

**TUESDAY 30 AUGUST**

## Arrangements now in place for the Pope's historic visit

ESC representatives met yesterday with Italian and Vatican security services to ensure the Papal visit proves an enjoyable, historic experience, while maintaining the security of the Pope and all ESC participants.

- On Wednesday 31 August there will be airport-style security at the main entrance, with designated fast-lanes for delegates with only hand luggage. Those with suitcases should leave them at the Cloakroom after clearing security.
- Buses will drop off delegates at the main entrance only. Delegates

should arrive by 11:00. The entrances will be closed shortly afterwards and remain closed until the end of the Pope's visit (by 13:15). There will be no restrictions on leaving Fiera Roma after 11:00.

- To reach the congress, ESC hotel shuttles will continue as scheduled, with arrival time at approximately 08:00. Services from ESC transportation points have been extended and will now run every 15 minutes from 06:45 to 10:00.
- The ESC Clinical Practice Guidelines Highlights session will start at 08:30 and the Congress

Highlights Session will start at 09:45. There are no other changes to Wednesday morning's programme.

- After the Congress Highlights Session ends at 11:45, ESC staff will guide delegates to the 'Passarella' on Level 1, the upper walkway that extends the length of the Congress site.
- The Pope is due to arrive at 12:15 in his Popemobile and will be driven slowly along the Passarella, giving delegates every opportunity to see him and take photos.
- ESC President, Professor Fausto Pinto, will say a few words to

welcome His Holiness who will then deliver a short address. This will be televised on large screens along the walkway.

- ESC will be providing a bus service to the airport from the main parking area outside Fiera Roma near the train station. This service will be free of charge and run between 11:00 and 15:00. If you wish to return to the city, please take a taxi or train.
- We thank you once again for your patience and co-operation and offer our best wishes for the remainder of ESC Congress.




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# Non-invasive imaging cuts needless angiography rate

**HOT LINE SESSION RESULTS**

Patients with suspected CHD whose care was guided by cardiovascular magnetic resonance (CMR) had significantly less unnecessary angiography than those whose care was led by guidelines. The study, which was described in a Hot Line presentation yesterday, did find, however, that CMR was not superior to myocardial perfusion scintigraphy (MPS).

The Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2 (CE-MARC 2) trial results, also published in *JAMA*, could have implications for referral rates for invasive coronary angiography and potentially for costs.

Principal investigator John Greenwood from the University of Leeds, UK said: 'Rates of invasive angiography are considered too high among patients with suspected CHD. Our findings now show that both CMR and MPS significantly reduced rates of unnecessary angiography compared to guideline-directed care, with no penalty in terms of major adverse cardiovascular events. This suggests that functional imaging should be adopted on a wider basis, even in high-risk patient subgroups.'

Early diagnostic pathways in patients with suspected CHD commonly use invasive CA - and this despite wide availability and recommendations for non-invasive imaging in international guidelines.

In explaining the background to the study, Greenwood said that evidence from large populations presenting with chest pain has confirmed that most will not have significant obstructive CHD. One large US study, for



John Greenwood: 'Rates of invasive angiography are considered too high among patients with suspected coronary heart disease.'

example, reported that approximately 60% of elective cardiac catheterisations found no obstructive CHD.

The CE-MARC 2 trial thus aimed to compare CMR, guidelines (which were those of the UK's National Institute for Health and Care Excellence, NICE) or MPS in reducing unnecessary angiography in suspected CHD. The study also considered if a CMR approach reduced patient risk and made financial savings.

Between November 2012 and March 2015, 1202 symptomatic patients from six UK hospitals with suspected CHD were recruited. They were randomly assigned to care management according to the NICE guidelines (n=240), to care based on the results of CMR (n=481), or MPS

testing (n=481). The primary endpoint was unnecessary angiography as defined by the absence of significant stenosis measured by FFR or quantitative CA.

Those assigned to the NICE group with a low likelihood of CHD (10-29%) were allocated to cardiac computed tomography (CCT); those with an intermediate likelihood (30%-60%) to MPS; and those with a high likelihood directly to CA.

Results showed that 22% of study subjects had coronary angioplasty within 12 months. In the NICE guidelines group 43% had invasive CA, 18% CMR and 16% MPS.

A CMR-guided strategy did significantly reduce unnecessary angiography when compared with the NICE guided care.

*Continued on page 2*

**Want more insights on sessions? Watch the interviews with the speakers!**

**ESC TV**

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**Don't Miss**

- **08:30 - 10:00 / 11:00 - 12:30** Forum (The Hub) Heart Team Sessions
- **08:30 - 18:00** Join us in the Poster Area to view the poster and attend Rapid Fire Abstract sessions in the Agora
- **10:00 - 11:00** Copenhagen (Village 5) General Assembly
- **10:10 - 10:50 / 13:00 - 13:40 / 15:40 - 16:20** Meet the Guidelines Task Force & Meet the Trialists sessions at coffee break in The Hub
- **11:00 - 12:30** Michelangelo (The Hub) ECG & Cardiac Imaging Quiz
- **16:30 - 18:00** Forum (The Hub) ESC Cardiology Quiz

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## Two studies of apheresis: one in refractory angina, one in raised cholesterol

ONE STUDY in a Hot Line session yesterday suggested a new indication for apheresis among patients with refractory angina, while a second raised the possibility that apheresis could be replaced by a PCSK9 inhibitor in patients with familial hypercholesterolaemia.

Apheresis, which is both expensive and time consuming and can only be performed in specialist centres, is generally regarded as a last-resort for patients with persistently elevated LDL. A new study now suggests that it may also have a role to play in removing lipoprotein (Lpa) in patients with refractory angina.

It is known that around 15% of patients with angina do not respond to available therapies, explained Tina Khan, one of the study investigators from Imperial College, London. 'Refractory angina is a challenging condition,' she said, 'which continues in spite of optimal medical therapy and revascularisation and imposes much burden on patients. There's a desperate need for new therapeutic options.'

