Highlights: 12th Metabolic Syndrome, Type 2 Diabetes Mellitus and Atherosclerosis (MSDA) Congress

Saint-Petersburg, 8-10 June 2017

MSDA

R3i Residual Risk Reduction initiative

- **Why we need to rethink residual vascular risk**
- **Coming of age of SPPARMα with the launch of PROMINENT trial**

Metabolic syndrome is one of the key challenges in cardiovascular disease prevention in the 21st century. Clinical experts from across the disciplines of cardiology, endocrinology and atherosclerosis research came together at the 12th MSDA Congress, held at the Federal Almazov North-West Medical Research Centre, Saint-Petersburg, Russia.

Triglycerides take centre stage

Opening the Congress, **President of the International Atherosclerosis Society (IAS), Professor Yuji Matsuzawa, Sumitomo Hospital, Japan** emphasized the importance of finding new approaches to manage the metabolic syndrome, given the pandemic in obesity, prediabetes and diabetes, driven by an increasingly sedentary lifestyle. A new IAS Working Party will focus on this issue. **President of the European Atherosclerosis Society (EAS) Professor S. Lale Tokgözoğlu, Hacettepe University, Ankara, Turkey** echoed the need for collaborative approaches between academic societies to address this challenge.

In his Opening Ceremony lecture, **Co-Chair Professor Evgeny Shlyakhto, President of the Russian Society of Cardiology**, highlighted obesity as the key driver of the metabolic syndrome, underpinning the development of atherogenic dyslipidaemia (elevated triglycerides and low high-density lipoprotein cholesterol [HDL-C]), hypertension, prothrombotic changes, and insulin resistance.

> ***Studies show that already from a young age, one-half of adults in Russia have abdominal obesity, rising to 75% in those aged 50 years or more. Environmental factors, principally lifestyle, are the key driver of this epidemic, and their impact on genetic factors – epigenetics – is becoming increasingly relevant***
>
> Professor Evgeny Shlyakhto, Federal Almazov North-West Medical Research Centre, Saint-Petersburg, Russia

In support, Professor Shlyakhto cited recent research from Saint-Petersburg relating to the *FTO* gene, which codes for the Fat mass and obesity-associated protein (alpha-ketoglutarate-dependent dioxygenase *FTO*). **Professor Kostreva (Saint Petersburg, Russia)** added that studies have suggested a possible role for the *FTO* gene in regulation of appetite and metabolic balance. There is also emerging evidence that genetic polymorphisms in this gene are associated with increased arterial hypertension, low HDL-C, and hypercholesterolaemia (*Korelskaya 2014*). These findings are clearly relevant when considering the multifactorial pathogenesis of the metabolic syndrome. Studies indicate a mediating role for adipokines in the development of other complications associated with the metabolic syndrome, including atrial fibrillation, decreasing bone mass, and even dementia.[1-3] In a report from the Swedish Dementia Registry, patients with diabetes were at higher risk of both vascular and mixed dementia, and were also diagnosed at a younger age than those without diabetes.[3] The link between type 2 diabetes and dementia, exacerbated by aging, is truly a *'ticking time bomb'* for the future.

From a management perspective, a key question is whether healthy overweight individuals should also be targeted. The evidence, however, clearly reinforces the need for treatment, to improve insulin sensitivity, prevent progression of subclinical atherosclerosis, as well as improve the cluster of risk factors associated with cardiometabolic disease. In the extreme example, bariatric surgery for the obese has been shown to have beneficial effects beyond weight loss, notably improvement of atherogenic dyslipidaemia, remission of type 2 diabetes, and in the longer-term, improved cardiovascular outcomes.[4]

For the future, research is needed to explore the role of emerging risk markers, as well as to understand the impact of the environment on cardiometabolic disease. These strategies may offer new therapeutic targets, as well as the possibility of correcting risk by genome editing.

