl J Med*. 2015] patients 1-3 years following an MI had lower rates CV death, MI, or stroke when randomised to long-term therapy with aspirin and ticagrelor compared with aspirin alone. TIMI major bleeding was increased with prolonged DAPT, but there were no differences in fatal bleeding or intracranial haemorrhage (*P* = .43 and *P* = .47 for 90 and 60 mg ticagrelor, respectively). A recent meta-analysis of 6 randomised controlled trials involving over 33,000 patients with prior MI reported a reduction of ischaemic events with extended DAPT compared with aspirin alone (6.4% vs 7.5%; *P* = .001) at the cost of increased major bleeding (1.85% vs 1.09; *P* = .004), but not fatal bleeding (0.14% vs 0.17%; *P* = .75). There was no increase in non-CV death in patients with prolonged DAPT (RR 1.03; 95% CI, 0.86-1.23; *P* = .76) [Udell JA et al. *Eur Heart J*. 2016].

The new ESC guidelines recommend duration of DAPT be tailored based upon the risk of bleeding and ischaemic events. If bleeding is not a concern, DAPT can be maintained for 1 year or longer. In particular, the guidelines recommend ticagrelor 60 mg twice daily in those patients who are > 12 months following ACS and are being treated with prolonged DAPT. Prasugrel has not been to shown to improve outcomes in patients with ACS who are medically managed (Table 3).

Table 3. Recommendations for DAPT After PCI

Recommendations	Class	Level
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (eg, PRECISE-DAPT ≥ 25).	I	A UPDATED
In patients with ACS and stent implantation who are at high risk of bleeding (eg, PRECISE-DAPT ≥ 25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	B NEW
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.	IIb	A NEW
In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg BID for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.	IIb	B UPDATED

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; MI, myocardial infarction.

Stable CAD

Clopidogrel remains the $P2Y_{12}$ inhibitor of choice in patients with stable CAD. DAPT with ticagrelor or prasugrel in addition to aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI (IIb C). Pretreatment with clopidogrel can be considered for patients with stable CAD if the probability of PCI is high (IIb C). The updated guidelines have identified features that increase the risk of recurring ischaemic events due to the presence of a stent (Table 4).

The updated guidelines reflect the movement away from prevention of stent-related thrombosis to reducing ischaemic events. In patients with prior PCI, DAPT with aspirin and clopidogrel is generally recommended for 12 months, regardless of stent type (I A). Data from

Figure 1. Risk Scores Validated for DAPT Duration

	PRECISE-DAPT Score	DAPT Score
Time of use	**At the time of coronary stenting**	**After 12 months of uneventful DAPT**
DAPT duration strategies assessed	Short DAPT (3-6 months) vs Standard/long DAPT (12-14 months)	Short DAPT (12 months) vs Standard/long DAPT (30 months)
Score calculation	HB: ≥12 11-5 11 10-5 ≤10 WBC: ≥5 8 10 12 14 16 18 ≥20 Age: ≤50 60 70 80 ≥90 CrCl: ≥100 80 60 40 20 0 Prior bleeding: No / Yes Score points: 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	Age ≥ 75: -2 pt 65 to < 75: -1 pt < 65: 0 pt Cigarette smoking: + 1 pt Diabetes mellitus: + 1 pt MI at presentation: + 1 pt Prior PCI or prior MI: + 1 pt Paclitaxel-eluting stent: + 1 pt Stent diameter < 3 mm: + 1 pt CHF or LVEF < 30 %: + 2 pt Vein graft stent: + 2 pt
Score range	0 to 10 points	-2 to 10 points
Decision making cut-off suggested	Score ≥ 25 → Short DAPT Score < 25 → Standard/long DAPT	Score ≥ 2 → Long DAPT Score < 2 → Standard DAPT
Calculator	www.precisedaptscore.com	https://qxmd.com/calculate/calculator_373/dapt-score

CHF, congestive heart failure; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; HB, haemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; WBC, white blood cell count.

