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PEER-REVIEWED CONFERENCE REPORT

Late Breaking Clinical Trials - Lipid Lowering

The initial meeting was nearly full to bursting: the FOURIER trial showed PCSK9 inhibitor evolocumab reduces LDL-C levels by 59%, significantly lowering risks of cardiovascular events.

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Risk Factors: Revisited

A new study showed the potential novel biomarker "ceramide" is predictive for cardiovascular events, independent of known risk factor.

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2017 ACC International Conferences Best Posters Session

The six Poster Winners from the 65th ACC Conference.

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

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Biography

Prof. dr. 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.

Interview with
Richard A. Chazal, MD, MACC
American College of Cardiology, Past President

Interview taken on 18 March 2017 by Dr. Kirsten Westphal

> **ACC's ultimate goal is to transform cardiovascular care and improve heart health – and I believe the College has a duty to not only focus on this mission, but also to ensure that patient care remains at the centre of all that we do as an organisation and as professionals.**

Patient care remains the heart of the matter

Looking back on his year as ACC president, Richard A. Chazal, MD, shares his top presidential priorities and how they have influenced the ACC, as well as his hopes for the future.

What do you consider the highlights of this year's ACC?

Science and engagement. Pivotal findings were presented at the ACC.17 Late Breaking Clinical Trial Sessions in Washington DC. The quality of the science and the organisation of presentations organised by Scientific Sessions Chair Jeff Kuvin and Vice Chair Andy Kates was outstanding. The engagement of members from different segments of ACC (FIT's and senior members) and from around the world was stimulating and educational.

What were the most surprising results? And why?

There was some surprise at the lack of mortality benefit from the intensive LDL-cholesterol lowering therapy with the PCSK9 inhibitor evolocumab in the FOURIER trial, likely linked to a low overall mortality.

What do you consider the most important issues in cardiology today? How can ACC help to push these forward?

It is crucial to utilise new treatments and technologies in a responsible and cost effective manner and to avoid disparities in care across patient populations. ACC is striving to help by looking carefully at evidence and increasingly evaluating costs as well (per our Strategic Plan). The College and its leaders continue to focus on effective implementation of ACC's Strategic Plan, which is centred on the key areas of purposeful education, transformation of care, member value and engagement, and population health.

ACC's ultimate goal is to transform cardiovascular care and improve heart health – and I believe the College has a duty to not only focus on this mission, but to ensure that patient care remains at the center of all that we do as an organisation and as professionals.

What would you like your legacy as ACC President to be?

Hopefully any legacy left from my presidency would reflect efforts to operationalise the linear plans put in place by ACC, rather than any personal agenda while keeping the importance of patient care as the prime driver.

Do you have something special on your mind you want to share with your fellow Cardiologists?

Today is perhaps the most challenging and exciting time ever to be in the cardiovascular field. The opportunity to leverage rapidly evolving science toward the goal of helping our fellow man is a complicated puzzle with great reward that makes this the best job possible!

How has the College expanded its educational mission worldwide?

Increasing bi-directional engagement of fellow practitioners around the world for bi-directional learning has grown exponentially over the past decade. Doing so through our International Chapters (via cardiology societies in the various countries) has been crucial to this engagement.

It is my hope that the ACC continues to grow as a vehicle for serving cardiovascular professionals as the work to achieve the highest quality of care for patients.

Late Breaking Clinical Trials-Lipid Lowering

Lowering LDL cholesterol (LDL-C) is one of the cornerstones of cardiovascular disease prevention. The therapeutic availability of monoclonal antibodies against the proprotein convertase subtilisin/kexin type 9 (PCSK9) has opened up a new dimension in lipid-lowering, which was previously impossible to achieve by medical therapy. To date, the extent by which the strong LDL-C reduction by a PCSK9 inhibitor could also reduce the rate of cardiovascular events was unknown. This question was answered directly in the first session of the "Late breaking clinical trials" at ACC-17. The announced presentation of the large outcome trial FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), caused the initial meeting to be almost full to bursting.

FOURIER: evolocumab significantly reduces the risk of cardiovascular events

FOURIER, the first outcome trial with a PCSK9 inhibitor confirms a new belief that when it comes to LDL-C: "Lower is better". This large outcome study was presented at the ACC-17 by Marc E. Sabatine, MD, MPH, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (USA) [1] and published simultaneously in the New England Journal of Medicine[2]. The FOURIER trial was a randomized, double-blind, placebo-controlled, multinational clinical trial. The study randomized 27,564 high-risk patients with clinically evident atherosclerotic cardiovascular disease (ASCVD) and either a LDL-C ≥70 mg/dL or a non-HDL-C ≥100 mg/dL [1][2]. On average the participants were 62.5 years old, 75% were men. In total, 81% had already suffered a myocardial infarction, 19% an ischemic stroke and 13% had symptomatic peripheral arterial disease. All participants received an optimized treatment with statins, over two thirds (69%) a high dosage statin (at least 40 mg atorvastatin). Randomisation took place 1 : 1 for treatment with the PCSK9 inhibitor evolocumab subcutaneously (140 mg every 2 weeks or 420 mg once monthly, n = 13,784), or placebo subcutaneously (every 2 weeks or once monthly, n=13,780), respectively.

Strong and consistent LDL-C reduction

The median LDL-C level at baseline was 92 mg/dL (interquartile range [IQR], 80–109). At 48 weeks, the least-squares mean % reduction in LDL-C levels with evolocumab, compared with placebo, was 59% (95% confidence interval [CI], 58–60; P<0.001), for a mean absolute reduction of 56 mg/dL (95% CI, 55–57), to a median of 30 mg/dL (IQR, 19–46). The reduction in LDL-C levels was maintained over time (Figure 1) [2].

"These are the lowest values that have ever been shown in an outcome study", stated Dr. Sabatine.

The study with its primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina or coronary revascularization) and the key secondary composite endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). The superior LDL-C reduction with evolocumab was associated with a relative reduction in the risk for cardiovascular events by 15% in the primary composite endpoint (Hazard Ratio [HR] 0.85; 95% CI 0.79 to 0.92, P<0.0001) and by 20% in the secondary main endpoint (cardiovascular death, myocardial infarction and stroke) (HR 0.80; 95% CI 0.73 to 0.88, P<0.00001). This effect was evident very early on, after just 6 months, increased noticeably as time passed and was 25% after the first

Figure 1 FOURIER: Mean reduction of LDL-C from 92 mg/dL to 30 mg/dL (-59%) in evolocumab study arm [2]

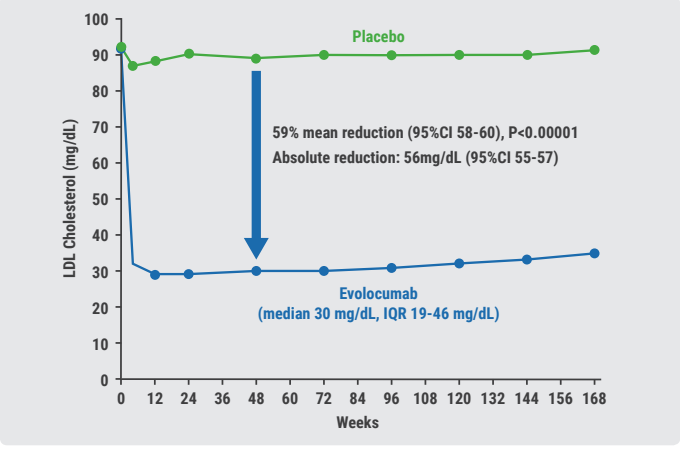
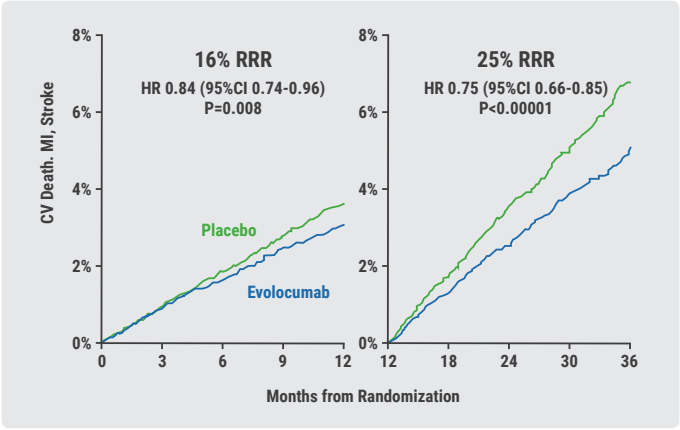


Figure 2 FOURIER: Secondary study end point. The effect increased considerably as time passed. The relative risk reduction was 25% after the first year [2]



year (Figure 2) [2]. This outcome was primarily due to the reduction in myocardial infarction and stroke, while there was no reduction in cardiovascular deaths.