Lpa has been established as an independent cardiovascular risk factor in a multitude of studies, but cannot be effectively lowered with conventional lipid lowering agents. 'We believe that Lpa contributes to angina by causing endothelial dysfunction through plasma viscosity, and in addition adheres to the intima more aggressively than LDL cholesterol,' said Khan.

The study randomised 20 patients with refractory angina and Lpa  $\geq 500$  mg/L to three months of blinded weekly Lpa apheresis or sham procedures. Results showed that the primary endpoint of myocardial perfusion reserve, measured by cardiovascular magnetic resonance, increased from 1.45 to 1.93 following apheresis, but decreased during sham procedures by -0.1, yielding a statistically significant increase for the active treatment group ( $p < 0.001$ ). Results also showed significant improvements in secondary endpoints including exercise capacity (measured by the 6 minute walk test), angina symptoms, quality of life and atheroma burden.

'Despite our small sample size we got a highly significant result for our primary endpoint,' said Khan. The investigators, she added, had been surprised to find that 60% of the 100 patients with refractory angina screened for the study had Lpa levels  $\geq 500$ mg/L. 'With drug therapies now emerging that reduce Lpa, apheresis may not represent the ultimate therapy for these patients. In future we would like to explore whether these new



Tina Khan: A 'desperate need' for new therapeutic options in refractory angina.

therapies match up to apheresis.'

In the second apheresis study, ODYSSEY ESCAPE, which was published simultaneously in the *European Heart Journal*, investigators set out to investigate whether alirocumab, a fully human monoclonal antibody that inhibits PCSK9-mediated hepatic catabolism of the LDL receptor, might reduce the need for apheresis.

For the study 62 patients with heterozygous familial hypercholesterolaemia (HeFH) started out with apheresis, and were then randomly assigned 2:1 to alirocumab 150 mg subcutaneously every two weeks for 18 weeks ( $n=41$ ) or placebo ( $n=21$ ). Until week 6 the apheresis rate was fixed according to an established schedule, then from weeks 7 to 18 the rate was adjusted according to individual LDL response.

In the alirocumab group the per cent change in apheresis between week 1 to 6 and then weeks 7-18 was -53.7 compared with +1.6 in the placebo group ( $P < 0.0001$ ). Furthermore LDL was reduced by approximately 50% from baseline in the alirocumab group versus a 2% increase in the placebo group.

'Alirocumab-treated patients had a 75% additional reduction in the standardised rate of apheresis treatments versus placebo-treated patients,' said study presenter Patrick Moriarty, from University of Kansas Medical Center. 'Treatment with alirocumab may allow patients with HeFH to terminate or reduce the frequency of lipoprotein apheresis.'

## CE-MARC 2 study in angina

Continued from page 1

However, there was no significant difference from an MPS-guided strategy.

There were no statistically significant differences between the three groups for the secondary endpoints of MACE and positive angiography. The latter was observed in NICE as 12.1%, CMR 9.8% and MPS 8.7%.

Greenwood said: 'These results show that a broader use of functional imaging - CMR or MPS - in low, intermediate and high risk patient groups could reduce the rates of invasive angiography which will ultimately show no obstructive coronary disease.'

'In addition, CE-MARC and CE-MARC 2 further support the role of CMR as an alternative to MPS for the diagnosis and management of patients with suspected CHD.'

**The Hot Line stem cell study presented on Sunday by Javed Butler is not named CHART-1 as reported in Congress News. Please excuse this error.**

## A combination concept for 'dramatic' lower risk

LONG-TERM exposure to the combination of even modestly lowered LDL cholesterol and systolic blood pressure (SBP) has the potential to deliver synergistic effects that dramatically reduce a person's lifetime risk of CVD, according to a study in yesterday's Hot Line.

'The results demonstrate for the first time that LDL cholesterol and systolic blood pressure have independent, multiplicative and cumulative causal effects on the risk of CVD,' said study presenter Brian Ference from Wayne State University School of Medicine, Detroit. 'Our study confirms that CVD events are largely preventable.'

Previous studies have suggested that people with ideal risk factor profiles have very low lifetime risks of CVD, but the causal effects of combined lowering of LDL and SBP are unknown.

In this study investigators used genetic and cardiovascular risk factor data from 102,773 subjects of 14 prospective cohort or case-control studies. Genetic LDL and BP scores were used as instruments to 'naturally randomise' the subjects to lower LDL, lower SBP, both or neither, using a 2x2 factorial randomisation design.

Results showed that a total of 14,368 major vascular events (a composite of major vascular event, CHD death, MI stroke or coronary revascularisations) occurred during up to 32 years of follow-up. In comparison to the reference group (where neither were lowered), subjects in the lower LDL group had 54.2% lower risk of the primary outcome (OR 0.454), subjects in the lower SBP group had 44.7% lower risk (OR 0.553), and those in the combined lower LDL and

SBP group had an 86.1% lower risk (OR 0.139).

'Because their effects are multiplicative and cumulative, long-term exposure to the combination of modestly lower LDL 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,' said Ference.

The prevention of CVD, he added, can be substantially improved and simplified by designing prevention programmes which focus on promoting long-term exposure to the combination of lower LDL levels and lower SBP beginning in early adulthood. Instead of using more pharmacotherapy, he said, it would be important to introduce lifestyle changes that included increased activity to lower blood pressure and cholesterol.



Brian Ference: LDL cholesterol and systolic blood pressure have independent causal effects

## Better PCI with optical coherence tomography

The invasive imaging technique of optical coherence tomography (OCT) can lead to better patient outcomes than with standard angiography-guided PCI, according to the Does Optical Coherence Tomography Optimise Results of Stenting? (DOCTORS) study presented in a Hot Line session yesterday and published simultaneously in *Circulation*. The study also demonstrated that OCT allowed clinicians to see significantly more thrombi and calcifications before stent implantation.

OCT involves introducing an imaging catheter into the coronary artery to check vessel size and lesion characteristics as well as stent positioning and expansion. It has several potential advantages over angiography including the ability to assess

post-procedural results that cannot be seen by angiography.

