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PEER-REVIEWED CONFERENCE REPORT

Catheter versus Surgery

Five years post-surgery the transcatheter and surgical aortic valve replacement intervention groups still did not differ in outcomes.

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Benefit of Statin Therapy

Loading doses of statins may be a great strategy in ACS patients with high likelihood of PCI, specifically those with STEMI.

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Anticoagulant Antidote

The first interim safety data on an antidote of factor Xa inhibitors show excellent or good haemostatis in the majority of patients.

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Editor Prof. Marc Peter Bonaca, Harvard Medical School, MA, USA

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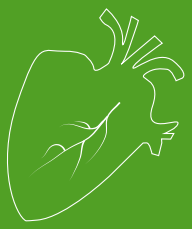

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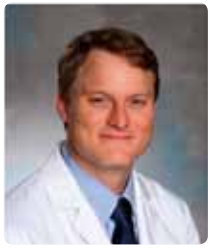


Prof. Marc Peter Bonaca

Marc P. Bonaca, MD, MPH

Marc P. Bonaca, MD, MPH is an Associate Physician in Cardiovascular Medicine at Brigham and Women's Hospital, an Assistant Professor of Medicine at Harvard Medical School and an investigator at the TIMI Study Group. Dr. Bonaca earned his medical degree (M.D.) from University of Connecticut School of Medicine and a Master of Public Health (M.P.H.) from the Harvard School of Public Health. He completed his internal medicine residency, fellowship in cardiovascular medicine and fellowship in vascular medicine at Brigham and Women's Hospital and is board certified in internal medicine and cardiology.

Dr. Bonaca's research interests include characterization and prediction of cardiovascular risk in patients with atherosclerotic vascular disease as well as investigation of therapies to reduce that risk. Specific disease states of interest include peripheral artery disease, stable coronary artery disease, and aortic disease. He is an active investigator in clinical trials investigating novel therapies including antithrombotic agents for the reduction of cardiovascular risk in patients with symptomatic peripheral artery disease and stable coronary disease. In addition, he is actively involved in the evaluation of established and novel biomarkers as well as clinical characteristics for risk prediction in specific patient populations. In addition to scientific investigation and clinical trial work, Dr. Bonaca leads the TIMI Safety Desk which includes 20 staff members and which is responsible for the monitoring and processing of safety data for multiple large international clinical trials. In addition to his scientific, clinical trial, and safety responsibilities, Dr. Bonaca is an active member of the clinical staff at Brigham and Women's hospital and attends on the inpatient cardiology and cardiology/vascular medicine consult services. He maintains a regular clinic and is the Medical Director of the the Brigham and Women's Aortic Center.

Devices – Advances in Understanding What, When and in Whom

The use of a wearable cardioverter-defibrillator (WCD) during the first 90 days after a myocardial infarction (MI) reduces all-cause mortality. However, it does not reduce the risk of sudden cardiac death within these 90 days among patients with reduced left ventricular ejection fraction (LVEF ≤35%) immediately post-MI compared with controls. Although the VEST study is an open-label trial with a negative primary endpoint, the presenter Jeffrey Olgin finds it reasonable, based on the observed decrease in all-cause mortality, to consider the use of WCD in appropriate patients—for example with cardiac arrest, severe left ventricular dysfunction, and non-sustained ventricular tachycardia [1]. Five years after a transcatheter or surgical aortic valve replacement (TAVR and SAVR, respectively), there are no differences in all-cause mortality, stroke or MI in low-risk patients with severe degenerative aortic stenosis aged ≥70 years. This emerged from an analysis of the first study in which the outcomes were evaluated five years after a TAVR and SAVR in patients with a low surgical risk [2]. Long-term right ventricular pacing (RVP) is associated with heart failure and an increased risk of death. His bundle pacing (HBP) is a physiological alternative to RVP. In a large real-world population study—the outcomes of which were presented during the ACC18 congress and published simultaneously in *Journal of the American College of Cardiology* (JACC) [3]—HBP was shown to be a feasible and safe intervention in this category of patients. In addition, its association with death, hospitalisations due to heart failure and upgrades to biventricular pacing (BiVP) was significantly less frequent. There are few effective treatment options for patients who have advanced heart failure and require advanced mechanical support. The MOMENTUM 3 – Long-Term Outcomes study demonstrated that magnetically-levitated, centrifugal-flow left ventricular assist systems (LVAD) are superior in preventing pump thrombosis, the need for reoperation to replace a malfunctioning device, and disabling stroke in patients than an axial LVAD. This difference was irrespective of the intended goal of bridging to transplant or destination therapy. The results appeared in the *New England Journal of Medicine* at the same with as the ACC18 meeting [4].

VEST: wearable defibrillator post-MI

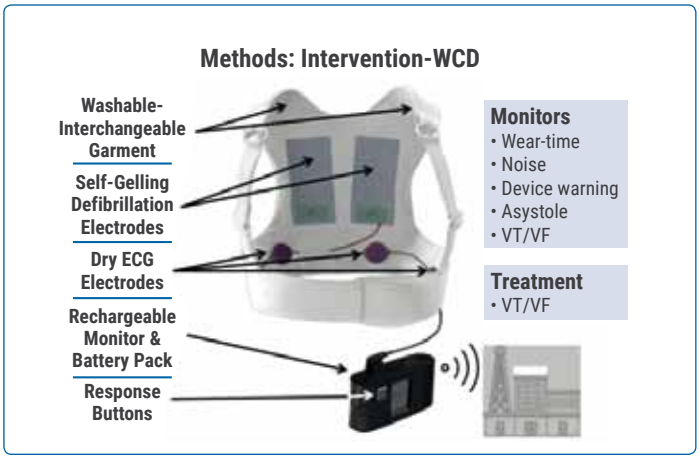
An implantable cardioverter-defibrillator (ICD) is not indicated in the immediate post-MI period, because some early mortality is not due to arrhythmia and is thus not preventable by ICD. LVEF may recover during the three months post-MI. The multi-centre, randomised, open-label VEST study evaluated whether a WCD (Figure 1) could reduce the risk of sudden cardiac death during the first 90 days post-MI in patients with reduced LVEF, as a bridge to evaluation for ICD. Disconnection could be requested if the participant had a shock, cardiac arrest, or syncope.

A total of 2,302 post-MI patients with moderate to severe LV dysfunction (LVEF of ≤35%) received or did not receive WCD within seven days of discharge from hospital, in addition to the optimal medical therapy. The primary endpoint was sudden cardiac death and death due to ventricular arrhythmias. The average follow-up time was 84.3 days. Of the 1,524 patients assigned to the WCD group, 1,481 received this device; however, 19% of them never used it. While, at the beginning of the study, about 80% of the patients in the WCD group wore the WCD, this dropped to around 45% on Day 90. Of the patients in the control group, 20 received a WCD, although this contradicted the protocol [1].

Differences in mortality rate?

Rates of the primary endpoint (sudden cardiac death) were numerically lower, but differences were not statistically significant between the WCD and control group (1.6% vs.

Figure 1. Intervention-WCD [1]



2.4%, P=0.18, Figure 2). Total mortality was lower (3.1%) in the WCD group than in the control group (4.9%). Similarly, the occurrence of overall non-sudden death, a secondary endpoint showed a trend towards lower rates with WCD than control (1.4% vs. 2.2%, P=0.15). However, stroke-related mortality was significantly lower in the WCD group in comparison with the control group (0.0% vs. 0.5%, P=0.01). A striking finding was that patients in the WCD group were less often dyspnoeic than those in the control group (38.7% vs. 45.4%) [1].

First RCT evaluating a WCD

VEST is the first randomised controlled trial to evaluate WCD. The use of this device did not reduce the risk of sudden cardiac death up to 90 days post-MI in patients with moderate to severe LV dysfunction. However, WCD use was associated with a significant decrease in all-cause mortality during this time frame. Unfortunately, the cross-over rate was quite high (around 20%) and compliance with the use of the WCD decreased over time [1]. Further research about the cost-effectiveness of this strategy and methods to risk-stratify the patients most likely to benefit from WCD use—such as those presenting with cardiac arrest, severe LV dysfunction, or non-sustained ventricular tachycardia—are needed.