"The 2.2 year period for lipid-studies was comparatively short", stated Dr.Sabatine. It must be presumed that the "gap in the event curves" will become ever wider as the period for treatment increases. "The LDL-C reduction needs time until it clinically takes effect", said Dr. Sabatine.

Safety profile comparable to control group

In addition, the FOURIER data confirms the known safety profile for evolocumab from the other studies in the PROFICIO study programme. In FOURIER, the safety profile was also comparable to the control group. This applied in particular for neurocognitive side effects. Evolocumab reduced the cardiovascular event rate "safely and significantly", emphasized Sabatine.

EBBINGHAUS: evolocumab does not impair neurocognition

Since randomized controlled trial (RCTs) had indicated that statins might possibly have a negative effect on cognitive function, in 2012, the US Food and Drug Administration added risk of adverse cognitive effects to the label of all statins. However, in 2014, after thorough analysis from large-scale RCTs, the Statin Cognitive Safety Task Force concluded that statins are not associated with cognitive side effects [3].

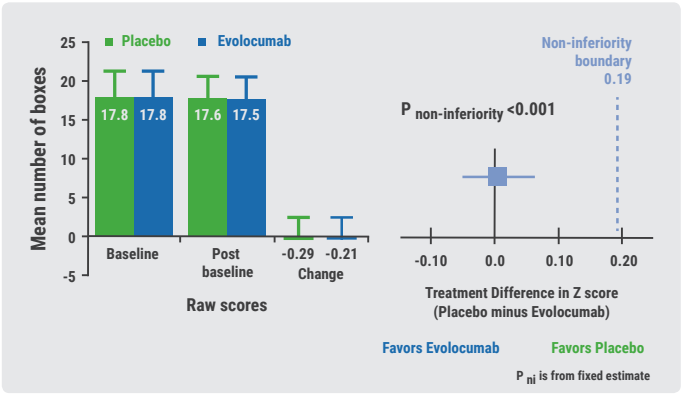
There were also similar concerns regarding PCSK9 inhibitors: even though these monoclonal antibodies are too large to cross the intact blood-brain barrier and the brain itself locally synthesizes cholesterol, there was concern regarding cognitive deficits. In a pooled analysis of previous studies with PCSK9 inhibitors with over 9,000 patients, a doubling of the risk for cognitive impairment was noticed in the active treatment groups even though the rate was very low with less than 1% [4]. In the large outcome study FOURIER, neurocognitive function was also specifically investigated. The rate for neurocognitive events was the same in both groups with 1.6% and 1.5% [2].

No memory loss or other cognitive issues

The cognitive function trial EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects) conducted in FOURIER patients also achieved its primary endpoint, demonstrating that evolocumab was non-inferior to placebo for the effect on cognitive function [5]. In this double-blind study, 1,974 patients were tested after 6, 12, 18 and 24 months for their executive functions, spatial thinking, learning ability and reaction time in the CAmbridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well- validated computer tablet-based testing platform. Primary endpoint was the Spatial Working Memory strategy index of executive function. The patients in EBBINGHAUS were 63 years old on average and 28% were women; 75% had suffered a myocardial infarction, 20% an ischemic stroke, and 19% had PAD. All were receiving moderate- or high-intensity statin therapy and subcutaneous evolocumab 140 mg every two weeks or 420 mg every month. Exclusion criteria were a diagnosis of dementia, cognitive impairment or another significant mental or neurological disorder. The mean change in the primary endpoint of executive function as measured by the Spatial Working Memory strategy index was -0.29 with placebo and -0.21 with evolocumab (P for non-inferiority <0.0001) implicating no clinical relevant change in neurocognition over the duration of the study (Figure 3).

The outcomes for all secondary endpoints were similar for placebo and evolocumab, too. Also similar were the patient self-reports via the questionnaire and the investigator reported cognitive adverse events for both placebo and evolocumab.

Figure 3 EBBINGHAUS: Primary endpoint. No negative effect on neurocognition with evolocumab [5]



"In patients with known cardiovascular disease on background statin followed for 20 months, there was no evidence of differences in cognitive tests by achieved nadir LDL-C, even < 25 mg/dL", said Robert P. Giugliano, MD, SM, FACC, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (USA) [5], adding that these findings should "enable physicians to feel more secure about adding evolocumab to a statin to achieve very low levels of LDL-C without worrying that patients' memory or cognitive functioning will be affected."

SPIRE 1 and SPIRE 2: the heartfelt story of the 3rd PCSK9 inhibitor

Alirocumab and evolocumab are both fully human monoclonal antibodies. LDL-C-lowering therapy with evolocumab significantly reduced cardiovascular events in the FOURIER trial [2] and patients treated with alirocumab showed promising cardiovascular outcomes in preliminary analyses [6].

Bococizumab is a 3rd inhibitor of PCSK9 that, unlike evolocumab and alirocumab, is a humanized monoclonal antibody in which approximately 3% of the murine sequence remains in the antigen-binding complementarity-determining region. As part of the "Studies of PCSK9 Inhibition and the Reduction of Vascular Events" (SPIRE) program, 2 large-scale trials to evaluate cardiovascular outcomes (designated SPIRE-1 and SPIRE-2) were initiated in October 2013 with the intent of evaluating the clinical efficacy and safety of bococizumab administered at a dose of 150 mg subcutaneously every 2 weeks among patients who had evidence of cardiovascular disease or who were at high risk for a first vascular event [7]. However, 2 outcomes trials were on their way, data became available from the 6 SPIRE lipid-lowering trials indicating that bococizumab was commonly associated with the development of high-titer antidrug antibodies that resulted in substantive attenuation of LDL-C lowering over time. In addition, the trials showed that bococizumab was associated with a wide variation in LDL-C lowering, even among patients who were antibody negative [8].

Based on the SPIRE lipid-lowering data, the sponsor elected to discontinue further development of bococizumab on November 1, 2016. Because of that decision, the sponsor also elected to prematurely stop the ongoing SPIRE-1 and SPIRE-2 outcome trials. This decision was made without the sponsor or the investigators having any knowledge of any unblinded data in SPIRE-1 or SPIRE-2.

The results of the SPIRE trials were presented by Paul Ridker, MD, MPH (Brigham and Women's Hospital, Boston, MA, USA) [9] and published simultaneously in the New England Journal of Medicine [10].

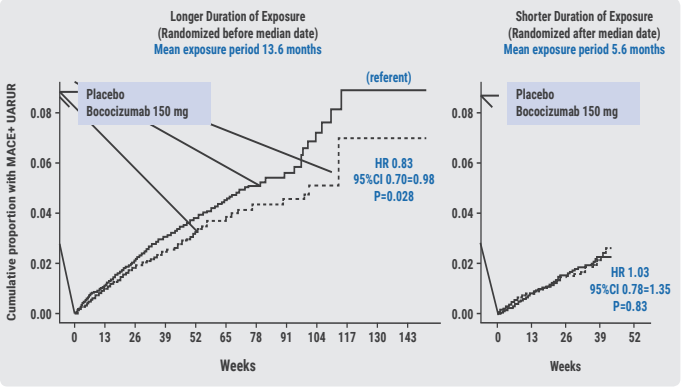
A contribution to the understanding of PCSK9 inhibition

Before the SPIRE 1 and 2 trials were stopped, they had enrolled 16,817 lower-risk patients (LDL ≥ 70 mg/dL or non-HDL ≥ 100 mg/dL) and 10,621 higher-risk patients (LDL ≥ 100 mg/dL or non-HDL ≥ 130 mg/dL), respectively. Both groups experienced attenuation in LDL-C reduction over time and the wide individual variability previously seen in the short-term lipid-lowering trials. While bococizumab did not affect the rate of the primary endpoint (nonfatal MI, nonfatal stroke, hospitalisation for unstable angina requiring urgent revascularisation, or cardiovascular death) for the lower-risk patients in SPIRE 1 compared with placebo (HR 0.99; 95% CI 0.80–1.22), there was a reduction for higher-risk patients in SPIRE 2 taking the drug, even during the shortened time frame of the study (HR 0.79; 95% CI 0.65–0.97).

When the patients from 2 trials were combined, those who had higher than the median % of LDL reduction saw a 25% decrease in primary endpoint events (HR 0.75; 95% CI 0.61–0.92). Additionally, when these patients were stratified by length of treatment, those who had a longer duration of exposure (mean 13.6 months) had a 17% reduction in events (HR 0.83; 95% CI 0.70–0.98), but there was no benefit observed in patients on bococizumab for a shorter duration of time (mean 5.6 months) (Figure 4).