The aim of DOCTORS was to evaluate whether the use of OCT during PCI would provide useful clinical information beyond that obtained by angiography alone. The aim was also to establish whether this information would modify physician decision-making, with impact on the functional result of angioplasty. The angioplasty assessment was based on fractional flow reserve (FFR) measured after stent implantation in a lesion responsible for NSTEMI-ACS.

The multicentre trial was performed in nine hospitals in France in 240 NSTEMI-ACS patients. They were randomised either to OCT before PCI and after stent implantation, or to standard fluoroscopy-guided PCI alone (angio group) performed before and after stent implantation.

The primary endpoint of FFR was significantly better in the OCT group than in the angio group (82.5% vs 64.2%). Also, the number of patients with a post-procedural FFR  $> 0.90$  was significantly higher in the OCT group (82.5% vs 64.2%).

Study presenter Nicolas Meneveau said additional prospective studies are needed before OCT can be recommended for standard use. However, he said the results from DOCTORS could translate into promising benefits. 'Our findings add to the cumulating body of evidence in favour of a potential benefit of OCT to guide angioplasty,' said Meneveau, from the University Hospital of Besancon, France.



Nicolas Meneveau: More evidence for OCT.

# New European guidelines on dyslipidaemias retain treatment targets for cholesterol



By Christian Funck-Brentano  
Pitié-Salpêtrière University  
Hospital, Paris



and Lina Badimon  
Hospital de la Santa Creu i Sant Pau  
Barcelona

THE 2016 ESC/EAS GUIDELINES for the management of dyslipidaemias have just been released, an update and revision of the 2011 guidelines and again the result of a collaboration between the European Atherosclerosis Society (EAS) and ESC.

With an estimated CVD death rate of >4 million people in Europe each year, prevention of CVD and related death remain a major public health objective. The recently published 2016 European Guidelines on CVD prevention has extensively reviewed this important issue and the 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias focus on measures targeting a healthy lifestyle and managing dyslipidaemias.

The guidelines first discuss the importance – and difficulty – of assessing total CV risk in an individual. Persons with documented CVD, type 1 or 2 diabetes, very high levels of individual risk factors and chronic kidney disease are automatically defined as persons at very high or high total CV risk. For all other people, emphasis is placed on the estimation of 10-year risk of CV death using HeartScore (<http://www.HeartScore.org>), a system calibrated to take into account

variable risk estimates across European countries. Four risk categories are defined: low, moderate, high and very high and a table describes intervention strategies for each of these four categories as a function of different LDL-cholesterol levels. These categories are used throughout the guidelines to make recommendations on how to handle dyslipidaemias.

Evaluation of laboratory lipid and apolipoprotein parameters is discussed. Screening for dyslipidaemias should be considered in all adult men  $\geq 40$  years of age and in women  $\geq 50$  years of age or postmenopausal. Total cholesterol, triglycerides, HDL-cholesterol, LDL-C and non-HDL-C are the suggested primary analyses used for baseline lipid evaluation. Apolipoprotein B is proposed as an alternative risk marker in subjects with high triglyceride levels. For risk estimation, except in patients with diabetes, non-fasting sampling for LDL determination has a predictive strength similar to fasting, so non-fasting LDL levels can be used in screening and in general risk estimation.

The Task Force, well aware that the AHA/ACC guidelines of 2014 on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults have abandoned treatment targets, has used a distinct approach and retained targets based on data from basic sciences, clinical observations, genetics, epidemiology and clinical trials. Thus, in patients at very high CV risk, an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended. Other secondary targets are indicated for non-HDL-C and apolipoprotein B.

A chapter is then dedicated to lifestyle modifications to improve the plasma lipid profile. It is stressed that lifestyle modifications

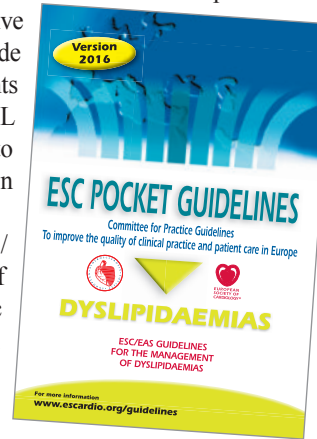
(diet, exercise, body weight control) are the primary treatment of dyslipidaemia, ahead of lipid lowering drugs and in combination with drug therapy when the latter becomes indicated. A section on strategies to encourage adoption of healthy lifestyle changes and adherence to lipid-modifying therapies is presented.

The demonstrated benefits of statins and their potential side effects and how to deal with them is discussed. Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are introduced in this 2016 version. The absolute benefit from ezetimibe added to a statin is described as small but significant. PCSK9 inhibitors are presented as very powerful LDL-C lowering drugs awaiting confirmation of a

therapeutic benefit based on ongoing randomised clinical trials looking at clinical outcomes. Recommendations are made for drug treatments of hypertriglyceridaemia.

Finally, a large chapter is dedicated to the management of dyslipidaemia in different clinical settings. Fourteen sub-chapters describe the management of dyslipidaemia in familial dyslipidaemias, children, women, older persons, diabetes, patients with coronary artery disease or stroke and other clinical situations.

In summary, this is a complete and well written guideline that will help physicians to treat patients with the best possible protocols.



Don't miss:

The new dyslipidaemias guidelines  
29 August 14:00-15:30 Rome - Main Auditorium

Passion for Innovation.  
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ENSURE-AF study data will be presented in the Hot Line session today at 14:00 in the Main Auditorium



Daiichi-Sankyo

## Hot line preventive strategies 2

Tuesday 30 August 2016 – Main Auditorium 14:00-15:30

**14:00 ENSURE-AF STUDY: EDOXABAN FOR CARдиоVERSION OF ATRIAL FIBRILLATION**  
Andreas GOETTE (Paderborn, Germany)

14:18 ANNEXA-4 - ANDEXANET ALFA FOR REVERSAL OF FACTOR XA INHIBITORS IN PATIENTS WITH ACUTE MAJOR BLEEDING  
Stuart J CONNOLLY (Hamilton, Canada)