'We need a paradigm shift in the management of cardiometabolic disease. In the era of precision medicine, we should focus on the 'hidden risk', derived from the underlying pathogenetic factors, as well as earlier, targeted prevention'

Professor Evgeny Shlyakhto,
Saint-Petersburg, Russia

Re-visiting residual risk in type 2 diabetes: what genetic insights offer

In his Opening Ceremony lecture, **Co-Chair Professor Jean-Charles Fruchart, President of the Residual Risk Reduction Initiative** (R3i, http://www.r3i.org/) discussed how genetic studies have provided the key to unlocking a number of novel targets with potential for managing elevated triglycerides, a marker for triglyceride-rich lipoproteins and their remnants. Chief among the important players in the regulation of plasma triglycerides are apolipoprotein AV (apoAV), lipoprotein lipase (LPL), apolipoprotein CIII (apoCIII), and the angiopoietins 3 and 4 (ANGPTL3, ANGPTL4).

Genetic studies have identified a causal role for triglyceride-rich lipoproteins in cardiovascular risk, supporting observational evidence that elevated triglycerides contribute to residual vascular risk. ApoAV and LPL were both shown to decrease plasma triglycerides; loss-of-function (LOF) variants in genes encoding these lipoproteins were associated with higher plasma triglycerides and, correspondingly, an increased risk of coronary artery disease.[5-8] In contrast, LOF mutations in *APOC3* and *ANGPTL4* were associated with decreased plasma triglycerides

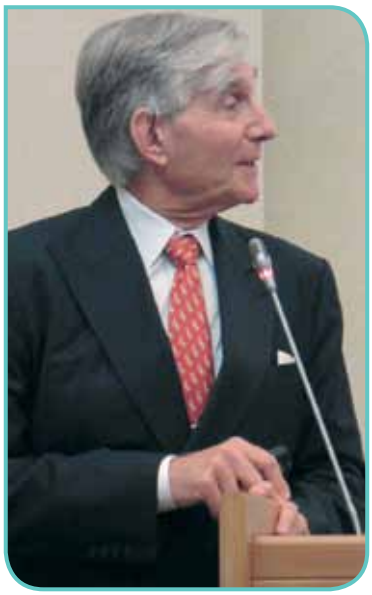
"These genetic findings have driven the development of pharmacotherapeutic approaches directed to some of these novel targets; the very latest clinical studies add significantly to this story. For example, as reported in late May, an antisense oligonucleotide targeting human ANGPTL3 reduced levels of atherogenic lipoproteins, triglycerides and very low-density lipoproteins by up to 60%[13]"

Professor Jean-Charles Fruchart, President of the Residual Risk Reduction Initiative

and reduction in the risk of coronary artery disease.[9-11] In very recent reports, genetic data from population studies provided proof of concept for the link between deficiency in *ANGPTL3* and coronary risk; heterozygous carriers of *ANGPTL3* LOF variants had 17% lower circulating triglycerides, as well as 34% lower coronary artery disease risk; similarly, subjects in the lowest tertile for circulating *ANGPTL3* plasma levels had 35% reduction in the risk of a coronary event.[12] The clinical relevance of these findings is underscored by prevalence data suggesting that these variants may be common, in the case of *APOA5* variants, contributing up to 50% of the increase in plasma triglycerides levels, depending on ethnicity.[6]

Importantly, these insights reinforce the pivotal role of **peroxisome proliferator-activated receptor α (PPARα)**, a member of the nuclear hormone receptor superfamily, as the master regulator of key genes involved in triglyceride regulation. PPARα also regulates non-lipid pathways, specifically inflammatory and vascular responses. Such findings are highly relevant when considering very recent data which implicate inflammation as an important contributor to residual vascular risk.[14]

Triglycerides, atherogenic dyslipidaemia and PPARα: targets for residual vascular risk