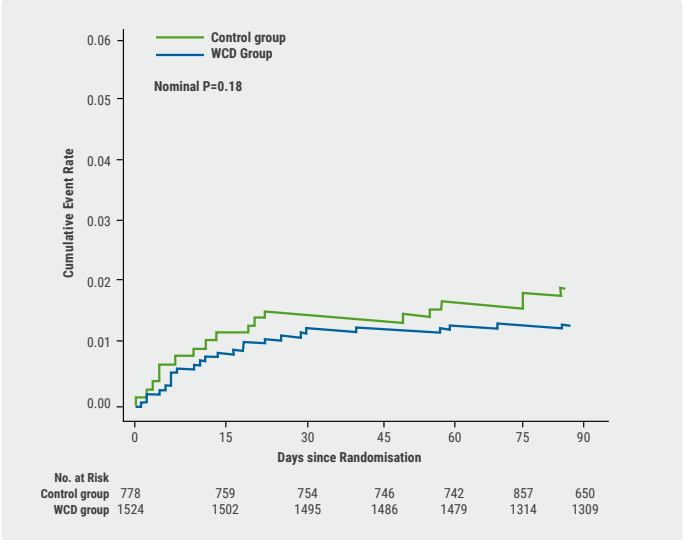
NOTION: catheter versus surgery

The NOTION study compared the primary composite outcome of all-cause mortality, stroke and MI five years after TAVR or SAVR placement in 280 patients aged ≥70 years with a life expectancy of >1 year (mean age 79.1 years, 47% female, and 10% diabetics). The relevant cardiopulmonary patient characteristics of the study population included:

- New York Heart Association (NYHA) class II/III symptoms (93%)
- Society of Thoracic Surgeons (STS) predicted risk of mortality score 3.0 (81.8% with STS score <3%), Logistic EuroSCORE: 8.6
- Peripheral arterial disease: 6%
- Chronic lung disease: 12%
- Pre-existing pacemaker: 4%

The patients underwent either TAVR (n=145) or SAVR (n=135). Patients in the TAVR group received the first-generation CoreValve self-expanding prosthesis. Transfemoral access was performed in 96.5% of the patients. Cross-over to SAVR was 2.1%. Nearly 89% received either a 26 or 29 mm prosthesis. All SAVR patients received a bioprosthetic valve [2].

Figure 2. Sudden and ventricular tachyarrhythmia death



Comparable mortality

The primary outcome—a composite of all-cause mortality, MI, and stroke—occurred in 13.1% of the TAVR group vs. 16.3% in the SAVR group after a one-year follow-up (P=0.43). The one-year mortality rates, which were published in 2015 [5], were 4.9% vs.7.5%, respectively (P=0.38).

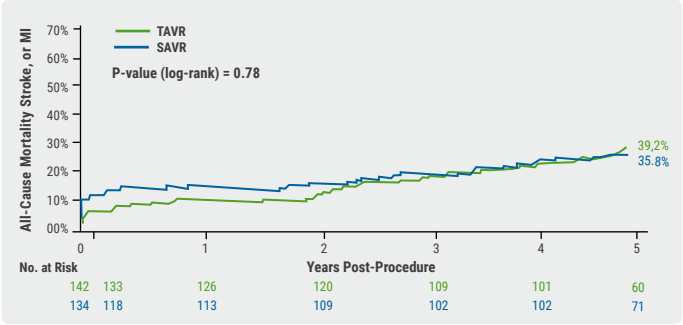
Secondary outcomes 30 days and one year, and all outcomes five years after the intervention, are shown in Table 1.

Five years after the interventions, outcomes did not significantly differ between the two intervention groups. For example, the primary endpoint occurred in 39.2% in the TAVR group and 35.8% in the SAVR group (Table 1 and Figure 3). In contrast, the percentage of patients with a pacemaker implantation, aortic valve reintervention and effective orifice area were all significantly higher in TAVR- than SAVR-treated patients.

Table 1. Secondary outcomes at 30 days and 1 year: NOTION study [2]

Secondary outcomes at 30 days			
Outcomes	**TAVR**	**SAVR**	**P-value**
Major vascular complications	5.6%	1.5%	0.10
Cerebrovascular accident	2.8%	3.0%	0.94
Cardiogenic shock	4.2%	10.4%	0.05
Major, life-threatening, or disabling bleeding	11.3%	20.9%	0.03
New onset or worsening atrial fibrillation	16.9%	57.8%	<0.0001
Permanent pacemaker implantation	34.1%	1.6%	<0.001
Secondary outcomes at one year			
Outcomes	**TAVR**	**SAVR**	**P-value**
Moderate to severe aortic regurgitation	15.7%	0.9%	<0.001
NYHA class II symptoms	29.5%	15.0%	0.01
Outcomes at five years			
Outcomes	**TAVR**	**SAVR**	**P-value**
Primary endpoint	39.2%	35.8%	0.78
All-cause mortality	27.7%	27.7%	0.9
Stroke	10.5%	8.2%	0.67
Endocarditis	11.3%	5.8%	0.10
Pacemaker	41.8%	8.4%	<0.001
Aortic valve reintervention	2.5%	0%	0.09
Effective orifice area	1.66 cm^2	1.23 cm^2	<0.001

Figure 3. All-cause mortality, stroke, or MI after five years [2]



In patients with a low surgical risk (STS score of <4%), the primary endpoint occurred in 31.5% in the TAVR group and in 35.2% in the SAVR group. A higher proportion of patients who were implanted with a new permanent pacemaker during the TAVR died within the first five years after the intervention in comparison with those who underwent surgery (38.2% vs. 21.7%). In comparison with absent or mild aortic regurgitation, the presence of moderate or severe aortic regurgitation three months after surgery was associated with a higher all-cause mortality (22.2% vs. 30.8%).

Other variables associated with higher all-cause mortality include:

- age of ≥75 years;
- male gender;
- body mass index (BMI) of ≤30 kg/m^2; and
- STS of ≥4%.

Discussion

The results of this trial indicate that, among patients with severe degenerative aortic stenosis and mostly with low STS predicted risk of mortality scores, TAVR results were similar in one-year clinical outcomes to those of SAVR. While SAVR resulted in more bleeding events and atrial fibrillation (AF), a higher percentage of TAVR-treated patients had aortic regurgitation, less symptomatic benefit, and more need for a permanent pacemaker. At 5 years, rates of death, MI, and stroke were comparable between TAVR- and SAVR-treated patients. However, in patients with STS ≥4, the results seemed to favour SAVR. The latter observation is contrary to the results of two trials evaluating TAVR in intermediate-risk patients—Placement of Aortic Transcatheter Valve (PARTNER) 2A [6] and SURTAVI—and may be a chance finding. Because nearly 80% of screened patients in the NOTION trial were excluded, the overall generalisability is unclear. Hans Gustav Hørsted Thyregod, who presented these results of the NOTION study, considered a longer follow-up necessary in order to determine the lifespan of the valve after a TAVR [2].

His bundle pacing versus right ventricular pacing

Chronic RVP is associated with an increased risk of LV dysfunction, which is secondary to electrical and mechanical dyssynchrony. Furthermore, RVP is associated with heart failure and increased mortality. Recent studies suggest that only 20% of ventricular pacings lead to hospitalisation due to heart failure. His bundle pacing (HBP) is a physiological alternative to RVP. HBP induces depolarisation of the ventricles through the His-Purkinje system, leading to normal synchronous activation of the ventricles, thus preventing ventricular dyssynchrony.

This non-randomised retrospective observational cohort study aimed to:

- Determine the feasibility and safety of permanent HBP in patients requiring permanent pacemaker implantation; and
- Compare the clinical outcomes of HBP and RVP in all-cause mortality, first episode of hospitalisation due to heart failure, and upgrades to biventricular pacing (BiVP).

All patients for whom a first pacemaker implantation was needed in the period 2013–2016 were included. Permanent HBP was performed in one hospital and RVP in another in consecutive patients [3].

Results

HBP was performed in 332 consecutive patients and RVP in 433 patients. HBP was successful in 92% of consecutive patients. The primary endpoint—a composite of death, hospitalisation due to heart failure, or an upgrade to BiVP—occurred significantly less often in the HBP than in the RVP group: 25% vs. 32%, respectively (HR 0.71, P=0.02, Figure 4). This difference was predominantly present in patients with ventricular pacing of >20% (25% in HBP vs. 36% in RVP, HR 0.65, P=0.02). Secondary endpoints were hospitalisation due to heart failure, and mortality. The incidence of hospitalisation due to heart failure was significantly lower with HBP than with RVP (12.4 vs. 17.6%, HR 0.63, P=0.02). Furthermore, there was a trend towards reduced mortality in HBP (17.2 vs. 21.4%, P=0.06) [3].