14:36 REVERSE II - MULTI-NATIONAL VALIDATION OF THE MEN CONTINUE AND HERDOO2 RULE TO IDENTIFY LOW RISK UNPROVOKED VENOUS THROMBOEMBOLISM PATIENTS WHO CAN DISCONTINUE ANTICOAGULANTS  
Marc RODGER (Ottawa, Canada)

14:54 SENTINEL TRIAL - A RANDOMIZED MULTICENTER TRIAL OF CEREBRAL PROTECTION IN TAVR  
Susheel KODALI (New York, United States of America)

15:12 YEARS - SAFETY AND EFFICIENCY OF A SIMPLIFIED DIAGNOSTIC MANAGEMENT ALGORITHM FOR 3500 PATIENTS WITH CLINICALLY SUSPECTED ACUTE PULMONARY EMBOLISM  
Tom VAN DER HULLE (Leiden, Netherlands)

ENSURE-AF

This session is an official scientific session of the ESC Congress, Daiichi Sankyo has, in no way been involved in, contributed to, or affected the outcome of this/these scientific session(s), wholly devised and organised by the ESC Congress Programme Committee.

# A new President of ESC, with a keen commitment to legacy and continuity

AT 50 YEARS OF AGE, Jeroen Bax today becomes the youngest and latest President of the European Society of Cardiology. 'The ESC is like a big ship moving steadily forward,' Bax told *Congress News*. 'I see it as a privilege to continue the visionary legacies of my immediate predecessors Fausto Pinto, Panos Vardas, Michel Komajda and especially Kim Fox and William Wijns, who entrusted me with my first contributions to the ESC.'

'Continuity is of tremendous importance. There's no point in change for the sake of change. I aim to build on the strengths of a ship that has already embarked on a successful voyage.'

For ESC Congress 2017, to be held in Barcelona, Bax plans to expand the clinical track. 'Since 90% of people attending our meeting are involved in treating patients,' he explains, 'it's important to provide a strong clinical component. My aim is to use case studies to demonstrate how new drugs and technology translate into guidelines and clinical practice for better care of patients.'

Bax, from Leiden University Medical Centre in the Netherlands, says this approach should not detract from strong basic science and translational tracks, which remain vital components of the Congress.

Greater emphasis, he says, will be placed on registry studies. 'Randomised clinical trials don't always cater sufficiently for real life patients with multiple co-morbidities. Registries reflect daily, clinical patient care and therefore provide a valuable contribution to clinical trials.'

Bax, a staunch believer in effective teamwork, has appointed a variety of new chairs to ESC committees, including Stephan Achenbach to the Congress Programme Committee, Alec Vahanian to the Registry Committee, Stephan Windecker to the Committee for Practice Guidelines and Paulus Kirchhof to the Education Committee. In addition, he looks forward to working



with the elected members of the ESC board and the Heart House staff in Nice and Brussels.

Interaction between the guidelines, registry and education committees, he stresses, will be especially important. 'We are building a continuous cycle whereby guidelines will be written and then tested in registries, and any differences and discrepancies identified will automatically be fed back into guidelines,' he says. 'These activities will form the basis of our educational materials.'

ESC Education has many initiatives planned, including the highly anticipated launch of the next edition of the ESC Cardiovascular Textbook. The textbook, edited by Thomas Luscher, Patrick Serruys, Gerald Maurer and John Camm and scheduled for publication in 2017, has a new online component, which allows a much more dynamic format and the possibility of regular updates.

As Vice President of the ESC for National Societies (2012-14), Bax gained insights into the wider organisation of the Society when he toured more than 50 national and affiliated societies. 'These visits,' he says, 'opened my eyes to the inequalities in healthcare that still need to be addressed in Europe and beyond.'

Bax has previous experience with ESC committees, including chairing the Practice Guidelines Committee (2010-12), Press Committee (2008-10), Scientific Programme Committee for the 2007 and 2008 ESC Congresses, and ESC Working Group on Nuclear Cardiology and Cardiac CT (2004-6). It allowed him greater appreciation of the importance of the ESC Associations and Working Groups. 'They're the recognised driving force of the ESC community,' he says, 'and we need to provide them with autonomy, but at the same time avoid fragmentation. Providing a united front in cardiology allows us to stand stronger to promote better access for patient care.'

Bax describes himself as a 'multimodality imager, interested in how to apply technology to improve day-to-day patient care'. He has expertise in nuclear cardiology, CT, MRI and echocardiography. Imaging, he says, provides the bridge between pathophysiology and therapeutics. 'Visualisation allows you to better determine how to treat patients and lays the foundation for personalised care,' he adds. 'Now, the opportunity to further contribute to the ESC in the role of President is an extraordinary honour.'

## How the gut may yet hold a key to CVD prevention

THE WAY TO a man's heart is through his gut microbiota. So in a Symposium this afternoon Marius Trøseid will suggest that gut bacteria may provide the 'missing link', explaining why some diets, such as the Mediterranean diet, are beneficial for the heart, while others, such as those rich in red meat, are detrimental.

The human gut microbiome is a complex ecosystem harbouring a staggering 100 trillion microbes, representing an estimated 5000 species. 'The range of possible bacteria combinations creates the possibility for extreme variation between individuals,' says Trøseid, a consultant in infectious disease from Oslo University Hospital. 'We are learning how diet can shape both the composition and metabolic output of the gut microbiota.'

There is growing realisation that gut microbes function as 'dynamic endocrine organs' generating biologically active metabolites that enter the circulation and have biological effects at distant sites. Aberrant gut microbiota profiles have been associated with obesity, types 1 and 2 diabetes and non-alcoholic fatty liver disease. Indeed, studies demonstrate that transfer of microbiota from obese animals to their lean germ-free counterparts produces an obese phenotype associated with insulin resistance.

Recent studies have described new pathways through which gut microbiota participate in the pathogenesis of CVD. In a two-step process, trimethylamine-N-oxide (TMAO), a substance known to have detrimental CVD effects, is formed following ingestion of dietary nutrients from the trimethylamine group (consisting of choline, phosphatidylcholine and carnitine) found in meat, eggs and high-fat dairy products. First, specific intestinal microbes have been shown to form TMA,

which is absorbed into the circulation, and then catalyzed in the liver by the host enzyme hepatic flavin monooxygenase into TMAO (Nature Med 2013, 19: 576-585).