Atherogenic dyslipidaemia, recognized as a key driver of residual cardiovascular risk, is conventionally defined as the combination of low HDL-C levels and elevated triglycerides. As discussed by **Professor Peter Libby (Brigham and Women's Hospital, Boston, USA)**, much of the past focus has been on HDL-C, supported by extensive epidemiological evidence that low HDL-C is an important modifiable risk factor for cardiovascular disease. However, genetic studies failed to deliver; in particular, a key study showed no association between an increase in HDL-C levels according to genetic score (based on 14 variants associated with HDL-C levels) and risk for myocardial infarction (MI), whereas there was concordance for low-density lipoprotein cholesterol (LDL-C).[15] Added to this, clinical studies investigating novel approaches to raising HDL-C levels have been disappointing. The latest of these trials, **ACCELERATE (A Study of Evacetrapib in High-Risk Vascular Disease)**, failed to show any benefit on cardiovascular outcomes in high risk patients treated with the cholesteryl ester transfer protein (CETP) inhibitor evacetrapib, against a background of best-evidence based treatment including statin.[16]

At the same time, genetic studies support a causal role for triglyceride-rich lipoproteins and their remnants, as well as other mediators involved in the regulation of triglyceride metabolism (apoAV, apoCIII, ANGPLT3 and 4, and LPL) in risk for cardiovascular disease. The clinical evidence so far is encouraging albeit not definitive. Post hoc analyses of the major fibrate trials have shown a significant association with cardiovascular outcomes, and, as reported in 22-year follow-up of the **BIP (Bezafibrate Infarction Prevention)** trial, independent association with all-cause mortality in patients with established coronary heart disease.[17] Imaging studies have also linked fasting levels of triglyceride-rich lipoprotein cholesterol with coronary artery calcium score, a marker of early stage coronary atherosclerosis.[18]

Clearly, a definitive cardiovascular outcomes study is needed, as well as further research into the mechanism(s) underlying this association. The latest thinking implicates low-grade inflammation as a contributor to the atherogenicity of triglyceride-rich lipoproteins and remnant cholesterol.

Professor Børge Nordestgaard (University of Copenhagen, Denmark) added further support, discussing the link between remnant cholesterol and ischaemic heart disease risk. Triglycerides are mainly carried by remnants, a collective term that refers to intermediate-density lipoproteins, very-low-density lipoproteins, and chylomicron remnants, the products of the lipolytic degradation of triglyceride-rich lipoproteins produced by the liver and intestine. Plasma levels of nonfasting triglycerides have been shown to be highly correlated with the cholesterol content of remnants, *i.e.* remnant cholesterol. Thus, elevated nonfasting triglycerides are a marker of elevated remnant chol-esterol levels. Evidence from prospective Danish studies in more than 75,000 individuals, of whom nearly 12,000 had ischaemic heart disease, provides strong support that remnant cholesterol is a causal risk factor for ischaemic heart disease.[19] Using a Mendelian randomization design, a type of 'natural' clinical trial, Professor Nordestgaard and his research team showed that a 1 mmol/L (39 mg/dL) increase in remnant cholesterol (due to carriage of genetic variants associated with increased levels) resulted in 2.8 fold higher risk for ischaemic heart disease; this association was independent of HDL-C levels.

> ***"There has been a sea change in therapeutic thinking; snowballing evidence from genetic studies has succeeded in turning the tide in favour of triglyceride – rich lipoproteins and their remnants"***
>
> Professor Peter Libby, Boston, USA

The mechanism underlying the atherogenicity of remnant cholesterol was discussed. It was postulated that accumulation of intimal cholesterol remnants may cause low-grade systemic inflammation, supported by mechanistic evidence that elevated levels of remnant cholesterol were associated with increased arterial wall and cellular inflammation.[20] Finally, Professor Nordestgaard reported novel data indicating an association between remnant cholesterol levels and body mass index, which adds to evidence for the overproduction of remnants by the intestine during obesity.

He added: ***'Elevated nonfasting remnant chol-esterol is causal for cardiovascular disease, and thus contributes to residual vascular risk. However, it is also important to consider other lipoprotein contributors to this risk, notably lipoprotein(a), which may be thrombogenic.'***

Following on this point, **Professor Michel Hermans (Cliniques universitaires St-Luc, Université catholique de Louvain, Brussels, Belgium)** discussed the role of lipoprotein(a) in residual microvascular risk. He presented preliminary data suggesting that higher levels of lipoprotein(a), while associated with increased prevalence of macrovascular disease, may paradoxically confer a lower risk for microvascular complications of type 2 diabetes, possibly mediated by the effects of lesser ß-cell function loss and less severe insulin resistance. Further study is merited.