Figure 4. Primary endpoint: a composite of death, hospitalisations due to heart failure, or an upgrade to BiVP [3]

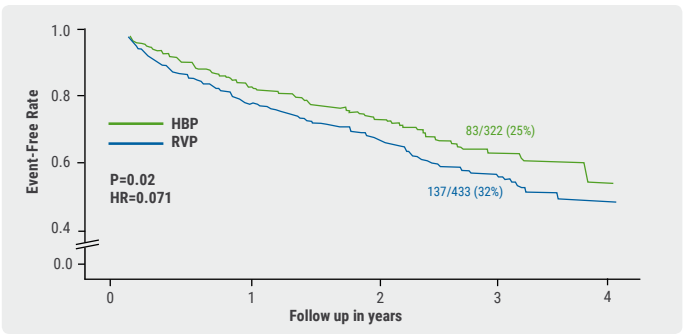
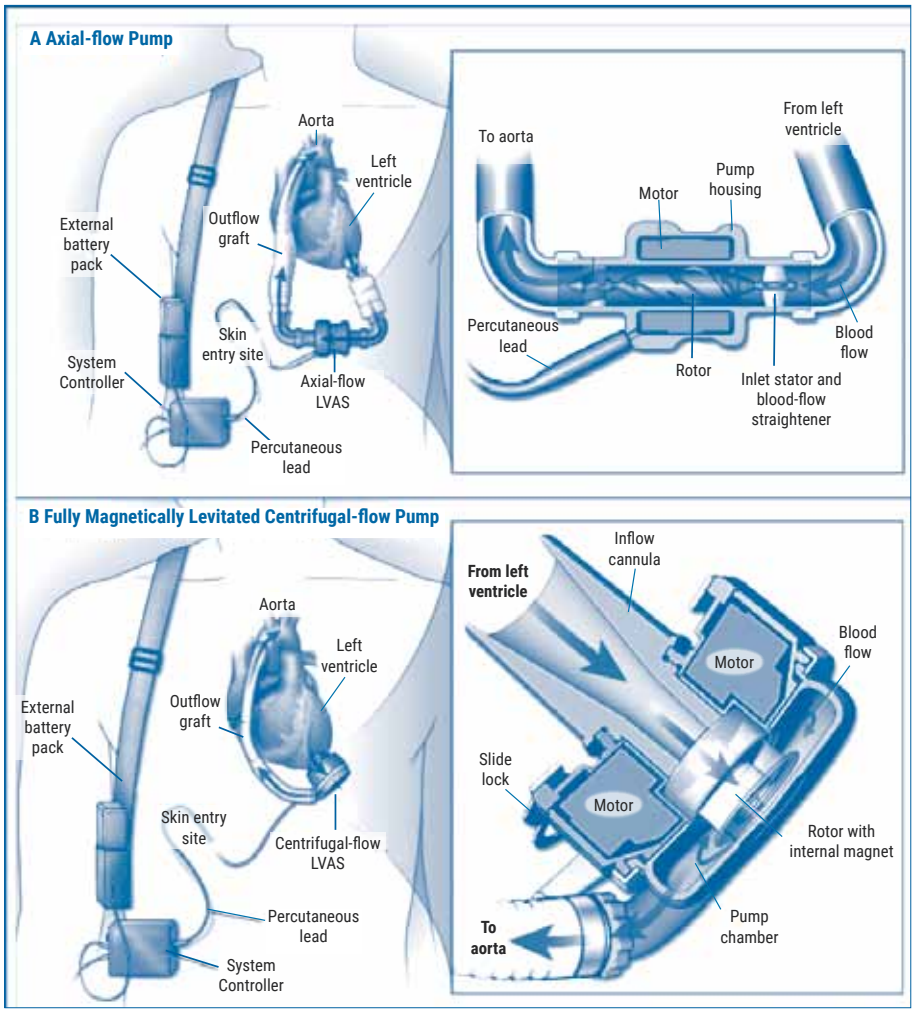


Figure 5. Axial-flow (A) and centrifugal-flow (B) pump [4]



Restrictions and conclusions

This study has some limitations. Firstly, it was non-randomised. In addition, there may have been selection bias due to possible differences in clinical practice at the two attending hospitals. Finally, the majority of HBP interventions were carried out by electrophysiologists with extensive experience. In summary, this large real-world study showed that, in a population requiring permanent pacemakers, permanent HBP was associated with significantly less-frequent occurrence of the combined endpoint of death, hospitalisations due to heart failure, or upgrade to BiVP compared to RVP [3].

MOMENTUM 3: fewer pump failures and thromboses

Left ventricular assist devices (LVAD) improve the survival rate and quality of life of patients with advanced heart failure. However, these devices have several limitations, including increased risk of infections, bleeding and neurological events, and pump failures, mainly due to pump thrombosis. The centrifugal-flow pump contains wide blood passages to reduce shear stress, no mechanical bearings to reduce friction, and intrinsic pulse to prevent thrombosis. These characteristics are aimed at preventing disabling stroke or reoperation to replace or remove a malfunctioning device (Figure 5B).

Less strokes or reoperations

In this trial, 294 patients with advanced heart failure (median age 61 years, 21% women) requiring mechanical support, were randomised to either:

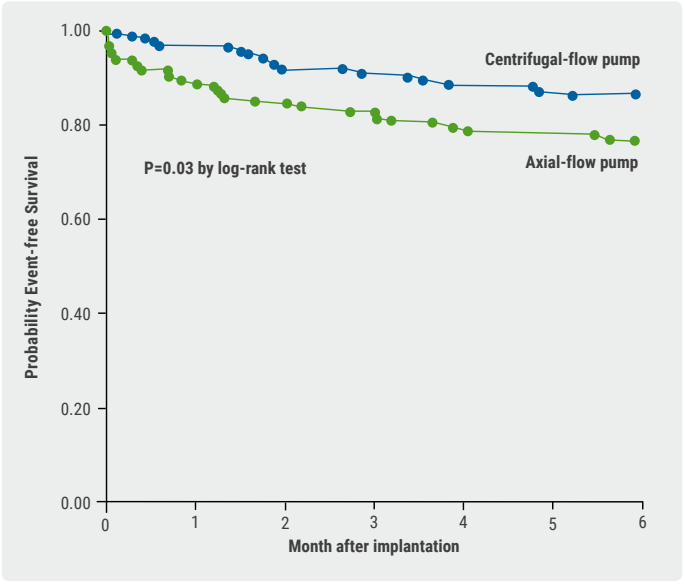
- Magnetically levitated HeartMate 3 centrifugal-flow LVAD (n190); or
- Heartmate II axial-flow LVAD (n=176).

Patients with planned biventricular support, irreversibly of the presence of end-organ dysfunction or active infection, were excluded from participation in this study [4].

The primary endpoint—survival free from disabling strokes or reoperations to replace or remove a malfunctioning device after six months—occurred in:

- 86.2% in the group with centrifugal-flow LVAD; and
- 76.8% in the group with the axial-flow pump (P<0.001 for non-inferiority, P=0.04 for superiority; Figure 6).

Figure 6. Kaplan–Meier estimates of event-free survival in the intention-to-treat population [4]



The secondary outcomes were also significantly different between the two groups (Table 2).

Table 2. Secondary outcomes at six months when treated with axial or centrifugal LVAD [4]

Outcome measures	Centrifugal LVAD	Axial LVAD	P-value
Re-operation due to pump failure	0.7%	7.7%	0.002
Pump thrombosis	0%	10.1%	

After 24 months, 79.5% of the centrifugal-flow pump group and 60.2% of the axial-flow pump group were free from strokes or reoperations to replace or remove the device (P<0.001 for non-inferiority, P<0.001 for superiority; Table 3).

Table 3. Secondary outcomes at 24 months when treated with axial- or centrifugal-flow LVAD [4]

Outcome measures	Centrifugal LVAD	Axial LVAD	Hazard ratio	P-value
Overall survival	82.8%	76.2%	0.71	0.16
Freedom from disabling strokes	92.5%	92.8%	1.25	0.6
Overall stroke rates	10.1%	19.2%		0.016

Conclusions

In patients with advanced heart failure who needed mechanical support, the use of a centrifugal-flow LVAD was superior to the axial-flow pump in preventing disabling stroke or reoperation to replace/remove a malfunctioning device. Survival was similar between the groups. The centrifugal-flow pump was associated with a reduction of overall stroke rates. The benefit was observed up to a follow-up period of 24 months and was mainly due to a reduction in pump failures and pump thrombosis [4].