'These studies provide a clear pathway for CVD which appears responsive to red meat consumption but is much reduced in vegetarians,' says Trøseid.

Studies in mice treated with broad spectrum antibiotics suppressing intestinal flora demonstrate the essential role for gut microbiota in the formation of both TMA and TMAO (N Engl J Med 2013; 368: 1575-1584). In this same study the investigators, led by Stanley Hasen, showed that TMAO promotes

atherosclerosis through foam cell formation and interferes with reverse cholesterol transport from atherosclerotic plaques. Plasma levels of TMAO have been shown to predict prospective CVD risks, including incident heart attack, stroke and death.

Such studies raise the possibility that TMAO levels might be modifiable, with potential therapeutic approaches - including using antibiotics to kill the microbes, faecal transplants to promote good bacteria, and the development of selective enzyme pathway inhibitors targeting pathways involved in production of harmful metabolites.

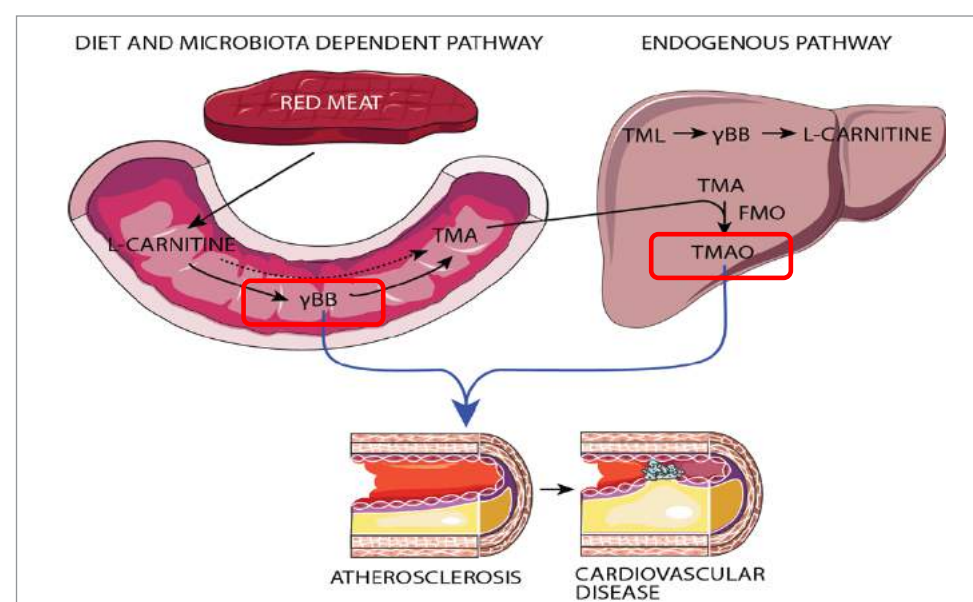
One recent mouse study by Zeneng Wang

and colleagues from the Cleveland Clinic showed that inhibiting microbial TMA lyase production through microbial TMA lyase inhibition both reduced TMAO levels and inhibited macrophage foam cell formation and atherosclerotic lesion development.

'Such research raises the future possibility that people's personalised treatment selection for CVD prevention might eventually be based on their microbiome readouts,' suggests Trøseid. 'Variations in gut microbiota might also be used for personalising diets.'

In a separate presentation, Ana Timoteo will explore how one-day dietary interventions might also be individualised. While some studies show low fat diets are more effective for weight loss, others have found low carbohydrate diets to be more effective. In a recent analysis (combining data from the POUNDS LOST and DIRECT studies) Qibin Qi and colleagues found that subjects with a cholesteryl ester transfer protein mutation (CETP rs3764261) on high-fat diets had larger increases in HDL cholesterol (P=0.0001) and decreases in triglycerides (P=0.0007) than those on low-fat diets. The differences were not observed among those with other genotypes.

'This suggests that some populations may not respond well to low fat diets and that it may be related to specific genetic variants. It raises the possibility for future personalized dietary interventions based on people's genetic backgrounds,' says Timoteo, from Santa Marta Hospital, Lisbon.



Gut microbiota - the missing link between diet and atherosclerosis?

Recent studies suggest that the gut microbiota plays a role in development of atherosclerosis by interacting with specific nutrients such as carnitine from red meat and choline from egg and dairy products. These nutrients are precursors of gamma-butyrobetaine (gamma-BB), trimethylamine (TMA), and trimethylamine (TMAO), the latter produced after oxidation in the liver. gamma-BB and TMAO have been linked to atherosclerosis in animal models, and elevated plasma levels predict cardiovascular disease in humans. Therapeutic strategies include targeting the gut microbiota composition, tailoring the diet or inhibiting bacterial enzymes. As the gut microbiota composition is highly variable, a personalized approach is probably necessary. Figure modified from Skagen, Trøseid et al, Atherosclerosis 2016.

Don't miss: Coconut oil and avocado, saturated fat and other hot topics in diet.  
30 Aug 16:30-18:00 Reykjavik - Village 7

# Number of elderly people with heart failure set to double by 2040

THE NUMBER of elderly people with heart failure has been predicted to double by 2040, and triple by 2060, according to the AGES-Reykjavik study summarised at an ESC press conference on Sunday. The session featured other studies showing that four out of five people with HF do not receive optimal treatment and frequent admissions to hospital are associated with high death rates.

'The findings are a wake-up call for policymakers that more must be done to prevent HF,' said Ragnar Danielsen from Landspítali University Hospital, Iceland, and lead author of the AGES-Reykjavik study. 'This includes prompt treatment for heart attacks and adherence to preventative therapies and lifestyle changes afterwards,' he said.

The study, a collaboration between the Icelandic Heart Association and US National Institute on Aging, analysed 5706 randomly selected elderly subjects aged between 66 and 98 years (mean age 77 years, 58% men). Results showed an overall HF prevalence of 3.7% (4.8% for men, 2.8% for women); prevalence was 1.9% for those  $\leq 69$  years, 2.5% for those 70-79 years and 6.0% for those  $\geq 80$  years, with HF higher in men across all groups.