Time to re-consider residual vascular risk

Residual vascular risk: lipids and beyond

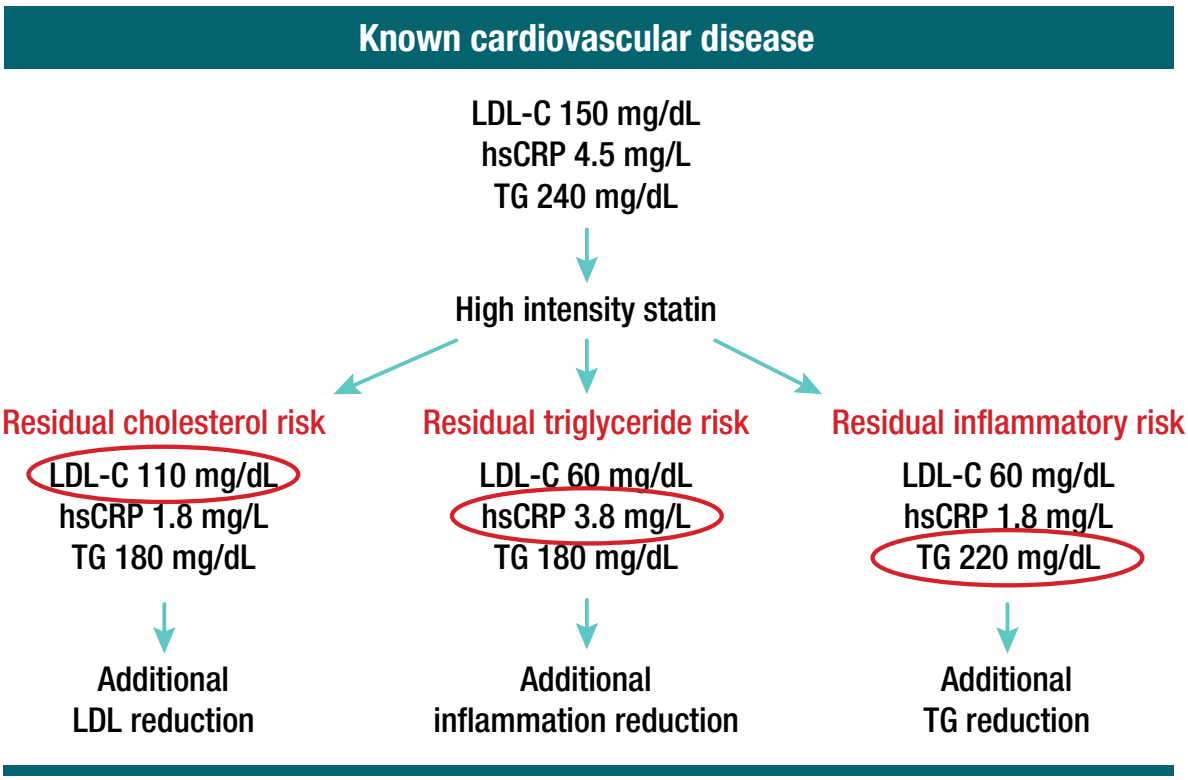
'It is time to re-consider how we categorize residual vascular risk,' according to **Professor Paul Ridker (Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, USA)**.

Initially, LDL-C was the main focus of residual vascular risk, prompting the development of highly efficacious agents able to lower LDL-C beyond current goals. Yet while the **FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)** showed that lowering LDL-C to extremely low levels with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab (to a median level of 30 mg/dL or 0.78 mmol/L) improved cardiovascular outcomes, some of these very high risk patients continued to experience cardiovascular events.[21]

A contributor to this residual vascular risk after LDL-C is atherogenic dyslipidaemia, already highlighted by the R3i in 2008.[22] The subsequent failure of HDL-C targeted therapies in cardiovascular outcomes studies, together with accumulating genetic evidence that triglyceride-rich lipoproteins and their remnants are causal for cardiovascular disease, has prompted refinement of this concept to *'residual triglyceride risk'*. Evidence to date from trials targeting this risk, however, has been less than definitive.