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Lipids: Statins and PCSK 9 Inhibition

Despite evidence-based preventive therapies, residual CV-risk remains high after acute coronary syndrome (ACS), which is partly related to elevated low-density lipoprotein cholesterol (LDL-C) levels. Treatment with alirocumab, a proprotein convertase subtilisin-kexin type 9 serine protease (PCSK9) inhibitor, leads to a 15% reduced risk of CV events compared with placebo among patients with recent ACS, who are already on intensive or maximum-tolerated statin therapy. The ODYSSEY Outcomes trial met its primary endpoint, showing that alirocumab significantly reduces the risk of major adverse cardiovascular events (MACE) in patients who had suffered a recent ACS event, such as a MI [1]. During the presentation, the comparison was made with the FOURIER trial [2] which evaluated evolocumab. ODYSSEY Outcomes is the second outcomes trial of a PCSK9 inhibitor to show a reduction in LDL-C level and CV outcomes. Several small studies have suggested that a loading dose of a statin in the periprocedural setting can reduce MACE and MI at 30 days. Most of the evidence derives from studies, which include patients with stable coronary disease and elective percutaneous coronary intervention (PCI). Evidence in ACS is based on a low number of patients and events. The large-scale randomised SECURE-PCI trial showed that routine administration of two early doses of high-dose atorvastatin is not superior to placebo in reducing cardiovascular events at 30 days among patients presenting with ACS and scheduled to undergo an early invasive intervention. The results were published in *JAMA* simultaneously with the ACC18 meeting [3].

ODYSSEY: survival benefit on top of maximal statin therapy

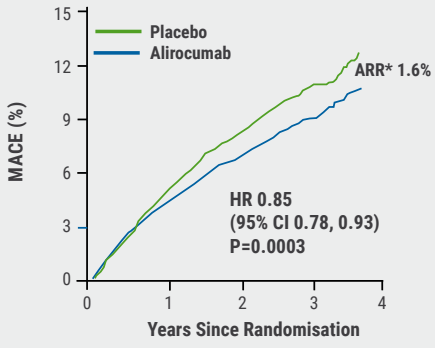
A total of 18,924 patients from 57 countries, who had had an ACS event within the preceding 1–12 months participated in the ODYSSEY Outcomes study. 29% of participants had diabetes mellitus and 19% had a prior MI. The median time from ACS to randomisation was 2.6 months. The most frequent ACS types were non-ST-segment elevation MI (NSTEMI, 49%) and STEMI (35%). Almost 90% of these patients had already been treated with a high dose of high-intensity statin therapy (atorvastatin or rosuvastatin). In addition, they randomly received subcutaneous injections with 75 mg of alirocumab every other week or placebo. The drug was titrated between 75 and 150 mg to keep the LDL-C level between 25 and 50 mg/dL but above 15 mg/dL meaning some patients with low LDL-C had the dose reduced or treatment stopped [1].

Reductions in Cardiovascular Outcomes

After a median follow-up of 2.8 years, LDL-C levels were 53.3 mg/dL in the alirocumab group compared with 101.4 mg/dL in the placebo group (an absolute reduction of 54.7%). The primary endpoint was the first occurrence of any MACE, including death from coronary heart disease (CHD), non-fatal MI, unstable angina requiring hospitalisation, and ischaemic strokes. This composite endpoint occurred 15% less frequently in the alirocumab-treated group than in the placebo group, who only received maximally-tolerated statins (9.5% versus 11.1%, HR 0.85, P=0.0003, Figure 1).

Regarding the individual components of the primary endpoint, non-fatal MI occurred in 14%, strokes in 27%, and unstable angina in 39% of alirocumab-treated patients compared to the placebo group (all significant differences: Table 1A).

Figure 1. Primary efficacy MACE endpoint in the alirocumab vs placebo group [1]



MACE: CHD death, non-fatal MI, ischaemic stroke, or unstable angina requiring hospitalisation

All-cause mortality was lower in the alirocumab group (Table 1B and Figure 2, nominal P-value of 0.026), there was no significant difference between both groups in mortality due to coronary artery disease (CHD, 2.2 vs. 2.3%) and CV mortality (2.5 vs. 2.9%). There were no new safety signals in the trial. Treatment-emergent adverse events occurred in 75.8% and 77.1% of the alirocumab and placebo groups, respectively. Alirocumab-treated patients had a more common experience of minor local site reactions at the injection site compared to the control group (3.1% vs. 2.1%). There was no difference in neurocognitive events (1.5 vs 1.8%) or new-onset diabetes (9.6% vs. 10.1%, Table 1C) [1].

In a pre-specified post-hoc analysis by LDL-C level at baseline, the patients with LDL-C levels of ≥100 mg/dL experienced the highest benefit from alirocumab, reducing their risk of MACE by 24% (11.5% vs. 14.9%; HR 0.76). These data should be interpreted in the context of knowing that those patients who had a very low LDL-C (likely those with lower baseline LDL-C) had their dose reduced or stopped due to the trial protocol which may have influenced this subgroup analysis. In a post-hoc analysis of this group, alirocumab was associated with a 29% risk reduction in all-cause mortality (HR 0.71). The results of this landmark trial indicate that the use of alirocumab, taken every other week, significantly reduces ischaemic events, including all-cause mortality and MI, among patients with an ACS event within the preceding year [1].

Table 1. Components of the composite primary endpoint (A), main secondary outcome measures (B) and adverse events (C) in alirocumab- and placebo-treated patients [1]

A Outcome parameters	Alirocumab	Placebo	P-values
CHD-related mortality	2.2%	2.3%	0.38
Non-fatal MI	6.6%	7.6%	0.006
Ischaemic stroke	1.2%	1.6%	0.01
Unstable angina	0.4%	0.6%	0.02

B Outcome parameters	Alirocumab	Placebo	P-values
Death, MI or ischaemic stroke	10.3%	11.9%	0.0003
All-cause mortality	3.5%	4.1%	0.026
Ischemia-driven coronary revascularisation	7.7%	8.8%	0.009

C Outcome parameters	Alirocumab	Placebo	P-values
ALT level of >3 x ULN	2.3%	2.4%	0.38
CK level of >10 x ULN	0.5%	0.5%	0.006
Neutralising antibodies against drugs	n=42	n=6	0.01
New-onset diabetes	9.6%	10.1%	0.02

Comparison with FOURIER and Cholesterol Treatment Trialists meta-analysis

There are some differences between the ODYSSEY Outcomes and the FOURIER trial, which evaluated another PCSK9 inhibitor, evolocumab. Firstly, the patient population that they studied differed: post-ACS in ODYSSEY vs. stable established atherosclerotic disease. The differences in mortality rates, as found in the ODYSSEY study, were not noted in the FOURIER study. This differences is most likely due to the longer duration of ODYSSEY acknowledging that the benefits of lipid lowering emerge over time and most trials of statins lasted 4-5 years whereas the FOURIER trial was approximately two. The degree of LDL-C reduction appeared to be qualitatively similar in these two studies. The ODYSSEY Outcomes trial further reinforces the "lower is better" hypothesis with LDL-C. The question is whether it is better to treat patients based on lipid levels rather than intensity of statin therapy alone. Interestingly, a frequently cited meta-analysis of the Cholesterol Treatment Trialists (CTT), which analysed the data from 90,000 participants in 14 statin trials, suggested an approximate 22% reduction in CHD events with every 1 mmol/L (38 mg/dl) reduction in LDL-C level [4]. Based on the duration of follow up the results from ODYSSEY and FOURIER appear consistent. Next, there was a slight attenuation of reduction in LDL-C level over the long-term follow-up in this trial. This trend upward in the LDL-C is thought to be due to the study design of reducing the treatment dose in the face of very low LDL-C levels and not due to a significant presence of neutralising antibodies. The SPIRE trial programme with bococizumab had to be abandoned due to this issue of neutralising antibodies [5].

SECURE-PCI: statins in coronary procedures and revascularisation

The SECURE-PCI trial compared the safety and efficacy of two loading doses of atorvastatin 80 mg or placebo among 4,191 patients (mean age 61.8 years, 26% female). These presented with ACS and an early invasive approach was planned for them. Almost one third of patients (29%) had previously used long-term statin therapy. STEMI was present in 25%, NSTEMI in 60%, and unstable angina in 15%. The initial treatment strategy included PCI in 65%, coronary artery bypass grafting (CABG) in 8%, and medical management in 27%. The study medication was given before and 24 hours after the planned early invasive approach. All patients in both groups received atorvastatin, 40 mg daily after the procedure for 30 days [3]. The principal findings are shown in Table 2 and Figure 2.

Interpretation

The results of the SECURE-PCI trial indicate that routine administration of two early doses of high-dose atorvastatin is not superior to placebo in reducing cardiovascular events at 30 days among patients presenting with ACS and scheduled to undergo an early invasive approach. However, among patients who underwent PCI, there were significant reductions in MACE and non-PCI-related MI. Thus, a loading dose of atorvastatin might be an attractive treatment strategy in patients with ACS with a high likelihood of undergoing PCI, particularly those with STEMI. Considering that LDL-C levels were similar in both arms (which received 40 mg of atorvastatin daily after the initial load), and that the benefit in the PCI patients occurred early, the mechanism for benefit in these patients is likely due to the pleiotropic effects of statins. The study also highlights how heterogeneous an ACS population can be, both from a risk and a clinical response perspective [3].