Further analysis calculated that the predictive



Ragnar Danielsen: Growth in prevalence of heart failure a 'wake-up' call for policymakers.

relative increase would be 1.20 by 2020, 1.8 by 2030, 2.2 by 2040, 2.60 by 2050 and 2.9 by 2060.

A second study, led by Pardeep Jhund from the University of Glasgow, Scotland, was designed to investigate whether HF patients in the UK receive treatment consistent with European guidelines. The guidelines recommend that those with reduced ejection fraction (HFrEF) should receive an ACE inhibitor and/or ARB combined with a beta blocker, and also that in many patients a mineralocorticoid receptor agonist (MRA) should be added.

The study examined the records of 14,546 HF patients included in the UK Clinical Practice Research Datalink to check if therapy was in line with guidelines. Results showed that 80% of patients were receiving an ACE inhibitor or ARB, 57% a beta blocker; and 31% an MRA. However, many of the prescriptions failed to achieve recommended target doses.

'Our results emphasise how evidence-based guideline recommended therapies are under-used and used at lower doses than those shown to be effective,' said Jhund. 'Prescription rates of therapies must increase, and therapies must be prescribed at higher doses to reduce hospitalisations.'

## A beta blocker for HF may help prevent anthracycline toxicity

A BETA BLOCKER used to treat HF and hypertension prevents doxorubicin-induced cardiotoxicity, according to a study presented at the same press briefing. Additionally, the investigators showed that newer imaging modalities, such as tissue Doppler and speckle tracking, led to earlier detection of cardiac injury in cancer patients.

The cardiotoxic effects of anthracyclines, which can occur up to 20 years after treatment, are thought to be caused by heart cells experiencing free radical exposure. Nebivolol is a cardioselective beta blocker known to have anti-oxidant, anti-apoptotic and vasodilator properties.

In this current study, 60 women with HER-2 negative breast cancer (mean age 52 years) scheduled for doxorubicin chemotherapy were randomised to nebivolol (n=30) or placebo (n=30).

After six cycles of doxorubicin, the investigators found left ventricular ejection fraction and fraction shortening and left ventricular diameters measured by two-dimensional echocardiography did not change significantly in either group. However, in the control group

tissue Doppler imaging revealed significant alterations of LV diastolic function, and speckle tracking showed statistically significant alteration of LV systolic function of longitudinal and radial strains.

'Our study also demonstrated the utility of new echocardiographic methods, such as tissue Doppler and speckle tracking imaging, in the early detection of ventricular dysfunction induced by cytostatic treatment,' said Mirela Tomescu, from Timisoara, Romania.



Mirela Tomescu used new echocardiographic technologies to detect anthracycline effects.

## Practical management of patients with atrial fibrillation – individualized approaches to stroke prevention

Find out more at our Satellite Symposium

Join us on Tuesday 30 August 2016, 12.45–13.45, Room Berlin – Village 4

Moderated by chairs:  
John Camm and Riccardo Cappato

Bayer Satellite Symposium at ESC Congress 2016.  
Bayer Pharma AG, June 2016.  
L.IT.MKT.06.2016.1478

# More than 2000 MiRNAs in the human genome - and most have a role in CVD

## Therapeutic options for MiRNAs include delivery by DES

A SCIENTISTS OF TOMORROW Symposium this morning will hear how microRNAs (miRNAs) play a major role in the pathogenesis of CVD and may soon be targeted by novel therapies.

MiRNAs, first discovered in 1993 but not identified in humans until early in the new millennium, are defined as short non-coding RNAs whose main mechanism of action is to up-regulate or downregulate RNA. Over 2000 miRNAs have now been identified in the human genome and shown to influence a wide range of CVD processes, including cell death, fibrosis, angiogenesis, cardiomyocyte proliferation and cardiac reprogramming.

'Non-coding RNAs, such as miRNAs, were initially dismissed as junk DNA,' says Lars Maegdefessel, who will speak about miRNAs as therapeutics for heart disease. 'But we have since learnt they play a major role in almost all biological processes through influencing stability and translation of messenger RNA. We know miRNAs are involved in the development and progression of most CVD.'

MiRNAs, which are around 20 nucleotides in length, are transcribed just like regular messenger DNA but processed differently to form 'double hair pin loop' structures. 'These small folded structures can be transported out of the nucleus into the cytosol, a key characteristic that makes them eminently druggable,' explains Maegdefessel, from the Karolinska Institute, Stockholm.

Therapeutic approaches in development for modulating miRNA levels include antagomiRs (synthetic reverse compliments of oligonucleotides) that bind and silence target miRNAs, or miRNA mimics simulating the effects of increased levels of miRNAs.

The first miRNA inhibitor to enter clinical trials was miravirsen (SPC3649) for treatment of chronic hepatitis C virus infections. Miravirsen was developed as an antagomiR to miR-122, a miRNA known to be essential for the replication of HCV RNA. The phase 2a study showed dose-dependent reductions in HCV RNA levels that lasted up to 10 weeks beyond the active treatment phase, with good safety and side effect profiles. A phase 3 trial is currently under way. 'Hepatitis is undoubtedly the poster boy for miRNAs,' says Maegdefessel. 'The reason it's



Lars Maegdefessel, left, will review the therapeutic possibilities of MiRNAs, while Mauro Giacca will address their potential in cardiac regeneration.

ahead of the game is that most drugs end up in the liver, so there aren't many targeting issues.' The heart is also a front runner since it is possible to gain access through catheters.

Addressing the problem of miRNA delivery, Maegdefessel and colleagues have recently demonstrated the feasibility of using a coatable drug eluting stent to deliver miR-21. 'Such technology opens the way for using miRNAs to stabilise plaques prone to rupture,' he says. Avoiding off-target effects in organs in which miRNA modulators assimilate to a much higher extent than the CV system is crucial, making the search for suitable delivery platforms important.

In CVD the greatest advances have been obtained targeting miR-92a, a miRNA known to inhibit angiogenic sprouting and vessel formation.