Table 4. High-Risk Features of Stent-Driven Recurrent Ischaemic Events

Prior stent thrombosis on adequate antiplatelet therapy.
Stenting of the last remaining patent coronary artery.
Diffuse multivessel disease especially in diabetic patients.
Chronic kidney disease (ie, creatinine clearance < 60 mL/min).
At least three stents implanted.
At least three lesions treated.
Bifurcation with two stents implanted.
Total stent length > 60 mm.
Treatment of a chronic total occlusion.

small trials (RESET [Kim BK et al. *J Am Coll Cardiol*. 2012]; OPTIMIZE [Feres F et al. *JAMA . 2013]*) support a shorter DAPT period of 3 months in stable CAD patients at high risk of bleeding (IIa B). If the 3-month regimen has safety concerns for patients receiving drug-eluting stents, the findings of the ZEUS [Valgigli M et al. *Am Heart J*. 2013] and LEADERS FREE [Urban P et al. *N Engl J Med*. 2015] trials indicate that a 1-month DAPT could be considered (IIb C).

Switching of Therapy

In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel unless contraindications to ticagrelor exist (I B). Contraindications to ticagrelor include prior intracranial haemorrhage or continuing bleeding events. Further switching between oral $P2Y_{12}$ inhibitors may be considered in cases of drug intolerance or drug-related side effects (IIb C).

Oral Anticoagulation (OAC) Patients

Of all the DAPT studies done over the past 2 decades, only 3 have addressed the duration of DAPT in patients receiving OAC therapy. Decisions concerning DAPT for OAC patients need to be done on a case-by-case basis, considering the higher risk of clinically significant bleeding during DAPT and with the knowledge that these patients have an unfavourable patient profile compared with those not requiring OAC therapy, including shorter life expectancy, poor expected adherence to treatment, advanced age, end-stage renal failure, history of major bleeding/haemorrhagic stroke, and anaemia [Valgimigli M et al. *Eur Heart J*. 2017].

The decision to treat needs to first consider the nature of the concern—ischaemic risk or bleeding risk. The prevailing concern will dictate whether triple therapy with aspirin, clopidogrel, and OAC is continued after the first month for up to 6 months and followed by dual aspirin/OAC or clopidogrel/OAC therapy (ischaemic risk), or whether the triple therapy is replaced at 1 month by the dual therapy that is continued for up to 12 months (bleeding risk).

In the PIONEER AF-PCI trial [Gibson CM. *N Engl J Med*. 2016], clinically significant bleeding was less frequent for participants with atrial fibrillation (AF) undergoing PCI with placement of stents treated with low-dose rivaroxaban plus a $P2Y_{12}$ inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months, compared with standard therapy with a vitamin K antagonist plus DAPT.

Patients Undergoing Surgery

The final portion of the updated guidelines considers the type, duration, and management of DAPT in patients undergoing surgery. For cardiac surgery patients, decisions need to consider the patient's status, coronary anatomy, and when it is safe to resume DAPT for the surgery. Reflecting this complexity, the updated guidelines have 8 recommendations based on patient status.

Patients requiring nonemergent cardiac surgery can continue aspirin at a low daily dose, given the meta-analysis evidence of aspirin's benefit in lessening subsequent MI [Hastings S et al. *Brit J Anaesth*. 2015]. For patients receiving $P2Y_{12}$ inhibitors who require nonemergent surgery, the procedure should be delayed for at least 3, 5, and 7 days after stopping ticagrelor, clopidogrel, and prasugrel, respectively (IIa B).

No studies have addressed the resumption of DAPT after cardiac surgery. Evidence gleaned from a meta-analyses, subgroup analyses of larger ACS trials, and observational studies suggests that DAPT can be resumed as soon as it is judged safe to do so. The optimal timing to resume DAPT is unclear, but 24-96 hours after CABG is reasonable, with a shorter time for following stent implantation and a longer time if AF is a concern. Once treatment is resumed, the length of treatment is standard.

The recommendations for noncardiac surgery patients are fairly similar with 2 exceptions. DAPT should not be discontinued within the first month of treatment (III B). Secondly, following implantation of a coronary stent, elective surgery that necessitates the discontinuation of $P2Y_{12}$ inhibitor should not be done until after 1 month (IIa B).

DAPT is not utilised only to reduce the risk of stent thrombosis, but rather to reduce all CV events in patients with CAD. Decisions regarding the use of DAPT (indication, time of initiation, therapy choice, interruptions, duration) are complex and multiple factors need to be taken into account, including clinical setting, treatment modality for ACS/CAD, devices, bleeding risk, and concomitant therapies.