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Table 2. Principal findings of the SECURE-PCI trial [3]

Primary outcome

Outcomes	Statin	Placebo	P-values
MACE	6.2%	7.1%	0.27
Death	3.2%	3.3%	0.84
MI	2.9%	3.7%	0.18

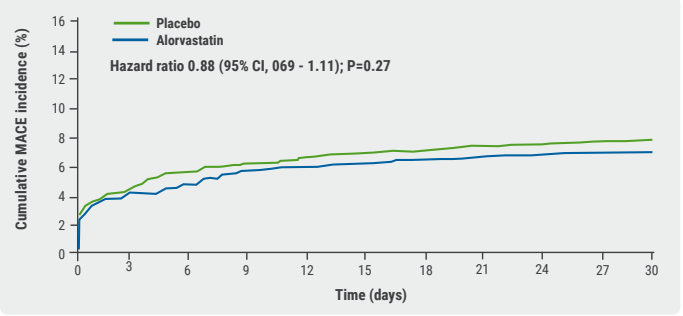
Secondary outcome

Outcomes	Statin	Placebo	P-value
Stroke	0.5%	0.5%	0.85
Stent thrombosis	0.3%	0.7%	0.10
LDL-C level	79.6 mg/dl	75.8 mg/dl	

Among patients undergoing PCI (P=0.02 for interaction)

Outcomes	Statin	Placebo	P-value
MACE	6.0%	8.2%	0.02
MI	3.6%	5.2%	0.04

Figure 2. Cumulative incidence of primary MACE outcome [3]



Anticoagulants: Real-World, Specific Populations and Antidote

During the ACC18 meeting, the largest real-world data analysis to date reporting outcomes among different direct oral anticoagulants (DOACs)—including apixaban, rivaroxaban and dabigatran—was presented and simultaneously published in a supplement of *JACC* [1]. Patients with peripheral artery disease (PAD) have an increased risk of suffering major adverse limb events (MALE), which are associated with a high risk of subsequent amputation and death. Therefore, preventing MALE in this patient population should be a high priority. The COMPASS study showed that a combination therapy of low-dose rivaroxaban and acetylsalicylic acid (ASA) leads to a significantly reduced incidence of MACE and MALE in patients with PAD in the lower extremities. At the same time as the ACC18 conference, the results were published in *JACC* [2]. Every year, more than eight million adults worldwide are affected by myocardial damage after non-cardiac surgery (MINS). The direct thrombin inhibitor dabigatran leads to a significantly reduced risk of death, MI, stroke, and other CV complications in patients with MINS. That was recently found in the MANAGE study, which was presented during a Late Breaking session of the ACC18 meeting [3]. Andexanet is a recombinantly modified factor Xa molecule that binds to factor Xa inhibitors, allowing factor Xa to fulfil its normal role in the formation of blood clots. In previous studies in healthy volunteers, andexanet rapidly reversed the anticoagulant effect of factor Xa inhibitors without significant safety concerns. This has been confirmed in an interim analysis of the ongoing ANNEXA-4 study [4].

Real-world experiences with DOACs

Most observational studies on DOACs have used single data sources with limited generalisability. In the ongoing ARISTOPHANES study, multiple data sources to compare stroke/systemic embolism, major bleeding, and net clinical outcome (composite of embolisms and bleeding events) among a large number of patients with non-valvular AF (NVAF) on different DOACs are used. This ongoing real-world data analysis initiative currently includes anonymised patient records from >300,000 patients. A retrospective observational study pooled data from NVAF patients who initiated a DOAC in the period 2013–2015. It derived its data from Medicare and four US commercial claims databases, covering more than half of the US population. This study included 162,707 patients who were followed for a mean of six months. Pre-specified endpoints including three 1:1, a propensity score and individually matched DOAC cohorts were utilised; apixaban vs. rivaroxaban (n=125,238), apixaban vs. dabigatran (n=54,192), and dabigatran vs. rivaroxaban (n=55,076). While apixaban, in comparison to dabigatran and rivaroxaban, was associated with a lower risk of stroke/systemic embolism, major bleeding, and net clinical outcome, dabigatran was associated with a lower risk of major bleeding and net clinical outcome compared to rivaroxaban (Table 1) [1].

Limitations

Real-world data have the potential to supplement randomised controlled trial data by providing additional information about how a medicine performs in routine medical practice.

Table 1. Pooled data from NVAF patients initiating a DOAC in the period 2013–2015: incidence per 100 person-years

Outcomes	Apixaban	Dabigatran	Hazard ratio	P-value
Stroke/systemic embolism	1.21	1.73	0.69	<0.001
Major bleeding	3.05	3.90	0.77	<0.001
Net clinical outcome	4.02	5.38	0.74	<0.001

Apixaban vs. rivaroxaban

Outcomes	Apixaban	Rivaroxaban	Hazard ratio	P-value
Stroke/systemic embolism	1.41	1.66	0.83	0.004
Major bleeding	3.64	6.54	0.54	<0.001
Net clinical outcome	4.70	7.71	0.59	<0.001

Dabigatran vs. rivaroxaban

Outcomes	Rivaroxaban	Dabigatran	Hazard ratio	P-value
Stroke/systemic embolism	1.72	1.43	1.18	0.080
Major bleeding	3.88	5.76	0.67	<0.001
Net clinical outcome	5.35	6.74	0.78	<0.001

However, real-world data analyses, such as the current ARISTOPHANES analysis, have several limitations. Firstly, the source and type of data used may limit the generalisability of the results and of the endpoints. Furthermore, observational real-world studies can only evaluate association and not causality.

Due to these limitations, real-world data analyses cannot be used as stand-alone evidence to validate the efficacy and/or safety of a treatment. Although, in this analysis [1], propensity score matching was used to control for multiple confounders, there is still potential for residual bias.

Claims for a filled prescription do not indicate that the medication was consumed or taken as prescribed. In addition, medications filled over the counter or provided as samples are not captured in the claims data.

Conclusion

This is the largest observational study to date on direct comparisons of DOAC. It is important to note that, currently, no head-to-head clinical trials comparing DOACs are available [1].

COMPASS: rivaroxaban plus acetylsalicylic acid in PAD

Patients with PAD of the lower extremities are at increased risk of MACE and MALE. In the randomised double-blind, placebo-controlled COMPASS study, 27,395 patients (mean age 68 years, 23% female, 38% with diabetes) randomly received:

- low dose rivaroxaban 2.5 mg twice daily plus ASA;
- rivaroxaban monotherapy; or
- ASA monotherapy.

The results for some patient groups appeared at the end of last year in The New England Journal of Medicine [5] and, earlier this year, in The Lancet [6;7]. The current analysis of the COMPASS study evaluated whether the risk of hospital admissions, MACE, amputations and death was higher after the first MALE compared with PAD patients who had never experienced a MALE before. In addition, the impact of low-dose rivaroxaban plus ASA treatment was compared with ASA monotherapy on the incidence of MALE, peripheral vascular interventions, and all peripheral vascular outcomes during a median follow-up period of 21 months. The 6,391 participants (mean age 68 years, 23% female and 38% with diabetes) had atherosclerosis in ≥2 vascular beds or two additional risk factors, i.e. current smoking, diabetes, renal insufficiency, heart failure, or non-lacunar ischaemic stroke ≥1 month [2].

Predictors for MALE

MALE was defined as severe limb ischemia leading to an intervention or major vascular amputation. A total of 128 patients suffered a MALE incident. After MALE, the one-year cumulative risk of a subsequent hospitalisation was 95.4%, vascular amputation was 22.9%, mortality was 8.7%, and MACE was 3.8%. Some independent predictors for MALE were found:

- severe symptoms of severe intermittent claudication at baseline (OR 4.70);
- prior foot or limb amputation (OR 3.62);
- history of peripheral bypass surgery (OR 2.39); and
- randomisation to ASA therapy in this study (OR 1.79).

In contrast, diabetes, smoking, female gender and a history of coronary arterial disease (CAD) were not independent predictors for MALE. Overall, the incidence of MALE was highest (3.8%) in PAD patients who had previously experienced peripheral revascularisation or amputation, and the lowest (0.5%) in patients with asymptomatic PAD (ankle-brachial pressure index of <0, 90) [2].