In a pig model of MI, Stephanie Dimmeler and colleagues from the German Centre for Cardiovascular Research showed catheter-based delivery of antisense miR-92a reduced both miR-92a expression and infarct size. A first-in-man study is now planned for 2017, and a first-in-patient study for 2018.

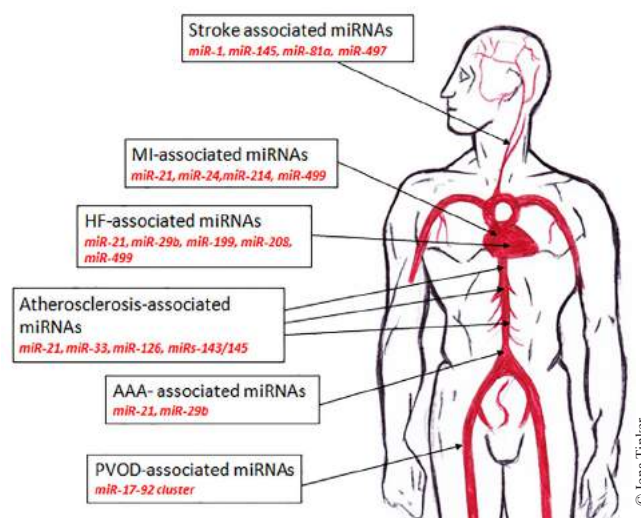
Mauro Giacca will address the potential for miRNA in myocardial regeneration. 'In mammals the capacity for myocardial regeneration is more or less lost at birth. After lack of progress with stem cells investigators have changed track and started to explore miRNAs as the switch to turn back

on the cardiomyocyte's ability to proliferate,' says Giacca, from the International Centre for Genetic Engineering and Biotechnology, Trieste, Italy.

First, Giacca and colleagues screened a library of human miRNAs by transfecting rat neonatal cardiomyocytes in vitro with different miRNAs. From the resulting proliferation and cell division, the team identified 40 miRNAs prompting cells to proliferate and further narrowed the field down to miR-199a as the most effective agents in rodents, pigs and humans. In experimental mouse models of MI the team used viral vectors to deliver miR-199a and demonstrated cardiac regeneration.

The challenge, says Giacca, who recently replicated his results in pigs (unpublished), is that human hearts are far bigger, making it necessary to have the capacity to regenerate billions of cardiomyocytes. 'Another issue is that we have performed our experiments in healthy young animals, and don't quite know how proliferation will affect older people's hearts or whether there may be a risk of creating arrhythmias,' says Giacca.

MiRNAs in cardiovascular disease and regeneration  
30 Aug 11:00-12:30 Bernini - The Hub



Micro RNAs that have been associated with cardiovascular disease.

## Bringing the medics and surgeons back together

A SYMPOSIUM WILL today explore the interaction between cardiologists and cardiac surgeons on heart teams - and highlight the need for improvement.

Multidisciplinary team-working in cardiology is already widely adopted in TAVI, revascularisation and HF. Now well established in oncology, this heart team approach involves specialists - including surgeons, consultants, nurses and anaesthetists - sharing knowledge and expertise on the best way forward for patients without an obvious treatment pathway.

Surgeons on TAVI and revascularisation teams will be involved throughout. However, adult intensive care specialist Susanna Price says this is not the case with HF teams where surgeons are only visible at the initial and end stages. This mind-set, however, needs to change, says Price, a consultant cardiologist and intensivist at the Royal Brompton and Harefield NHS Foundation Trust in London. 'I'm concerned that this is far removed from what a multidisciplinary team should be,' she adds. 'We're missing a trick because it's the surgeons who are developing all these new therapies based on robotics and extracorporeal circuits. They're very innovative but don't have a role [on HF teams] - it's a missed opportunity.'

In addition, Price believes that surgeons are vital in specialist teams set up to treat cardiogenic shock. Apart from in isolated centres, she says, 'very little' is being done to improve mortality rates for this condition, which are currently around 50%. They could be reversed though if institutions deployed 'shock' teams dedicated to delivering early intervention to patients - for example, extracorporeal membrane oxygenation



Susanna Price and Hendrik Treede will each make the case for a stronger multidisciplinary heart team with the inclusion of cardiac surgeons.

(ECMO). These teams would bring together cardiac surgeons, interventional cardiologists, perfusionists, imaging specialists, cardiac anaesthetists as well as nurses. Says Price: 'It would be like having a cardiac arrest team but with an added surgeon and identifying patients immediately. The 2015 resuscitation guidelines acknowledged that ECMO might be used in cardiopulmonary resuscitation, so using ECMO earlier could become a thing of the future.'

The degree of co-operation between cardiologists and surgeons is an issue too in the interventional treatment of valvular disease. Hendrik Treede will acknowledge in today's Symposium that TAVI has become the perfect example of

successful collaboration between cardiologists, cardiac surgeons and imaging specialists. However, he will also highlight how the extent of collaboration varies, not only between centres but also between countries.

'In many countries interventional treatment of heart valve disease is often in the hands of cardiologists alone and surgeons are not involved,' says Treede from the Comprehensive Heart Center, University Hospital Halle, Germany. 'The consequence is that indications and treatments are no longer discussed, choice of access routes is limited and additional risks may be taken.'

In some centres, a situation even exists where two TAVI teams work in parallel. The impact is that they are not profiting from the wealth of skills which exists among the respective specialists. Treede believes an 'everybody does everything' policy is necessary to improve the interaction between cardiologists and surgeons. His vision is for them to be cross trained in all relevant skillsets, for financial budgets to be shared and for all interventional heart valve therapies to be done together. He adds: 'What's also required are regular heart team sessions and decision-making for every patient where different treatment options are available.'

Don't miss: The heart-team based practice in 2016: space for improvement in the interaction between cardiologists and cardiac surgeons?  
30 August 14:00-15:30 Sarajevo - Village 2

# Disappointing trial results have not yet shut the door on renal denervation

FALLOUT FROM the surprisingly negative SYMPLICITY HTN-3 trial in catheter-based renal artery denervation will be explored in a Symposium this afternoon. One of the Symposium's speakers, Felix Mahfoud, described the findings as 'a complete shock to many of us because the pathophysiology rationale behind renal denervation had seemed so plausible'.