There was a higher incidence of significant adverse events leading to drug discontinuation in patients on bococizumab compared with placebo (6.3% vs. 4.2%; P<0.001). This difference was primarily driven by a higher rate of injection site reaction in the study arm (10.4% vs.1.3%; P<0.001). "While bococizumab may not be available for clinical use, the public presentation of these data honours the altruism of our 31,887 trial participants and contributes to our understanding of PCSK9 inhibition and cardiovascular health", concluded Ridker.

Figure 4: SPIRE 1 and SPIRE 2: Combined trials primary endpoint (non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death), stratified by magnitude of LDL-C reduction (%) [9]



CARAT: HDL-mimetic fails to show benefit in acute coronary syndrome patients

Epidemiological studies suggest that high-density lipoproteins (HDL) protect against cardiovascular disease. However, HDL-C raising agents have not proven to reduce cardiovascular events in recent clinical trials. CER-001 is a negatively charged, engineered pre-beta HDL mimetic containing apoA-I and sphingomyelin with favourable effects on measures of lipid transport. Early studies demonstrated potential coronary plaque regression infusing low dose CER-001 in patients with acute coronary syndrome (ACS) and high plaque burden and on carotid plaque in genetic dyslipidaemia.

CARAT (CER-001 Atherosclerosis Regression ACS Trial) was designed as a proof of concept study to determine whether ten infusions of CER-001 at a dose of 3 mg/kg would provide a signal suggesting an impact on coronary atherosclerosis in patients with a recent ACS and higher plaque burden [11].

For CARAT, 301 ACS patients were randomized. All patients were on a background of contemporary therapy in the post ACS setting. Additionally, 150 patients received placebo and 151 patients CER-001. Primary study endpoint was the median change in percent atheroma volume (PAV) after 9 weeks of treatment. PAV was measured by intravascular ultrasound (IVUS), today's gold standard for atherosclerosis imaging. IVUS provides cross-sectional images of both the arterial wall and lumen with excellent resolution, reveals the diffuse nature of atherosclerosis and the involvement of reference segments, and considers vessel wall remodelling.

Another "victory" for placebo

There were no differences observed between the study drug and placebo in the overall primary endpoint (-0.09% vs. -0.41%; P=0.15) (Figure 5) or when looking specifically at the entire vessel length (P=0.64) or the most diseased 10-mm segment (P=0.51) (Figure 6). Further, there were no advantages observed for the study drug among any prespecified subgroups, but there were apparent benefits for placebo in patients with greater plaque burden and in those who had never been treated with a statin.

"Whether HDL therapy can impact plaque or clinical events in the setting of contemporary therapy remains to be determined, although with each disappointing study result the considerable challenge remains," said study presenter Stephen Nicholls, MBBS, PhD (University of Adelaide, Australia).

Figure 5 CARAT: Primary endpoint. No significant difference in the median change in percent atheroma volume (PAV) between placebo and HDL mimetic CER-001 [11]

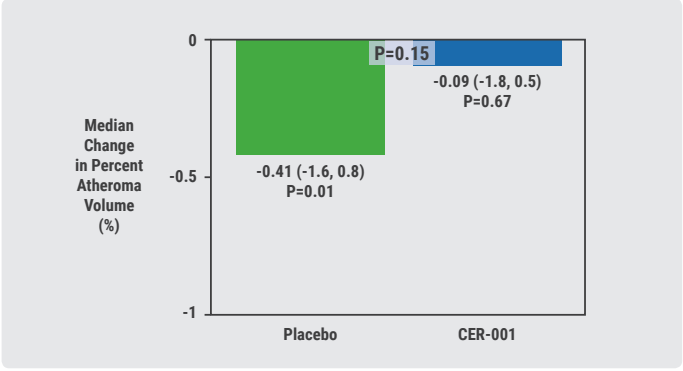


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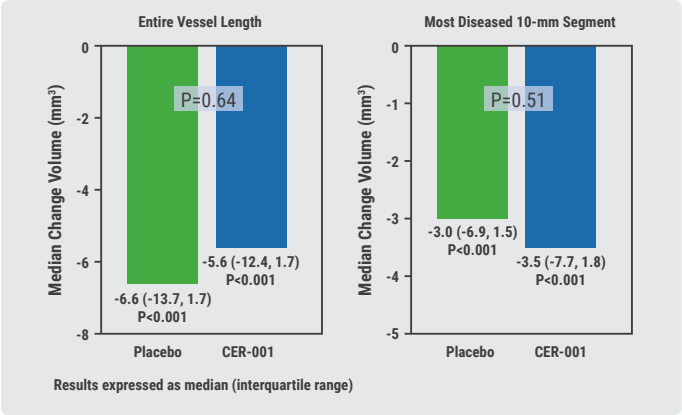
Figure 6 CARAT: No significant differences in the change in total atheroma volume in the entire vessel length or the most diseased 10-mm segment between placebo and study drug [11]



Late Breaking Clinical Trials - Oral Anticoagulation

Rivaroxaban is an oral anticoagulant, direct factor Xa inhibitor in clinical deveopment. A presentation of the outcome trial EINSTEIN CHOICE, showed the results that low dose of rivaroxaban is better than aspirin for preventing recurrence of venous thromboembolism (VTE) and safe for the patients with acute coronary syndrome (ACS). This was answered in the second session of the "Late breaking clinical trials" at ACC-17.

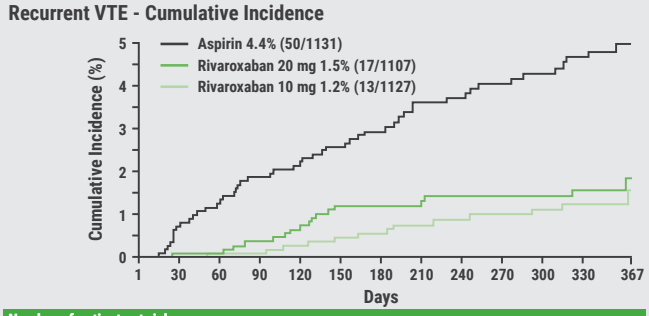
EINSTEIN CHOICE: low-dose rivaroxaban better than aspirin for preventing recurrence of VTE

In patients without reversible risk factors, the risk of recurrent venous thromboembolism (VTE) is up to 10% in the first year if anticoagulation therapy is stopped. Although extended anticoagulation therapy prevents recurrent venous thromboembolism, concerns about bleeding often lead to reluctance to continue treatment beyond 6 to 12 months. Lower dose anticoagulant therapy, or aspirin instead of an anticoagulant may reduce this bleeding risk. "To remove this uncertainty, head-to-head comparison is necessary to determine the relative efficacy and safety of these approaches", said EINSTEIN CHOICE co-investigator Phil S. Wells, MD, McMaster University, Hamilton, Canada, when presenting the results at the "Late breaking clinical trials" session [1]. The study was simultaneously published in the New England Journal of Medicine [2].

EINSTEIN CHOICE is the first randomized, double-blind, phase 3 study that directly compared low-dose rivaroxaban and aspirin in patients with VTE who had completed 6 to 12 months of anticoagulation. The patients were assigned to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or non-fatal VTE, and the principal safety outcome was major bleeding.

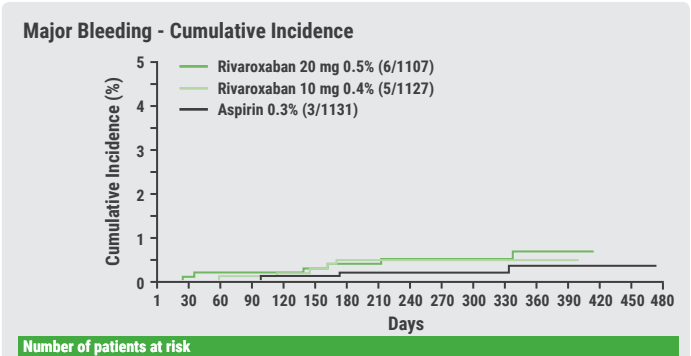
A total of 3,365 patients were included in the intention-to-treat analyses (median treatment duration, 351 days). The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1,127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1,131 patients (4.4%) receiving aspirin (Figure 7) (hazard ratio [HR] for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20–0.59; HR for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14–0.47; P<0.001 for both comparisons) [1] [2] "Compared with aspirin, numbers

Figure 7 EINSTEIN CHOICE: Both rivaroxaban regimens (20 or 10 mg once daily) were superior to aspirin for the primary efficay outcome of symptomatic recurrent VTE [1]



Number of patients at risk													
Rivaroxaban 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

Figure 8 EINSTEIN CHOICE: Similar rates of bleeding with both rivaroxaban regimens (20 or 10 mg once daily) and aspirin [1]



Number of patients at risk																
Rivaroxaban 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

needed to treat with rivaroxaban 20 or 10 mg for one year to prevent one VTE without an increase in bleeding are 33 and 30, respectively", Wells said.

Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group (Figure 8); the rates of clinically relevant non-major bleeding were 2.7%, 2.0%, and 1.8%, respectively [1] [2].

"Extended treatment with low-dose rivaroxaban provided nearly a three-fold greater reduction in recurrent VTE than aspirin with a similar rate of bleeding", Wells said. "Our findings show that it's a safe option and appears to be highly protective against potentially life-threatening recurrent VTE."

A follow-up study is planned to explore whether low-dose rivaroxaban is equally effective in other patient populations. Wells noted that the patients enrolled in EINSTEIN CHOICE were younger than the typical patient with VTE, which may limit the generalizability of the study results. In addition, the generalizability is limited by the fact that the study was not powered to detect differences between rivaroxaban 10 and 20 mg. Moreover, nearly 60% of the patients had provoked VTE and therefore do not qualify for longer treatment than 3 months.

GEMINI ACS 1: low-dose rivaroxaban as safe as aspirin in ACS patients

Dual antiplatelet therapy (DAPT, aspirin plus a P2Y12 inhibitor) has become standard of care treatment in patients with acute coronary syndromes (ACS), while nearly 10% of patients still suffer a major cardiovascular event during follow-up. The factor Xa inhibitor rivaroxaban reduced mortality and ischaemic events when added to DAPT, but caused increased bleeding. In-vivo thrombosis and bleeding studies have suggested that rivaroxaban in combination with a P2Y12 inhibitor had similar efficacy to DAPT, but with lower risk of bleeding. These findings, in concert with studies in post-PCI patients with atrial fibrillation (where aspirin was dropped), suggest that dual-pathway therapy with rivaroxaban and a P2Y12 agent may be a way to enhance overall outcomes in ACS.

The double-blind, multicentre, randomised trial GEMINI-ACS-1 aimed to assess rivaroxaban 2.5 mg twice daily vs. aspirin 100 mg daily, in addition to clopidogrel or ticagrelor, for patients with ACS started within 10 days after presentation and continued for 6 to 12 months. Patients received a minimum of 180 days of double-blind treatment with rivaroxaban 2.5 mg twice daily or aspirin 100 mg daily. The choice of clopidogrel or ticagrelor during trial conduct was not randomised and was based on investigator preference. The primary endpoint was thrombolysis in myocardial infarction (TIMI) clinically significant bleeding not related to coronary artery bypass grafting (CABG; major, minor, or requiring medical attention) up to day 390. Primary analysis was by intention to treat.

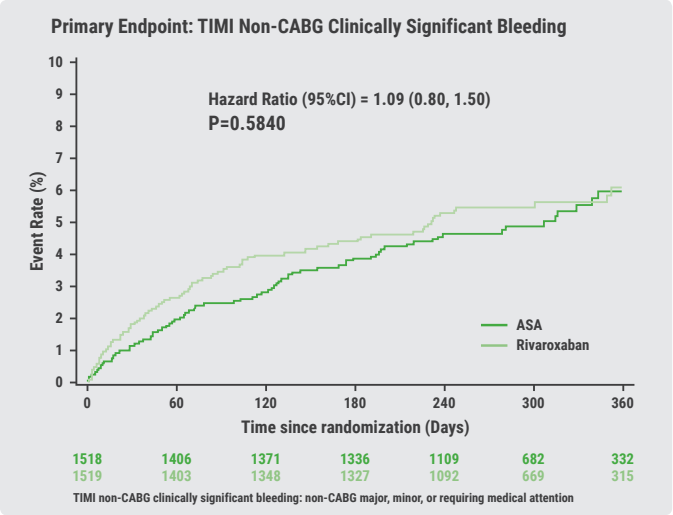
The study was presented by Magnus E. Ohman, MB, FRCPI, FESC, FACC, FSCAI, Duke University Medical Center, Durham, NC (USA) [3] and simultaneously published in the Lancet [4].

In total, 3,037 patients with unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI), with positive cardiac biomarkers and either ischaemic electrocardiographic changes or an atherosclerotic culprit lesion identified during angiography were randomly assigned. Of these, 1,518 received aspirin and 1,519 rivaroxaban. 1,704 patients (56%) were in the ticagrelor and 1,333 (44%) in the clopidogrel strata. Median duration of treatment was 291 days (IQR 239–354).

TIMI non-CABG clinically significant bleeding was similar with rivaroxaban vs. aspirin therapy (total 154 patients [5%]; 80 participants [5%] of 1,519 vs. 74 participants [5%] of 1,518; HR 1.09 [95% CI 0.80–1.50]; P=0.5840) (Figure 9).

Physician's choice of P2Y12 inhibitor varied significantly with country and baseline characteristics: ticagrelor treated patients were younger, and randomized earlier; more likely to have Non-STEMI, PCI, and use in Western Europe and North America (all P<0.001). The choice of P2Y12 inhibitor was therefore analysed as a subgroup. No significant treatment interaction with P2Y12 inhibitor use and randomized re-treatment for primary bleeding (P=0.5889) or exploratory ischemic endpoints (cardiovascular death, myocardial infarction, stroke, or definitive stent thrombosis; P=0.3889)

Figure 9 GEMINI ACS 1: TIMI non-CABG clinically significant bleeding was similar with rivaroxaban vs. aspirin therapy (primary endpoint) [3]



was shown. A limited post-hoc multivariate model for the primary endpoint noted a higher association of bleeding with ticagrelor use (P=0.0006), but it was also associated with region (P=0.02).

"In this phase 2 trial, we observed similar risk of TIMI non-CABG clinically significant bleeding with the combination of rivaroxaban 2.5 mg twice daily and a P2Y12 inhibitor compared with DAPT", said Ohman, adding that the exploratory composite ischemic outcomes were also similar, but that the trial was not powered for assessing this endpoint. There was no treatment interaction between the choice of P2Y12 inhibitor and randomized treatment of rivaroxaban 2.5 mg twice daily or aspirin on either the primary bleeding or the exploratory ischemic endpoint. Defining the best intensity of antithrombotic therapy while patients transition from the acute thrombotic setting to chronic prevention deserves more research", Ohman concluded.

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Prevention

Life style changes are an effective way to modulate cardiovascular risk. New data on physical exercise demonstrate that even a moderate increase in activity such as brisk walking can be beneficial.

Moderate activity improves cardiovascular fitness

Up to now, there have been no randomized trials regarding physical exercise in patients with hypertrophic cardiomyopathy. Therefore, extremely conservative physical-activity restrictions were recommended to these patients, and many abstained from any exercise. During the meeting, the results of the "Randomized Exploratory Study of Exercise Training in hypertrophic Cardiomyopathy (RESET-HCM)" were presented, the first randomized controlled trial to examine the feasibility of moderate exercise, such as brisk walking, for patients with hypertrophic cardiomyopathy [1].

The reassuring results: this moderate activity improved cardiovascular fitness without causing any harm to the patients. The moderate regular exercise did not trigger ventricular arrhythmia and sudden cardiac arrest or appropriate defibrillator shock, and none of the patients died. Dr. Sara Saberi, MD, University of Michigan, Ann Harbor (MI/USA) pointed out during the presentation, "our study provides support for a regimen of unsupervised brisk walking 4-7 days/ week for minimum 30 minutes, as a targeted intervention for patients with hypertrophic cardiomyopathy". The trial was simultaneously published [2].

From 2010 to 2015, the authors randomized 136, 18 to 80-year old adults (mean age 50) with hypertrophic cardiomyopathy. 17% of the patients had obstructive hypertrophic cardiomyopathy, 34% had an implantable cardioverter-defibrillator, and 4% had a history of sustained ventricular tachycardia or aborted sudden cardiac arrest, so generally they had a high risk of an adverse event. Genetic testing identified 49% as sarcomere mutation positive, 40% as mutation negative, and 11% as having variants of uncertain significance. The primary outcome was a change in exercise capacity (evaluated as change in peak VO2 from baseline to week 16). In addition, quality of life and exercise performance measures were performed as secondary outcomes. All patients received a pedometer and heart-rate monitor.