In total, 128 patients experienced MALE, resulting in a significantly increased cumulative risk of subsequent hospitalisations (95.4%), amputations (22.9%) and death (8.7%) after one year.

Lower risks with combination therapy

Compared with ASA monotherapy, the combination of rivaroxaban and ASA was associated with a significantly reduced incidence of:

- MALE by 43% (P=0.01);
- vascular amputations by 58% (P=0.01);
- peripheral vascular interventions by 24% (P=0.03); and
- all peripheral vascular outcomes by 24% (P=0.02) [2].

Another analysis of the COMPASS trial showed that the occurrence of CV death, MI, or stroke, occurred in 4.1% of the rivaroxaban-plus-ASA group, in 4.9% of the rivaroxaban-alone group, and in 5.4% of the ASA-alone group (P<0.001 for rivaroxaban-plus-ASA vs. ASA-alone; P=0.12 for rivaroxaban-alone vs. ASA-alone).

Conclusions

In patients with PAD of the lower extremities, the development of MALE is accompanied by a poor prognosis. MALE is associated with a six-fold increase in MACE or vascular amputations and a four-fold increase in mortality. The outcomes after MALE may be reflective of patient illness rather than due to the MALE event itself, particularly long-term mortality Preventing MALE in patients with PAD is of major clinical importance. Compared to ASA monotherapy,

the combination of low-dose rivaroxaban and ASA is associated with less MALE, amputations, peripheral vascular interventions, and total peripheral vascular hospitalisations in PAD patients, but with more major bleeding events. The researchers of the COMPASS trial regard treatment with low-dose rivaroxaban plus ASA as an important treatment option for PAD patients [2].

MANAGE: reduced mortality in myocardial injury after non-cardiac surgery

MINS affects ≥8 million adults worldwide per annum. Myocardial damage is independently associated with an increased risk of CV events and death over the first two years after the operation. It includes the occurrence of a MI and isolated troponin elevation—a sign of cardiac ischemia—during the first 30 days after surgery. It does not include non-ischaemic myocardial injury due, for example, to sepsis, rapid AF, pulmonary embolism, and a chronically elevated troponin level. No published trials have evaluated the potential value of preventive medication to reduce risk of CV events in patients with MINS. In non-operative patients, there is high-quality evidence demonstrating the benefits of anticoagulation therapy in the prevention of thrombotic complications. The MANAGE trial compared the safety and efficacy of the oral direct thrombin inhibitor dabigatran 110 mg twice daily against placebo in reducing major vascular events among 1,754 patients (mean age 70 years, 49% female) with evidence of MINS. The myocardial injury after noncardiac surgery was a MI in 20% of cases and an isolated troponin elevation in 80%. Of the participants, 74% used ASA, 69% a statin, and 8% a P2Y12 inhibitor. The patients received dabigatran for a minimum of four months and a maximum of two years [3].

Improvements of primary endpoint

The trial was terminated prematurely after a mean follow-up of 16 months due to loss of funding and slow enrolment (1,764 participants in total). Most patients (98.9%) completed the follow-up period. The primary efficacy endpoint was the occurrence of any major cardiovascular complications—a composite of CV mortality, MI, non-haemorrhagic stroke, peripheral arterial thrombosis and amputation, and symptomatic venous thromboembolism (VTE). After an average follow-up period of 16 months, 11.1% of patients in the dabigatran group had one or more events of the primary outcome measure, compared with 15.2% in the placebo group (HR 0.72; P=0.012; Figure 1).

Analysis of the individual parameters of the primary endpoint showed the following significant improvements in treatment with dabigatran compared to placebo:

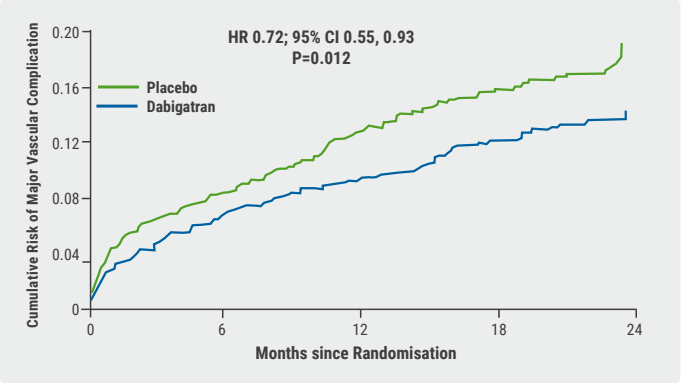
- 20% lower risk of cardiovascular mortality (6% vs. 7%);
- 20% lower risk of MI (4% vs. 5%); and
- 53% lower risk of VTE (1% vs. 2%).

The primary safety endpoint was a composition of life-threatening, major, and critical organ bleedings. There were no significant differences between the two groups regarding the occurrence of the primary safety endpoint (3% vs. 4%; HR 0.92, P=0.79). However, a larger number of dabigatran-treated patients developed mild bleeding events and bleeding occurring in the lower part of the gastrointestinal tract compared to the placebo group. Furthermore, >40% discontinued the drug [3].

Conclusions

The MANAGE trial showed that a dosage of dabigatran 110 mg twice daily among patients with mostly biochemical evidence of MINS had lower major vascular event rates compared with placebo. The incidence of bleeding complications was similar between the two groups. The results of this trial indicate that the addition of dabigatran 110 mg twice daily among patients with evidence of MINS had lower major CV event rates compared with placebo. Bleeding complications were similar in both groups. While these results are interesting, they need to be considered with the caveat that the trial was terminated early and the primary outcome definition was changed midway through it. Finally, this is likely a heterogeneous patient group; the utility of routinely measured troponins in asymptomatic patients without ECG changes is unclear [3].

Figure 1. Primary composite outcome in the dabigatran and placebo groups [3]



ANNEXA-4: antidote factor Xa inhibitors stops bleeding

Because factor Xa inhibitors and other anticoagulants reduce the body's ability to form blood clots, they have an increased bleeding risk: mitigating this can be a challenge. Unlike some other anticoagulants, there is currently no approved antidote for the factor Xa inhibitors. Andexanet alfa (Figure 2) is still under investigation.

In the ANNEXA-4 study, all evaluated patients had acute major bleeding within 18 hours of taking one of the currently available factor Xa inhibitors—apixaban, rivaroxaban, or edoxaban, or the low molecular-weight heparin enoxaparin. The participants first received an injection of andexanet and then a two-hour infusion with this drug. The dose was based on the specific factor Xa inhibitor used by the patient and the time elapsed since the last dose. In this study, two co-primary endpoints were assessed: reduction of anti-factor Xa activity and achieving clinical haemostasis within 12 hours after administration. Interim data on safety in 227 patients and effectiveness in 132 patients were presented during the ACC18 meeting.

There was a median reduction in the anti-factor Xa activity of:

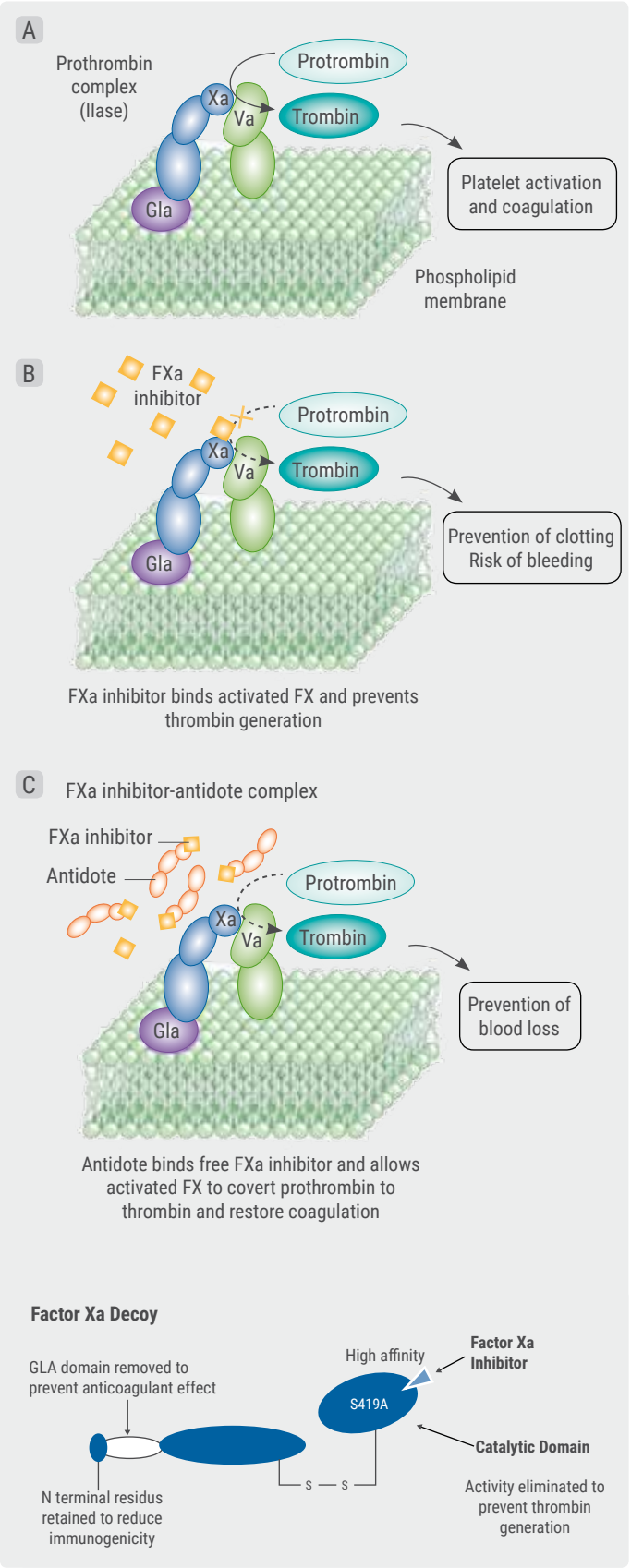
- 88% for patients taking rivaroxaban;
- 91% for patients taking apixaban; and
- 75% for patients taking enoxaparin.