In the Symposium, organised by the European Association of Percutaneous Cardiovascular Interventions (EAPCI), Mahfoud will explain how renal denervation procedures are being improved through better understanding of the anatomy of the renal sympathetic nerves, improved use of ablation techniques and better identification of populations most likely to derive benefit.

'The field is currently being rebooted with additional trials to build a new clinical basis to allow us to move forward,' says Mahfoud, from Saarland University Hospital in Germany. 'We are only just starting to understand the true complexity of the sympathetic nervous system in renal denervation and are far from ready to write off this technology.'

The unmet need in hypertension, says Mahfoud, is emphasised by the fact that at best only two out of three patients are controlled by the current pharmaceutical range. 'This means there are a huge numbers of people with uncontrolled hypertension who could benefit from different approaches to treatment.'

Renal denervation uses radiofrequency energy, ultrasound or chemical denervation to disrupt renal nerves within the renal artery wall, thereby reducing sympathetic efferent and sensory afferent signalling to and from the kidneys. It is known mechanistically that renal sympathetic fibres provide a key link between the central nervous system and the kidney, and play a role in the renal angiotensin aldosterone system.



Felix Mahfoud: SYMPLICITY HTN-3 'a complete shock to many of us'.

In 2009 the landmark proof-of-concept Symplicity HTN-1 study by Henry Krum and colleagues demonstrated the feasibility of catheter-based renal denervation for resistant hypertension. The non-randomised study in 45 patients showed a mean 27/17 mmHg decrease in blood pressure at 12 months.

Since then, however, the clinical evidence for renal denervation as an effective technique in patients with resistant hypertension has been conflicting. Three randomised trials - Symplicity HTN-2, PRAGUE 15 and DENERHTN - support both safety and efficacy of the therapy, but the sham-controlled

SYMPLICITY HTN-3 trial failed to show superiority over medical therapy alone.

However, post-hoc analysis studies of SYMPLICITY HTN-3 are providing insight into factors that may influence efficacy. One recent analysis found greater reductions in office and ambulatory blood pressure among patients who received both a higher number of ablations (>9) and ablations delivered in all four-quadrants within the renal artery. In another post hoc analysis Mahfoud and colleagues showed that the BP-lowering effects of denervation were significantly less pronounced in patients with isolated systemic hypertension (characterised by increased vascular stiffness) compared with patients with combined systolic-diastolic hypertension.

Currently, around seven randomised controlled trials are ongoing evaluating new catheter designs, including the SPYRAL HTN-ON MED study, the SPYRAL HTN-OFF MED study, both using the SPYRAL multi-electrode denervation system with sham control, the REDUCE HTN: REINFORCE trial using the Vessix denervation system, and the RADIANCE HTN trial using a dedicated ultrasound RDN system.

'It is to be hoped these results will be available in time for the next set of European Society of Hypertension and ESC guidelines on hypertension,' says Mahfoud. The current 2013 guidelines, he adds, give renal denervation a IIB recommendation for treating patients with hypertension. Undoubtedly, he adds, the biggest mistake was to name the trial Symplicity. 'They should have called it the Complexity study!'

Don't miss: Hot topics in interventional cardiology 2016  
30 Aug 14:00-15:30 Helsinki - Village 2

## What science can do

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# Do the results of clinical trials influence your practice? Which ones have changed the way you work?



Madhav Menon  
Interventional cardiologist  
Waikato Hospital  
Hamilton, New Zealand

For me, one trial that's had a major impact is the PLATO trial. It demonstrated that ticagrelor was superior to clopidogrel in the reduction of cardiovascular death, MI and stroke. As a result, all ACS patients in New Zealand have been changed from clopidogrel to ticagrelor instead. Only the elective PCIs get clopidogrel now. It's hard to notice a difference (in outcomes) but stent thrombosis has decreased because of better stent technology, better use of imaging and better stents. But we're increasingly seeing older patients - octogenarians are now common in our practice - and it would be good to see clinical trials addressing this patient group.



Andrew Roy  
Interventional cardiologist  
Institut Cardiovasculaire Paris Sud,  
Paris, France

Evidence-based medicine is of course regarded as the gold standard. But it's important to understand trial design as well as endpoints - some endpoints can be regulatory driven and some clinically driven. And not all trials are applicable to all patient populations - physicians have to interpret them. PARTNER 1 and PARTNER II, which essentially compared TAVI with surgery, have impacted on my practice. My patients are elderly with severe aortic stenosis, a progressive condition with high mortality if left untreated. Those at high risk for surgery would be offered medical therapy, which has very poor outcomes. With TAVI as an option, we're treating patients with symptoms rapidly then seeing them discharged after a few days and returning to good function. So the impact has been pretty dramatic.

## faces in the crowd



Riet Dierckx, Heart failure  
cardiologist in OLV Ziekenhuis  
Aalst-Asse-Ninove Belgium

Of course clinical trials influence my practice. The SHIFT trial on heart failure is one that especially has had an impact. Now, if I see a patient who is well treated and on optimal beta blocker but still with a high heart rate such as 78 beats a minute, then I'd use ivabradine to slow the rate down. Before, I would probably have left it at this rate. We've had a few patients who've done quite well through this approach. Of course, the government must need convincing to reimburse these new treatments, which is especially the case when you have conflicting data.



Syed Fasih Ahmed Hashmi  
Professor of cardiology  
Liaquat University Hospital, Sindh, Pakistan

If there is not good evidence for best practice then that's malpractice in my view. Clinical trials are therefore vital in providing evidence for best practice to improve patient outcomes. For me, the PARADIGM-HF trial was a game changer. It showed that then novel drug LCZ696 reduced the risk of cardiovascular death by about 20% compared with treatment with enalapril. It means much better management of HF patients - those who didn't respond to treatment before now respond well with the new medication. Most of our patients are older - 70% are over 65. Before we'd use beta blockers but PARADIGM has changed all that.

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