Unsupervised excercise program allowed individual preferences

Patients in the exercise-training group were given an individualized exercise program, in which they could cycle, walk/jog, swim, or use an elliptical trainer, but not to do strength or interval training. Before the start of the program, they received 1-hour consultation with an exercise

physiologist and they were instructed to do 20 minutes of exercise, 3 times in the first week, at 60% of their heart-rate reserve (based on their baseline cardiopulmonary exercise test) and a perceived moderate intensity. During week 2 to 4 the exercise time was prolonged by 5 to 10 minutes a week (up to 60 minutes) and patients were asked to exercise 4 to 7 times a week at 70% of their heart-rate reserve and a perceived moderate intensity. They were to maintain this exercise regimen for the rest of the 16-week study.
Patients in the usual-activity group continued with the exercise they did before the trial. Patient's activity was tracked using heart monitor data, pedometer data, activity logs, and weekly phone calls. By 16 weeks, 28% of patients in the usual-activity group and 93% of patients in the exercise-training group regularly exercised. The most common types of exercise were walking, jogging /running, swimming, using an elliptical trainer, and cycling. Patients peak VO2 increased absolutely by 6%. Exploratory secondary end points showed no differences except for reduced premature ventricular contraction burden and improved quality of life scores in the exercise group.

As Dr. Anjali Owens, MD, Assistant Professor at Perelman School of Medicine, University of Pennsylvania in Philadelphia (PA/USA) and Dr. Thomas Cappola, MD from the same institution wrote in an accompanying editorial, the findings of this clinical trial, although preliminary, represent an important beginning in using data from randomized clinical trials to guide exercise recommendations for patients with hypertrophic cardiomyopathy [3]. The exercise prescription investigated was simple, practical, and easily implemented in clinical practice. However, the trial was far too small to assess safety. Assessing safety would require a much larger study powered to clinical events, a longer duration of follow-up, and a higher-risk population. Therefore, additional trials are required to address these questions.

Get the breast cancer patients active

Another group of patients, which particularly benefit from physical exercise are breast cancer survivors [4]. Cardiovascular disease is the leading cause of death among breast cancer survivors.
A study evaluated the association between physical activity and risk of cardiovascular events (CVE), such as heart failure, MI, angina, coronary revascularization, PAD, carotid artery disease, TIA, stroke, and cardiovascular death. 4015 participants with non-metastatic breast cancer were studied in the WHI study. Physical activity prior to and around the time of breast cancer diagnosis was assessed in metabolic equivalent task (MET)-hrs/wk. based on a questionnaire assessing level of intensity, frequency per week, and duration per event. In a follow-up period of 12.7 years, there was a decrease in cardiovascular events with increasing level of exercise. The relative risk for cardiovascular events could be reduced by 37%, the risks of CV death by 59% in the highest quartile of physical activity vs. the referent quartile.
According to the authors, clinicians may use this data to promote exercise to lower the risk for cardiovascular disease in breast cancer patients. However, a limitation of this data is the fact, that this was an observational study without a control group.

Diabetics: longterm benefit from regular exercise

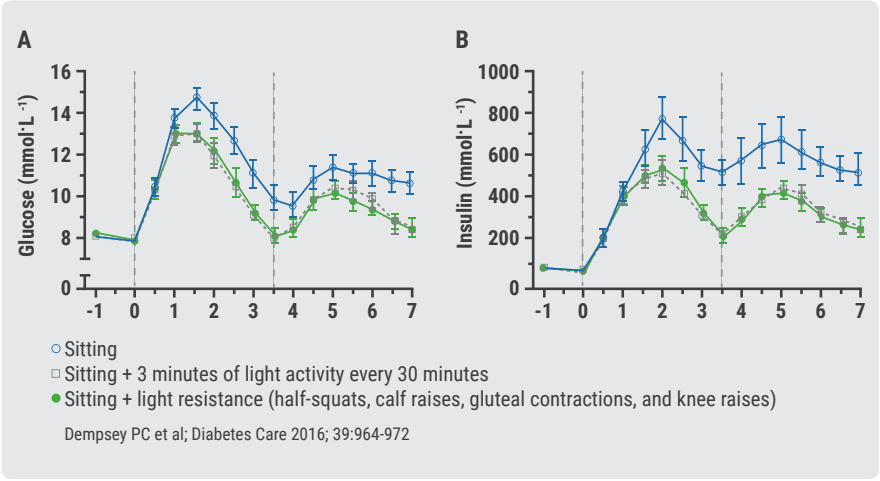
Prof. Stuart R. Chipkin, MD, endocrinologist at School of Public Health and Health Sciences in Amherst (MA/USA) answered the question, how much exercise is needed for glycemic control [5].
An exercise bout has not only an acute, but also a prolonged effect on glucose concentration. Acutely, glucose is lowered from muscle contractility, a process that does not involve insulin. However, late effects of exercise (12+ hours) make muscle more sensitive to insulin [6]. The study demonstrated that a single exercise bout is sufficient to reduce 24-hour average blood glucose concentrations during the first day. Therefore, the author takes up the cudgels for a daily training in diabetic patients.

Even short interruptions from sedentary time are beneficial

Light activity can improve glycemic control, e.g. breaks from sitting: a trial published last year showed that only 3 minutes of light activity (either light-intensity walking or simple resistance activities such as half-squats, gluteal contractions, and knee raises every 30 minutes) lower the post-meal glucose and insulin (Figure 1) [7]. Therefore, the American Diabetes Association took over the recommendation to reduce sedentary time separate from structured activity in a position statement [8]. Diabetics should decrease time spent in daily sedentary behaviours and interrupt prolonged sitting with bouts of light activity every 30 minute.

The Look AHEAD study was a large trial evaluation lifestyle intervention in overweight and obese patients with type 2 diabetes. Participants followed a modest diet and 175 minutes' exercise per week. This program had no effect on cardiovascular outcomes [9]. As Prof. Chipkin pointed out, this result might have been due to the fact that there was a very

Figure 1 Breaks from sitting lower post-meal glucose and insulin [7]



This showed a diabetes prevention program in 3234 participants with a BMI >24 and Glucose Tolerance Test (GTT) of 140-199 mg/dL. Patients were randomized to usual care, metformin or an intensive lifestyle intervention (diet and exercise) targeting 7% weight loss. Primary endpoint was the development of diabetes defined as fasting plasma glucose (FPG) > 126 mg/dL and/or Gamma GT > 200 mg/dL. The study was stopped early for evidence of benefit after a mean duration of 2.8 years. This modest weight loss of 5.6 kg in the intervention group reduced the risk of developing diabetes by 58% compared to placebo [13].

low overall rate of cardiovascular event. However, patients get benefit in multiple other ways: They had lower glucose and lipid levels, less kidney disease, less sleep apnea, less depression and a better quality of life. In addition, their insulin sensitivity improved and they were able to reduce diabetes medication. Although the greatest benefits were often seen at 1 year, participants still had greater improvements than the control group in weight, fitness, HbA1c, SBP, and HDL-C at 4 years [10].

Asymptomatic diabetics that plan on low-to moderate-intensity activity (e.g. brisk walking) do not need a pre-exercise medical clearance, which might only be an additional obstacle to start training. The American Diabetes Association recommends a moderate-to vigorous activity of 150 minutes or more weekly, spread over at least 3 days/week with no more than 2 consecutive days without activity. However, even shorter durations (75 minutes/week) of vigorous intensity or interval training may be sufficient activity. To prevent type 2 diabetes at least 150 minutes/week with goal of losing 5-7% of weight is recommended [8]. In general, supervised training is recommended over non-supervised training. According to Prof. Chipkin, regular exercise lowers HbA1c about 0.4-0.7%. A meta-analysis of aerobic exercise in diabetes showed that aerobic exercise lowers HBA1c by 0.7% [11]. "This effect would allow for approval of exercise by FDA as a medication", emphasized Prof. Chipkin.

How much weight loss is required to improve glycemic control in diabetics

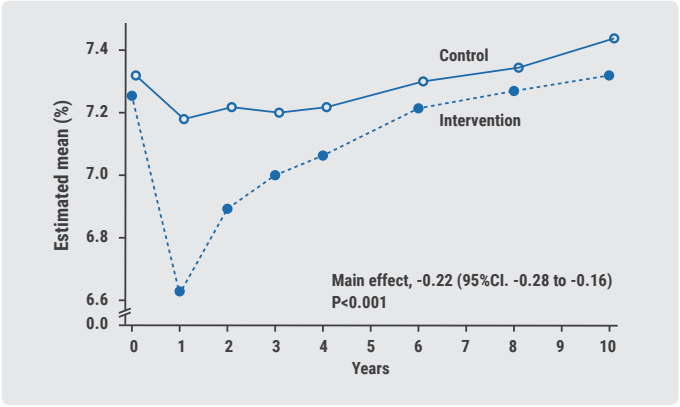
"It is well established already that a moderate weight loss can prevent type 2 diabetes in high risk patients", explained Dr. Steven E Nissen, Cleveland Clinic, Cleveland (OH/USA) [12].