Very few patients in the study had received edoxaban [4].

First-in-class antidote

Excellent or good clinical haemostasis was achieved in 83% of patients. The safety of andexanet was assessed in all 227 patients. By Day 30, 12% of patients had died and 11% had a thrombotic event. According to the presenter Stuart Connolly, the percentages of death and thrombotic events are in line with expectations given the high-risk profile of the patients. After a future approval by the medicines authorities, andexanet would be the first agent that can directly affect the action of the factor Xa inhibitors at the time of bleeding [4].

Figure 2. Mechanism of action of andexanet alfa, recombinant modified human factor Xa [8]



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Diabetes: SGLT-2 Inhibitors Improve Survival

The global prevalence of diabetes mellitus has been increasing and remains a major cause of morbidity and mortality. Type 2 diabetes mellitus (T2DM) is associated with the development of microvascular and macrovascular complications. Diabetics still succumb predominantly to CV diseases. Thus, preventing CV complications in these patients must be the priority. In patients with T2DM and an elevated CV risk, the sodium glucose cotransporter 2 (SGLT2) inhibitor canagliflozin reduced the risk of CV death or hospitalisation for heart failure across a broad range of different patient subgroups. Benefits may be greater in those with a history of heart failure at baseline. These results of the CANVAS trial presented at the ACC18 meeting were simultaneously published in Circulation [1]. Randomised trials, such as the CANVAS study, demonstrated lower risk of CV events with SGLT-2 inhibition in patients with T2DM at high CV risk. Prior real-world data suggested similar effects in T2DM patients with broader risk profile, but focused on heart failure and death, and were limited to the U.S. and Europe. In the large, international CVD-REAL study of patients with T2DM from the Asia-Pacific, Middle East and North America, initiation of SGLT-2 inhibition was associated with a lower risk of CV events. This treatment effect was found across a broad range of outcomes and patient characteristics. As well as the presentation at the ACC18 meeting, the results were published in *JACC* [2]. The ongoing VERTIS-CV outcomes trial is evaluating whether the SGLT2 inhibitor ertugliflozin is non-inferior vs. placebo in the following major adverse CV events: time to the first event of either CV death, non-fatal MI or non-fatal stroke. The VERTIS-CV study reflects T2DM patients at high CV risk, including those with kidney disease, heart failure, and older patients. Inclusion was just completed and no results were reported yet [3].

CANVAS: reduced CV mortality or hospitalisation for heart failure

Glucose-lowering therapy has demonstrably improved in microvascular complications such as retinopathy, neuropathy, and nephropathy. However, macrovascular benefits, such as a reduced rate CV mortality, stroke and MI, have been elusive. The UKPDS evaluated the sulfonylurea glibenclamide (also known as glyburide), metformin and insulin. Although treatment with these drugs resulted in impressive reduction in microvascular complications by 37% for every 1% reduction in hemoglobin A1c (HbA1C), tight glycemic control did not translate into a significant decrease in macrovascular complications [4]. Furthermore, the more recently conducted ADVANCE and ACCORD studies did not find any macrovascular benefit from intensive glycemic control [5]. The VADT study similarly did not reveal any early benefits in macrovascular events with intensive glycemic control (goal A1c 6%) in poorly controlled diabetics (A1c >9.4%) [6]. Consequently, diabetologists and cardiologists alike have focused on HbA1c as the primary target in diabetes management, without proof of any associated macrovascular benefit.

Changed perspective

Because of the negative results of these previous landmark studies, the goal of demonstrating CV risk reduction appeared to be unattainable. However, in 2015, the EMPA-REG OUTCOME changed this perspective by showing that treatment with the SGLT2 inhibitor empagliflozin resulted in a significantly reduced mortality in patients with T2DM and established CV disease. SGLT2 inhibitors prevent renal glucose absorption in the proximal tubule, inducing an osmotic diuresis and thereby reducing plasma glucose levels. The EMPA-REG OUTCOME trial was the first randomised, double-blind, placebo-controlled CV outcomes trial evaluating empagliflozin. This drug resulted in a 14% relative risk reduction in three-point major adverse cardiac events: CV mortality, non-fatal MI, or non-fatal stroke. During the follow-up period of 3.1 years, there was a relative risk reduction of 38% and a 2.2% absolute risk reduction in CV mortality. Other analyses revealed a 35% reduction in hospitalisation due to heart failure, a 38% risk reduction in macroalbuminuria and a 32% decrease in all-cause-mortality. In contrast, no significant differences between empagliflozin and placebo were found with regard to non-fatal MI and non-fatal stroke risk. Thus, the positive results of this trial were driven exclusively by a reduction in CV mortality [7].

CV outcomes of canagliflozin

The CANVAS programme is the longest, largest and broadest completed CV outcomes programme of any SGLT2 inhibitor to date and was the first to assess the efficacy, safety, and durability of canagliflozin in >10,000 patients with T2DM (mean age 63 years, 36% female) who had either a prior history of CV disease or ≥2 CV risk factors. Mean duration of diabetes was 13.5 years and 65.6% of participants had a history of CV disease. In 2017, data from the integrated analysis of the CANVAS and CANVAS-R trials were published in The New England Journal of Medicine [8]. Participants with a history of heart failure at baseline (14.4%) were more frequently women, white, and hypertensive and had a history of prior CV disease (all P<0.001). Furthermore, a greater proportion of these patients was using antihypertensive therapies, such as blockers of the renin angiotensin aldosterone system, diuretics, and β-blockers at baseline (all P<0.001). The patients were randomly assigned to canagliflozin or placebo and followed for a mean of 188 weeks.

The primary end-point —adjudicated CV death or hospitalisation for heart failure—was reduced in those treated with canagliflozin compared with placebo (16.3 versus 20.8 per 1000 patient-years; HR 0.78; 95% CI, 0.67 to 0.91). In addition, the occurrence of either fatal heart failure or hospitalisation for heart failure (HR 0.70; 95% CI, 0.55 to 0.89) and hospitalisation for heart failure alone (HR 0.67; 95% CI, 0.52 to 0.87) were lower in canagliflozin- vs. placebo-treated patients [1].

Greater benefit with a prior history

The benefit on CV death or hospitalisation for heart failure may be greater in patients with a prior history of heart failure (HR 0.61) compared with those without heart failure at baseline (HR 0.87; p interaction=0.021). The effects of canagliflozin compared with placebo on other CV outcomes and key safety outcomes were similar in participants with and without heart failure at baseline (all p interactions >0.130), except for a possibly reduced absolute rate of events attributable to osmotic diuresis among those with a prior history of heart failure (P=0.03). Rates of heart failure varied according to baseline characteristics, such as age, renal function and other disease history characteristics, but effects of canagliflozin on risk of CV death or hospitalisation for heart failure were mostly comparable across numerous subgroups. In addition, the data confirmed that proportional effects of canagliflozin compared to placebo were comparable across a broad population of patients with T2DM with high CV risk. Specifically, patients from the CANVAS programme included those with and without heart failure at baseline for MACE, CV death, MI, stroke, all-cause mortality, and serious decline in kidney function [1].