Additionally, focusing solely on *'residual cholesterol risk'* among statin-treated patients ignores the fact that these agents have activity beyond their lipid-lowering properties. Indeed, there is clear and consistent evidence across the statin trials of the relevance of inflammatory biomarkers, usually measured as high-sensitivity C-reactive protein (hsCRP), and this was again confirmed in the **IMPROVE-IT trial (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin)** in the post-acute coronary syndrome setting. Patients who achieved both an LDL-C <70 mg/dL (<1.8 mmol/L) and hsCRP <2 mg/L were at lower risk of recurrent vascular events compared with

Figure 1. Categorizing residual vascular risk: consider three key targets



hsCRP high-sensitivity C-reactive protein; LDL-C low-density lipoprotein cholesterol; TG triglycerides

those who attained one or none of these treatment targets.[23] These findings underpin the concept of *residual inflammatory risk* **(Figure 1)**. Moreover, when considering the IMPROVE-IT population, the number of patients affected was not inconsequential: 14% had residual cholesterol risk, 33% residual inflammatory risk and another 14% both types of residual risk.[24] The concept of *'dual targets'* for residual vascular risk also makes sense mechanistically. Based on current understanding, atherosclerosis is considered to be the result of chronic inflammation at the sites of cholesterol accumulation in the artery wall; cholesterol crystals act as a potential source of inflammation, activating the inflammasome pathway, thereby driving both innate and adaptive immunity mechanisms.[25]

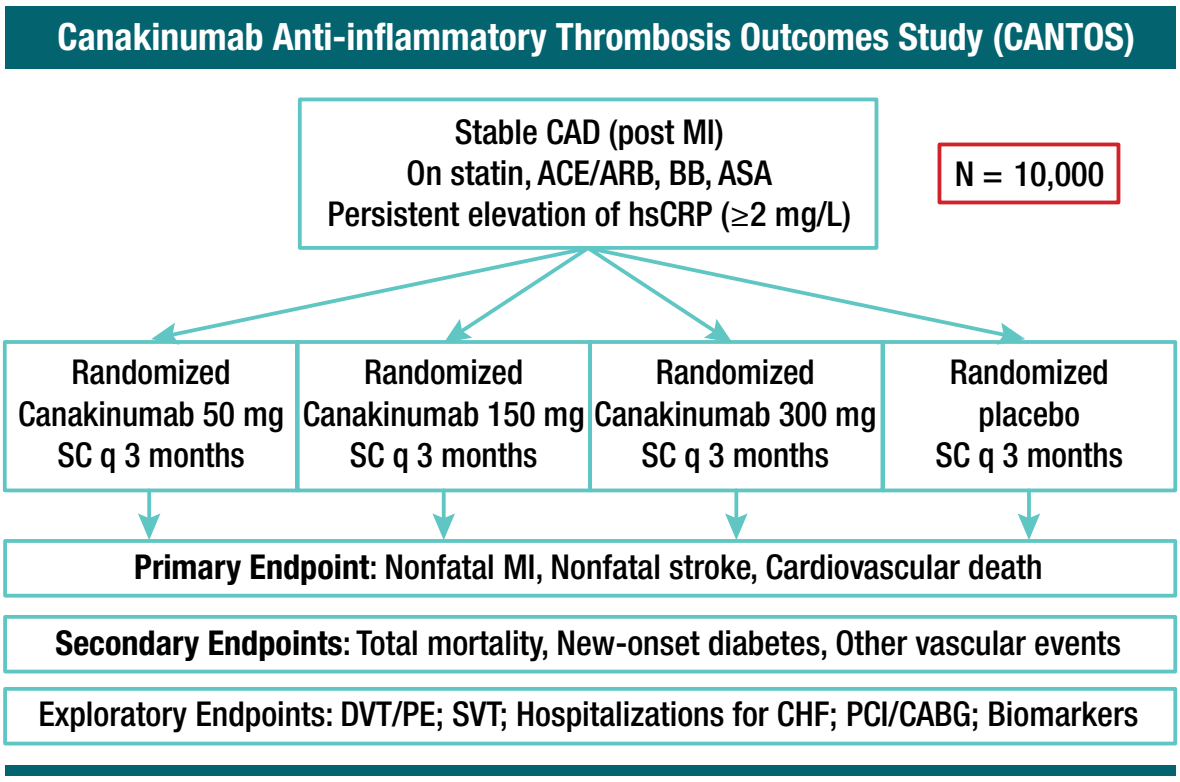
How to target different residual risk components?