However, in most cases intensive lifestyle mediated weight loss is not sustainable, as it could be shown in the Look Ahead Trial: the initial mean weight loss in the intensive lifestyle intervention group was 8.6%. This was followed by weight regain through year 5 and then a subsequent gradual decrease in weight, resulting in an average weight loss of 6.0% at the end of the trial 2 [14]. Even this modest weight loss improved the glycemic control. Although patients in the intervention group only lost 4 kg compared to the control group over a period of 10 years, this translated in a significant reduction of HbA1c values, especially over the first year of the intervention, that were at least partly sustained throughout follow-up (P<0.001, Figure 2).

Disappointing results of pharmacotherapy against weight loss

Can pharmacotherapy-assisted weight loss improve the glycemic control? Dr. Nissen pointed out, trials regarding medications for weight loss were disappointing. In 10,744 type 2 diabetes patients with cardiovascular disease, the additional therapy with sibutramine lead to a mean weight difference of 1.7 kg compared to placebo. However, patients treated with sibutramine had an increased risk of non-fatal myocardial infarction and non-fatal stroke [15]. In contrast, bariatric surgery proofed to be successful in the STAMPEDE trial. Over 5 years, change in HbA1c were compared in type 2 diabetes patients with a BMI of 27 - 43 undergoing intensive medical therapy or intensive medical therapy plus bariatric surgery (Plus Roux-en-Y gastric bypass or sleeve gastrectomy) [16]. Patients who underwent surgical procedures had a greater mean % reduction from baseline in HbA1c level, than the patients who received medical therapy alone (2.1% vs. 0.3%, P=0.003). In addition, triglycerides,

Figure 2 HbA1c values over 10 years in the Look Ahead trial [14]



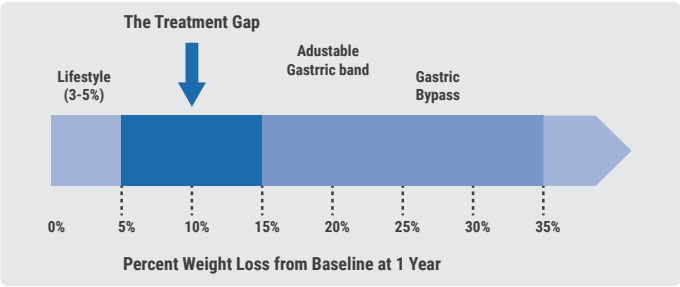
fasting glucose levels and HDL-levels over 5 years were significant better than placebo. In conclusion, lifestyle interventions lead to a weight loss up to 5% within a year, only with bariatric surgery a loss of more than 15% is realistic (Figure 3) "Unfortunately, our options between lifestyle and surgery are limited now", concluded Prof. Nissen.

Bloodpressure: how low is low enough?

One of the most effective ways to protect patients from cardiovascular events is to lower blood pressure. "Blood pressure trials showed that patients (at high risk /with systolic blood pressure ≥160 mm HG/diastolic blood pressure >90 mm) clearly benefit from this intervention", said Prof. Eva Lonn, Mc Master University in Hamilton (ON/Canada) [17].

In the HOPE-3 trial, it is less clear in patients with intermediate risk: treatment with candesartan at a dose of 16 mg/day plus hydrochlorothiazide at a dose of 12.5 mg/day over a period of 5.6 years, lowered the blood pressure by 6.0/3.0 mm Hg from baseline, but no significantly result in loweing the risk of major cardiovascular events (cardiovascular death, myocardial infarction, stroke) in an intermediate-risk population without cardiovascular disease [18]. In current

Figure 3 Regarding weight loss, there are limited options between lifestyle and surgery



guidelines, threshold for drug therapy is ≥140/90 in the American and European guidelines. According to JNC 8, in patients ≥60 years, treatment should be started ≥150/90. "In the very elderly, higher treatment targets reflects current evidence and heightened concern of precipitating adverse effect particularly in frail patients", said Prof. Lonn.

Optimal BP: around 130/80 mg

Prespecified subgroups of the HOPE-3-trial by 3rd of SBP showed that patients with SBP ≥143.5 mm Hg had a benefit of treatment regarding all primary and secondary endpoints [18]. "These data give a hint to the fact that 140 mm Hg is the BP level for initiation of pharmacological blood pressure lowering in primary prevention", said Prof. Lonn. The motto "the lower the better" does not apply to diabetic hypertensives. A trial published last year showed that anti-hypertensive treatment reduces the risk of mortality and cardiovascular morbidity in diabetics with a systolic blood pressure more than 140 mm Hg. If systolic blood pressure was less than 140 mm Hg, further treatment was associated with an increased risk of cardiovascular death, with no observed benefit [19].

Combined approach is most effective

Persons with ideal risk factor profiles have a low lifetime risk of CVD. "However, fewer than 5% of persons are able to maintain ideal risk factor profiles. Both LDL-C and systolic blood pressure (SBP) each have causal and cumulative effect on the risk of CVD", said Dr. Brian Ference, Wayne State University School of Medicine, Detroit (MI/USA) [20].
The HOPE-3-trial suggested benefit of combined LDL-C and SBP lowering was not greater than LDL lowering alone [21]. The results of this trial questioned the synergy between LDL- C and systolic blood pressure on the risk of cardiovascular events. To better understand the causal effect of combined exposure to LDL-C and SBP, Dr. Ference performed a Mendelian randomisation study design to assess the potential clinical benefit of long term exposure to combination of one mmol/L lower LDL-C and 10 mmHg lower SBP, which was presented during last year´s meeting of the European Society of Cardiology [22].

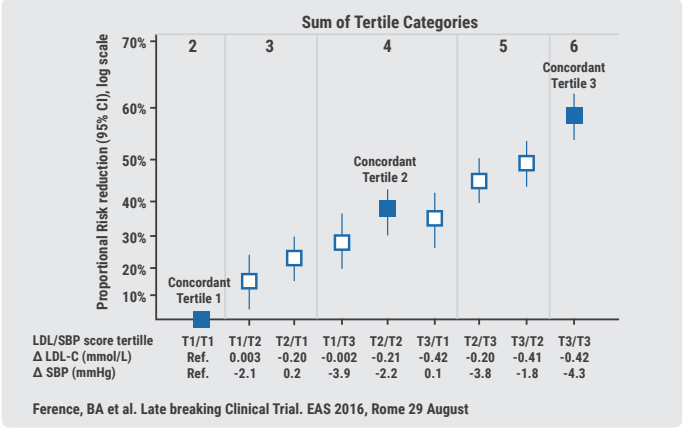
Simplified prevention strategy offers most effective protection

"We wanted to evaluate the potential clinical benefit of a simplified prevention strategy that focuses on 1 mmol/L lower LDL-C and 10 mm Hg lower SBP for a long period of time", said Dr. Ference. The study sample consisted of 102,7773

persons enrolled in one of 14 trials. Genetic score of LDL-C and SBP were used as both the instrument of randomisation and instrument of exposure. In this trial, long-term exposure to the combination of 1 mmol/L (18 mg/dL) lower LDL-C and 10 mm Hg lower SBP was associated with an almost 90% lower risk of major vascular events (first occurrence of CHD death, MI, stroke or coronary revascularization, Figure 4).

"We conclude from this that LDL-C and SBP have independent, multiplicative, and cumulative effects on risk of cardiovascular disease," said Dr. Ference. Because these effects are multiplicative and cumulative, long-term exposure to the combination of "modestly" lower LDL-C and SBP has the potential to dramatically reduce the lifetime risk of cardiovascular events, even among persons with apparently normal cholesterol and blood-pressure levels.

Figure 4 Dose-dependent effect of LDL-C and SBP. 1.0 mmol/L lower LDL-C and 10 mmHg lower SBP lead to 86% lower lifetime risk of CVD [22]



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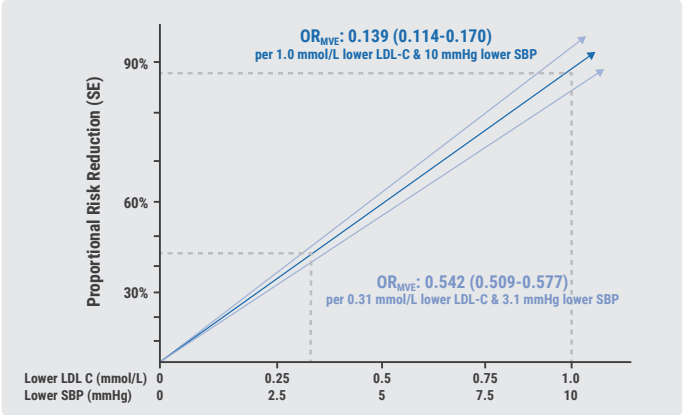

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Risk Factors: Revisited

This year in ACC conference, the risk factors for cardiovascular were discussed. Zika -infection associated with cardiovascular, marijuana use and its effect on heart. A new study, led by Jeffrey W. Meeusen, showed the potential novel biomarker, ceramide, is predictive for cardiovascular events, independent of known risk factors.