CVD-REAL: lower mortality, less heart failure hospitalisations

The large, real-world CVD-REAL trial examined a broad range of CV outcomes in patients with T2DM-initiated SGLT-2 inhibitor or another glucose lowering drug. This study was performed across six countries in the Asia-Pacific (South Korea, Japan, Singapore and Australia), Middle East (Israel) and North America (Canada). The data about new users of SGLT-2 inhibitors and other glucose-lowering drugs were obtained from anonymised real-world sources including medical records, claims databases and national registries. The meta-analyses were validated by the independent academic statistical group. Non-parsimonious propensity scores for initiation of an SGLT-2 inhibitor were used to match groups in which a broad population of patients with T2DM received treatment with either a SGLT-2 inhibitor or another glucose lowering drug. After propensity-matching, there were approximately 235,000 episodes of treatment initiation in each group. Around 27% of analysed patients had an established CVD. Patient characteristics were well-balanced between groups. The exposure time to the different SGLT-2 inhibitors were: 75% on dapagliflozin, 9% on empagliflozin, 8% on ipragliflozin (only available in South Korea and Japan), 4% on canagliflozin, 3% on tofogliflozin, and 1% on luseogliflozin (both only available in Japan) [2].

Lower risks

The CVD-REAL study showed that, across a broad population of patients with T2DM, treatment with an SGLT-2 inhibitor was associated with a 49% lower risk of all-cause mortality, 36% of hospitalisation for heart failure, 19% of MI, and 32% of stroke compared to other glucose-lowering drugs (Table 1). There was a 40% lower risk of the composite endpoint of hospitalisation for heart failure or all-cause mortality (P<0.001). The direction of the results was consistent across the countries, and the results were stable in multiple sensitivity analyses and across patient subgroups, including those with and without CVD.

Table 1. Hazard ratios for different outcomes during treatment with SGLT-2 inhibitors vs. other glucose-lowering drugs [2]

Outcomes	Hazard ratios	P-value
All-cause mortality	0.51	<0.001
Hospitalisation for heart failure	0.64	0.001
Death or hospitalisation for heart failure	0.60	<0.001
MI	0.81	<0.001
Stroke	0.68	<0.001

Conclusion and discussion

In the large, multinational CVD-REAL study of patients with T2DM from clinical practice, initiation of an SGLT-2 inhibitor was associated with a lower risk of all-cause mortality, hospitalisation for heart failure, MI, and stroke, as compared with other glucose-lowering drugs in a diverse population of patients with T2DM. The results were consistent across individual countries, patient subgroups, and in sensitivity analyses [2]. Although CVD-REAL was a large study with a robust propensity-matching technique, its observational nature meant that the possibility of residual, unmeasured confounding factors cannot be definitively excluded. The results of the CVD-REAL study align with the findings of the EMPA-REG OUTCOME study [7]. The investigators think that the observed benefits with SGLT-2 inhibitor treatment will translate into real-world clinical practice and may also extend across the ethnic and racial backgrounds of patients and across the CV-risk continuum, including patients with T2DM and a low CV risk. Results of the DECLARE-TIMI 58 study evaluating dapagliflozin and including over 17,000 patients with diabetes as well as both primary and secondary prevention populations are eagerly awaited.

VERTIS: cardiovascular outcomes of ertugliflozin

Next to the effect of ertugliflozin on major adverse CV events, the ongoing double-blind VERTIS-CV study has some secondary objectives of demonstrating superiority compared with placebo on time to:

- composite endpoint of CV death or hospitalisation for heart failure;
- CV mortality; and
- composite endpoint of kidney-related mortality, dialysis, transplant, or doubling of serum creatinine from baseline.

The 8,237 participants had T2DM (age ≥40 years, HbA1C 7.0-10.5%) and established arterial disease of the coronary (76.3%), cerebral (23.1%), and/or peripheral vasculature (18.8%). They were randomised to placebo or ertugliflozin in a dose of either 5 mg or 15 mg, added to existing glucose-lowering therapy. Of the patients, 21.6% had Stage 3 kidney disease, 30.2% had micro- and 9.2% had macroalbuminuria, and 11.0% were ≥75 years old [3;9].

Ongoing trials

Future analyses of the ongoing CVD-REAL study will be conducted. Other ongoing clinical trials evaluating SGLT2 inhibitors, include the DECLARE-TIMI 58 study examining the CV efficacy and safety of dapagliflozin. This trial is anticipated to read out in the second half of 2018 [10].

Concluding remark

The emergence of new glucose-lowering drug that confer CV benefit shift the paradigm of the preventive cardiologist's approach to the diabetic patient with established CV disease. Some new drugs on the block significantly lowered the risk of CV mortality, the ultimate goal of every preventive cardiologist. Thus, the preventive cardiologist must either initiate these drugs himself or herself, or consult with a diabetologist, nephrologist or the primary care physician to determine if the patient should take them. It is time for cardiologists to re-engage in the management of diabetic patients.

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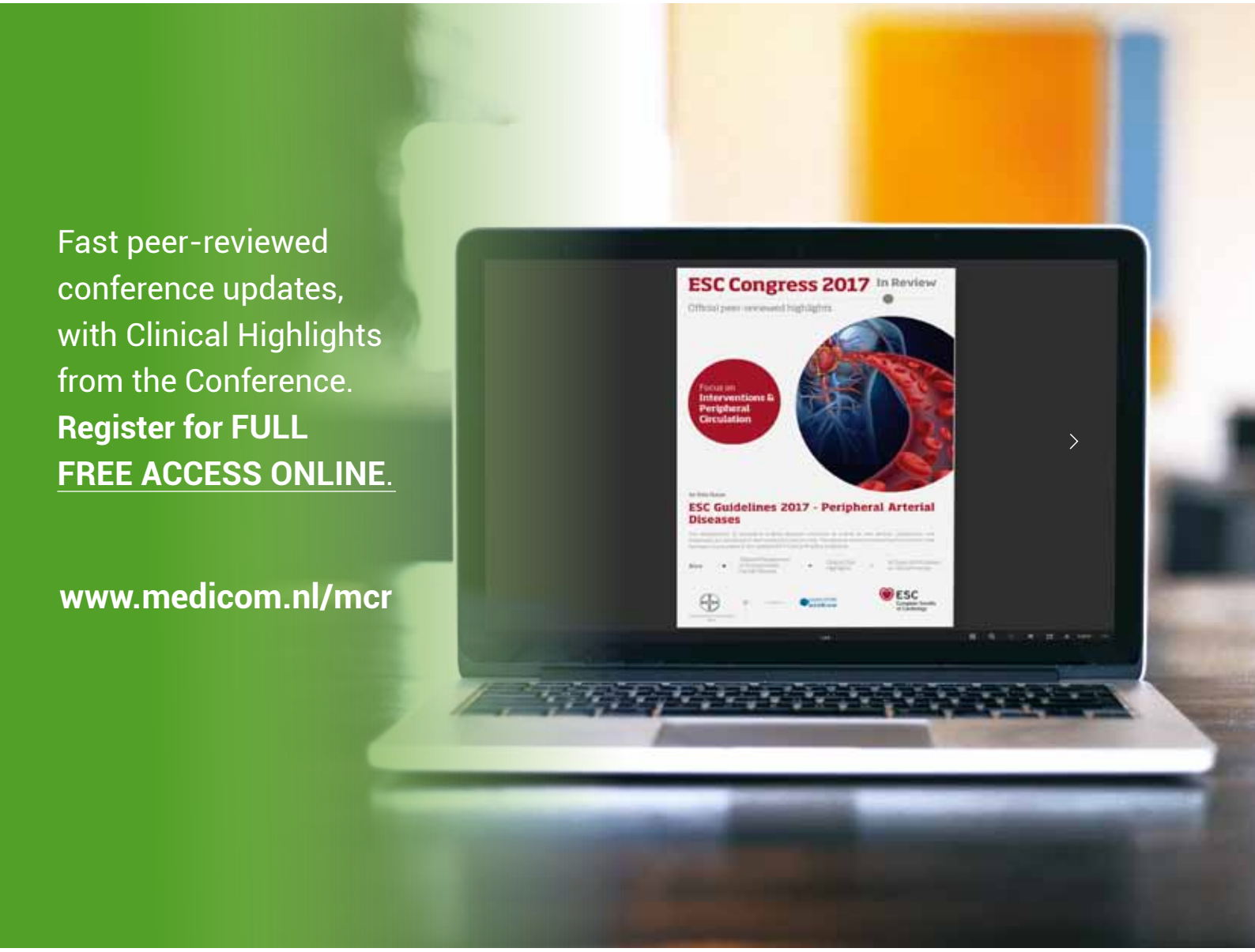

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