Residual inflammatory risk

As discussed by Professor Ridker, two ongoing studies are evaluating the impact of lowering residual inflammatory risk in patients with stable coronary heart disease, on statin therapy but with persistent evidence of subclinical low-grade inflammation (hsCRP >2 mg/L). Both focus on upstream targets of CRP, namely interleukin-6 (IL-6) in **CIRT (Cardiovascular Inflammation Reduction Trial)** with low-dose methotrexate (15-20 mg weekly), and IL-1β in the **CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)** (see **Figure 2**).

Canakinumab is a high affinity monoclonal antibody to IL-1β, a proinflammatory cytokine that has multiple roles in the atherothrombotic process and undergoes activation by the NLRP3 inflammasome as discussed above. In CANTOS, eligible patients are randomized to one of four regimens: subcutaneous canakinumab 50, 150 or 300 mg or placebo, administered every 3 months. The primary endpoint of both trials is the composite of cardiovascular death, nonfatal MI and nonfatal stroke.

Figure 2. Design of CANTOS

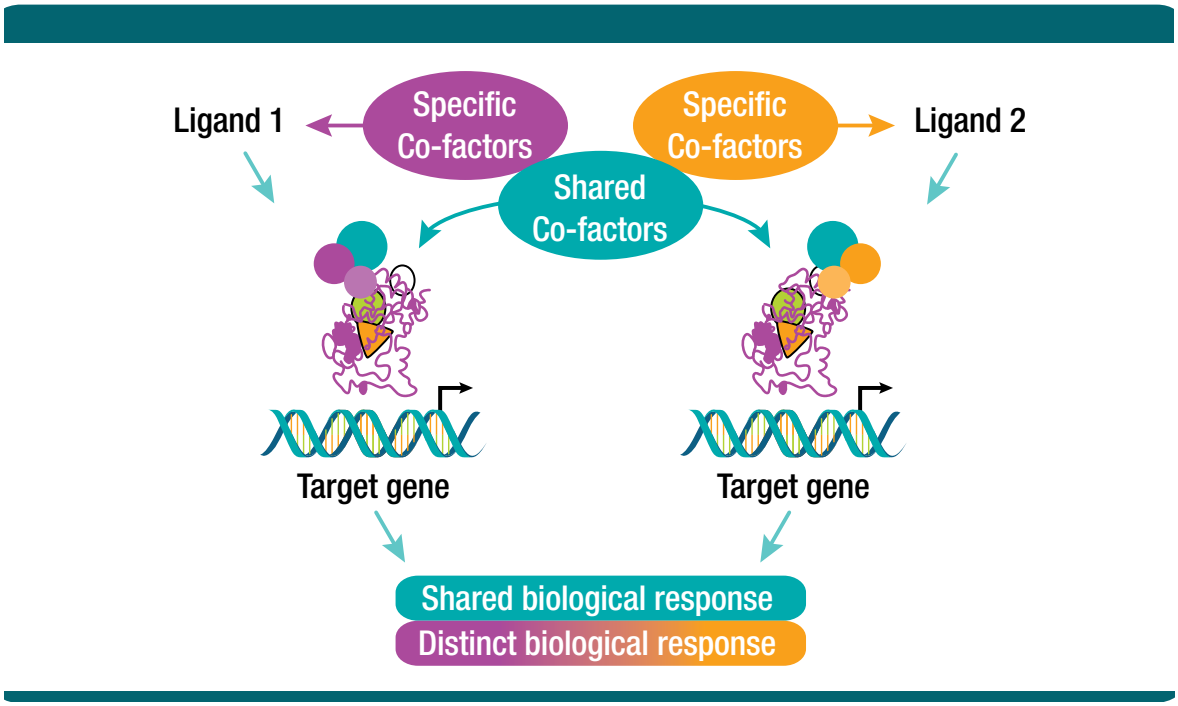


ACE angiotensin converting enzyme; ARB angiotensin receptor blocker; ASA aspirin; BB beta-blocker; CABG coronary artery bypass graft; CAD coronary artery disease; CHF congestive heart failure; DVT deep vein thrombosis; hsCRP high-sensitivity C-reactive protein; MI myocardial infarction; PCI percutaneous coronary intervention; PE pulmonary embolism; SVT silent venous thromboembolism; SC subcutaneous

Topline results from CANTOS reported recently show that this trial met its primary endpoint,[14] providing support for the residual inflammatory risk hypothesis, although full publication of the results is awaited.

Residual triglyceride risk: the potential of SPPARMα

Figure 3. The SPPARM concept



The binding of different ligands to nuclear receptors induces different conformational changes which influence cofactor affinity, resulting in distinct differences in the cofactor-receptor binding profile.

Targeting residual triglyceride risk has, however, proved more difficult. The agent of choice in previous trials has been the fibrates, PPARα agonists. However, while post hoc analysis of the major fibrate trials showed benefit specifically in those patients with elevated triglycerides (with or without low HDL-C), the main trial findings were neutral. Moreover, there were also side effect issues, largely due to the low potency and undifferentiated selectivity for PPARα of these agents.