Cardiovascular complications following Zika-infection

Up to now, there are no reports of cardiovascular manifestation of Zika. Results from a study led by Dr. Karina Auristela Gonzalez Carta, Department of Medicine, Vanderbilt University of Medicine, Nashville (TN/USA) suggest that- the Zika virus may be linked to cardiovascular complications. Dr. Carta and colleagues enrolled 9 patients who reported symptoms and were treated at the Institute of Tropical Medicine in Caracas, Venezuela. Their mean age was 47 years and 6 were women. Only one patient reported previously well-controlled high blood pressure.

From July 2016, follow-up was conducted every 6 months. Out of 9, 8 patients with an active Zika infection had arrhythmias including acute atrial fibrillation. In 3 cases, 2 paroxysmal and 1 persistent, non-sustained atrial tachycardia in 2 patients and ventricular arrhythmias in 2 patients. 6 patients had heart failure (one with preserved ejection fraction, with pre-eclampsia and moderate to severe pericardial effusion). The study highlights the need to raise awareness about Zika's possible link to cardiovascular complications, especially because the data shows an initial average lag time of 10 days. "It is likely that many more people are affected," Carta said. "This is the first report of cardiac involvement in patients with Zika. We need larger, systematic studies to understand the actual risk of Zika-related cardiac problems and what makes one patient more prone to develop them" [1].

Marijuana use: harmful for the heart?

Medical and recreational marijuana has recently been legalized in several states and more to come. But is its use really harmless? To answer this question, Dr. Aditi Kalla, Medical University of South Carolina in Charleston (SC/USA) utilized a large national database to examine the incidence of cardiovascular risk factors and events amongst patients with cannabis use [2]. Patients aged 18-55 years with marijuana use were identified in a US database. Demographics, risk factors, and cardiovascular event rates were collected on these cannabis users and compared to general population data. Of the 20 million health records of young and middle-aged patients were analysed, marijuana use was diagnosed in 1.5%.

The alarming results: incidence of heart failure, cerebrovascular accident, coronary artery disease, sudden cardiac death, and hypertension were significantly higher in cannabis user patients. After multivariate regression adjusting for age, gender, diabetes mellitus, hypertension, coronary artery disease, tobacco use, and alcohol intake, cannabis use was not only associated with a 24% increase in the risk of stroke and 10% increase in developing heart failure, it was also linked to obesity, high blood pressure, smoking and alcohol use (Table 1)."More research will be needed to understand the pathophysiology behind this effect, particularly with continued legalization of cannabis" said Dr. Kalla.

Ceramide: a new marker for predicting cardiovascular events?

Ceramides are lipids that accumulate in tissues during hyperlipidemia, inflammation and upregulation of proinflammatory cytokines. They disrupt nitric oxide signalling and thus promote endothelial dysfunction.

According to a new study, led by Jeffrey W. Meeusen, PhD, blood concentrations of ceramides are a better marker than LDL-C for cardiovascular disease [3]. 499 coronary angiography patients were studied and followed up for a median time of 5.9 years. The primary endpoint of the trial

Table. 1: Differences between cannabis users and non-users. * indicate statistically significant difference (P<0.001) [2]

	Cannabis Use Mean age: 33.1 years* Sex: 60% male*	No Cannabis Use Mean age: 26.3 years* Sex: 38% male*
Hypertension	19.9%*	15.7%*
Diabetes Mellitus	7%*	7.8%*
Hyperlipidemia	7.2%	7.1%
Tobacco Use	47.2%	11.4%
Alcohol Use	28.1%*	3.8%*
Obesity	7%*	6.5%*

was a composite of myocardial infarction, stroke, coronary revascularization and mortality (MACE). In all the patients, ceramides were measured by mass spectrometry. 191 events occurred over 3,736 persons in years. Those with the highest levels of ceramides were nearly 4 times more likely to experience a cardiovascular event than those with the lowest levels (7.2 vs. 2.2%). With each one-point increase in a patient's ceramide risk score, risk rose by 9%. Ceramides were both predictive for patients with low or high LDL-C. This risk was independent of established risk factors like age sex, hypertension or smoking.

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2017 ACC International Conferences Best Posters Session

Many posters were presented at the 65th ACC Conference. Among them six were selected as Poster Winners and presented at the 66th ACC International Conferences Best Posters Session.

Poster no. # 453: Macrophage migration inhibitory factor serum levels and its association with acute coronary syndrome in patients with diabetes mellitus type 2

Author- Ontiveros- Mercado H, Munoz-Valle JF, Valerdi-Contreras L et al.

The Macrophage Migration Inhibitory Factor (MIF) is a cytokine mediator in the formation of intra-coronary atheroma plaques and in the heart's inflammatory and remodelling responses after acute coronary syndromes (ACS). MIF serum levels increase in the first 6 hours after acute myocardial infarction, are related to infarction size, and remain elevated until day 21 [1]. MIF also has been linked to insulin resistance [2] and there has been shown an increased MIF expression with the polymorphism (-794 CATT)5-8 in the MIF gene [3].

This case/control descriptive study was to determine if there is a relation between incidence and complications of ACS and prevalence of DM type 2 with MIF serum levels or factors promoting its expression [4]. 101 patients were classified in four groups:

1) healthy controls
2) patients with diabetes mellitus type 2 (DM2)
3) patients with ACS, without DM2
4) patients with DM2 and ACS

All subjects had a measure of lipid profile and HbA1C. MIF serum levels were measured in 80 study subjects by enzyme/linked immunosorbent assay, and genotype and echocardiographic analyses were performed. MIF serum levels and history of ACS were not related in patients with DM2. MIF serum levels were lower in the groups of patients with history of ACS and DM2 when they were compared with those with DM2 only. According to the authors, this could be the result of treatment for secondary prevention after the ACS. There was no significant relation with MIF serum levels and HbA1c levels. MIF expression or genotype of the polymorphism -794 (CATT)5-8 were not related to severity of ACS. The presence of the allele 5 was related to a minor left ventricle index volume following ACS when compared to those with any other combination of alleles.

Poster no. # 454: HER2 positive breast cancer and subclinical cardiotoxicity by echocardiogram 2D strain: does chemo-therapy sequence matter?

***Author-** Perez- Montessoro V, Poblano- Anguilar I, Vasquez-Ortiz Z et al.*

Patients with HER2 positive breast cancer can be exposed to cardiotoxic drugs (anthracyclines and/or trastuzumab even when there are free schemes of anthracyclines. There is evidence that the left ventricular ejection fraction (LVEF) is not sensitive to detect early cardiac changes. Clinical trials didn't show any disadvantages (efficacy or toxicity) for sequences in which the taxane was administered first. The FinHer study demonstrated lower cardiotoxicity (0.5%) when taxanes plus trastuzumab are given before anthracyclines. In the neoadjuvant setting, studies have collectively shown similar or increased complete pathological response rates in chemotherapy sequences where taxanes are given first [5]. In a retrospective cohort study, 46 patients with HER2 positive breast cancer, the authors evaluated the sensitivity of the longitudinal strain (GLS) in the echocardiogram to detect subclinical cardiotoxicity compared to the LVEF and potential differences in the cardiotoxicity in relation to the chemotherapy sequence used [6]. The patients were treated with sequential chemotherapy (anthracyclines followed by taxanes plus trastuzumab or taxanes plus trastuzumab followed by anthracyclines), with a 240 mg/m2 cumulative dose of doxorubicin.

One patient (2.1%) presented with symptomatic heart failure (NYHA Class III). During follow up, subclinical cardiotoxicity was present in 9 patients with a non-significant "P" value; and a significant decline in the GLS was observed in 10 patients. Comparing the basal characteristics in cardiotoxicity vs. the non-cardiotoxicity group, no significant differences were identified. The GLS decline (≥10%) basal vs. 3 months' measurement and the sequence with anthracyclines followed by taxanes plus trastuzumab were independent variables for cardiotoxicity (Table 1).

Table 1: Logistic regression analysis. Risk of cardiotoxicity

Variable	Odds Ratio	CI 95%	P-Value
Decline in GLS ≥ 10% Basal versus 3 Months	7.63	(1.04 - 55.86)	0.042
Sequence A→T+H versus T+H→A	7.7	(1.07-55.43)	0.045

A decline in GLS is more probable an early marker of cardiotoxicity than the LVEF. According to this retrospective study, the authors believe that in the neoadjuvant or adjuvant setting the order of sequential chemotherapy may impact the development of cardiotoxicity.

Poster no. # 455: Comparison of different lung ultrasound methodologies for pulmo-nary congestion evaluation in heart failure outpatients

***Author-** Yanez JPG, Gargani L, Picano E et al.*

Evaluation of pulmonary congestion (PC) is a diagnostic challenge even for highly skilled clinicians. Recently, lung ultrasound (LUS) has been proposed for a reliable, easy evaluation of PC in outpatient clinic, by assessment of B-lines, significantly correlating to more established parameters of decompensation. However, different LUS methodologies for PC diagnosis have been described. In this study, different LUS methodologies were tested as part of the evaluation of heart failure (HF) patients in an outpatient clinic [7].

LUS evaluation was independently performed during the outpatient regular visit and evaluated according to 3 different methodologies: 1) the 4 points-scheme: anterior left and right hemithorax wall is divided into upper and lower halves; 2) the 8 points-scheme: left and right hemithorax wall is divided into anterior and lateral, upper and lower halves; 3) the 28 points-scheme: the anterior and lateral right and left hemithorax are scanned from the second to the fifth intercostal spaces, along the parasternal, mid-clavicular, anterior axillary and mid-axillary lines, for a total of 28 scanning sites. 97 patients with advanced systolic HF were enrolled (age 52 ± 9 yrs., 61% male); 48% had dilated cardiomyopathy HF (mean ejection fraction 28 ± 4%). LUS feasibility was 100% (mean duration of the exam was 8.7 ± 2 min.). It was shown that B-lines score evaluation performed with the 8-points or 28-points schemes had a similar accuracy in PC assessment (Table 2). According to the authors, both methodologies can be applied for a quick and reliable evaluation of PC in HF outpatients.

Table 2: Different lung ultrasound methodologies performance

Variable	B-lines score	2≥ positive sites bilaterally
4 points schema	AUC .82 (.74-.9) Cut-off ≥4 (Sb 71%; Sp 75%)	Sb 15 Sp 100 PPV 100 NPV 28
8 points schema	AUC .89 (.83-.96) Cut-off ≥10 (Sb 87%; Sp 79%)	Sb 48 Sp 92 PPV 94 NPV 36
28 points schema	AUC .89 (.83-.96) Cut-off ≥15 (Sb 85%; Sp 83%)	Sb 55 Sp 92 PPV 95 NPV 40

AUC: area under the curve; NPV: negative predictive value; PPV: positive value; Sb: sensitivity; SP: specificity

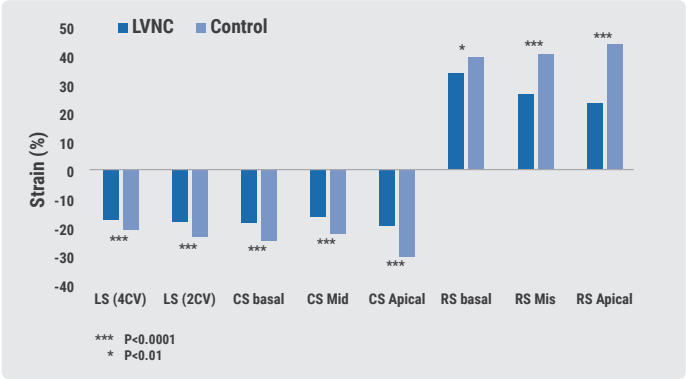
Poster no. #456: Assessment of left ventricular strain and its clinical correlations in isolated left ventricular non-compaction

Author- *Yubbu P, Montero A, Nawaytou HM et al.*

Isolated left ventricular non-compaction (LVNC) is a rare disorder characterized by numerous prominent trabeculation and deep intertrabecular recesses. The morphological distribution and clinical presentation are very variable. Myocardial deformation imaging demonstrates global and regional systolic dysfunction even with preserved ejection fraction.

The objectives of this study were to assess left ventricular (LV) global and regional strain patterns and clinical characteristic of isolated LVNC and to evaluate the correlation between the clinical characteristics and the morphological distribution of trabeculation [8]. In 30 patients with LVNC (47% male; median age 5.7 years) and 30 controls, longitudinal (LS), circumferential (CS) and radial strains (RS) were assessed by speckle tracking echocardiography (STE). The degree of non-compaction in each segment was graded and strain patterns were evaluated from a 16-segment model of LV. Compared to controls, global LS proved to be significantly lower (P=0.0008). CS at basal segments was significantly low in symptomatic patients compared with patients in NYHA class I (P=0.009). CS at basal, mid and apical regions was decreased (all P=0.0001) (Figure 1). LVEF correlated strongly with LS (r=-0.71, P<0.0001) and showed moderate correlation with CS (r=-0.43, P=0.02) but not with RS (r=0.2, P=0.27). Also strain pattern and clinical presentation correlated significantly with extension of non-compaction to mid- and basal- regions of LV. The authors concluded that LS and CS provide reliable information regarding regional myocardial function, adding that it is important to determine extension of LVNC to basal and mid septal regions, as it showed strong correlation with LV dysfunction.

Figure 1 Left ventricular strains



Poster no. #457: Nurse-led cardiovascular disease management program impact of 30-day re-admission in patients with heart failure

Author- *Odeh R, Alkhateeb M, Bdeir MB*

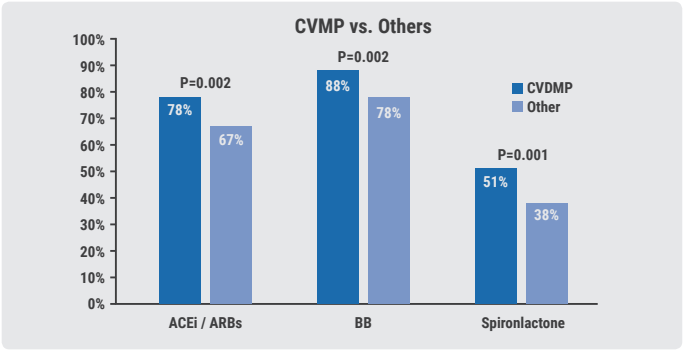
An observational retrospective cohort study from Saudi Arabia showed that a nurse-led program (CVDMP) was associated with a reduced 30-day re-admission rate and with improved utilization of guidelines medical therapy in patients with heart failure [9]. The study included all admissions to King Abdulaziz Cardiac center with the diagnosis of HF with reduced ejection fraction ≤ 45% or with symptoms of HF or with pulmonary edema. The patients were divided into two groups, those with 30-day readmission and no readmission. The study included the index admission of 786 patients with 825 index admissions with decompensated HF. Of these admissions, 35 (30 patients) and 790 admissions (756 patients) were categorized into 30-day re-admission and no re-admission, respectively. The overall 30-day re-admission rate was 4.2%. Patients who were followed up in the nurse-led HF program had significantly lower re-admission rates (1.8% vs. 5.2%; P=0.033) and showed a better adherence to the prescribed medical therapy (Figure 2). Stroke and longer length of stay were associated with higher 30-day readmissions rate.

Poster no. #458: Transcatheter aortic valve replacement vs. surgical aortic valve replacement in aortic stenosis patients at low to moderate risk of surgery: a meta-analysis of 25,737 patient's data

Author- *Elmaraezy A, Abushouk AI, Ismail A et al.*

The efficacy of transcatheter aortic valve replacement (TAVR) has been established for aortic stenosis patients at

Figure 2 Medical therapy in patients who were followed up in the nurse-led HF program (CVDMP) and others



high surgical risk. However, there is a lack in class-1 evidence about the efficacy and safety of TAVR in aortic stenosis patients at low to moderate risk of surgery. To provide a clear-cut evidence regarding the efficacy and safety of TAVR compared with surgical aortic value replacement (SAVR) for aortic stenosis patients at low to moderate surgical risk, the authors conducted a meta-analysis of published studies [10]. 14 studies (n=25,737 patients) were included in the final analysis. There was no difference between TAVR and SAVR in terms of short-term and long-term all-cause mortality. In terms of safety, SAVR was associated with lesser complications than TAVR. Due to the higher incidence of stroke (Figure 3), aortic regurgitation, permanent pacemaker implantation, and vascular access complications in the TAVR group, the author do not recommend this approach to be performed in aortic stenosis patients at low to moderate surgical risk.

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Figure 3 TAVR versus SAVR in aortic stenosis patients at low to moderate risk of surgery: Forest plot of stroke