As discussed, PPARα plays a pivotal role by controlling the expression of a number of key genes in triglyceride (including *APOA-V, APOC3, LPL* and *ANGPTL4*) and HDL metabolism. This is highly relevant, given evidence from recent genetic studies that either promotion or inhibition of these genes subsequently influences cardiovascular risk.

PPARα binds to DNA as a heterodimer with the Retinoid X Receptor, and together they recognize specific DNA sequences in and around target genes referred to as PPAR response elements, leading to conformational change. The involvement of specific cofactors renders the PPAR complex either 'transcriptionally active' (*transactivation*), or blocks the interaction between activated transcription factors and the promoter region of the target gene, thereby preventing transcription (*transrepression*). Each ligand triggers different conformational changes, due to a unique cofactor recruitment pattern, which in turn results in specific tissue- and gene-selective effects (**Figure 3**). Therefore, modulating the unique receptor–cofactor binding profile may lead to the development of a novel selective **PPARα modulator (SPPARMα)** with higher potency and without the side effects observed with the fibrates.

Pemafibrate (previously known as K-877) is the first SPPARMα registered for use in humans. This unique agent has been shown to have a favourable pharmacological profile in preclinical studies, with markedly increased potency for human PPARα (by >2,500-fold), as well as improved effects on atherogenic dyslipidaemia, inflammation and atherosclerotic lesion development, compared with fenofibrate (or its active metabolite, fenofibric acid).[26,27]

Results from recent trials with pemafibrate were discussed in a separate Symposium: **Update in the Management of Dyslipidemia for Vascular Prevention in Patients with Type 2 Diabetes**. As overviewed by **Professor Shun Ishibashi (Jichi Medical University, Japan)**, in statin-treated patients with elevated triglycerides (≥150 mg/dL or 1.7 mmol/L), add-on pemafibrate treatment was associated with robust reduction (by about 50%) in fasting triglycerides, remnant cholesterol and apolipoprotein B48, increase in HDL-C levels (by up to 20%), as well as improvement in the atherogenic lipoprotein profile. This lipid modifying efficacy was sustained over 24 weeks. Pemafibrate was also well tolerated, with a favourable profile for effects on renal and hepatic function compared with fenofibrate.[28]

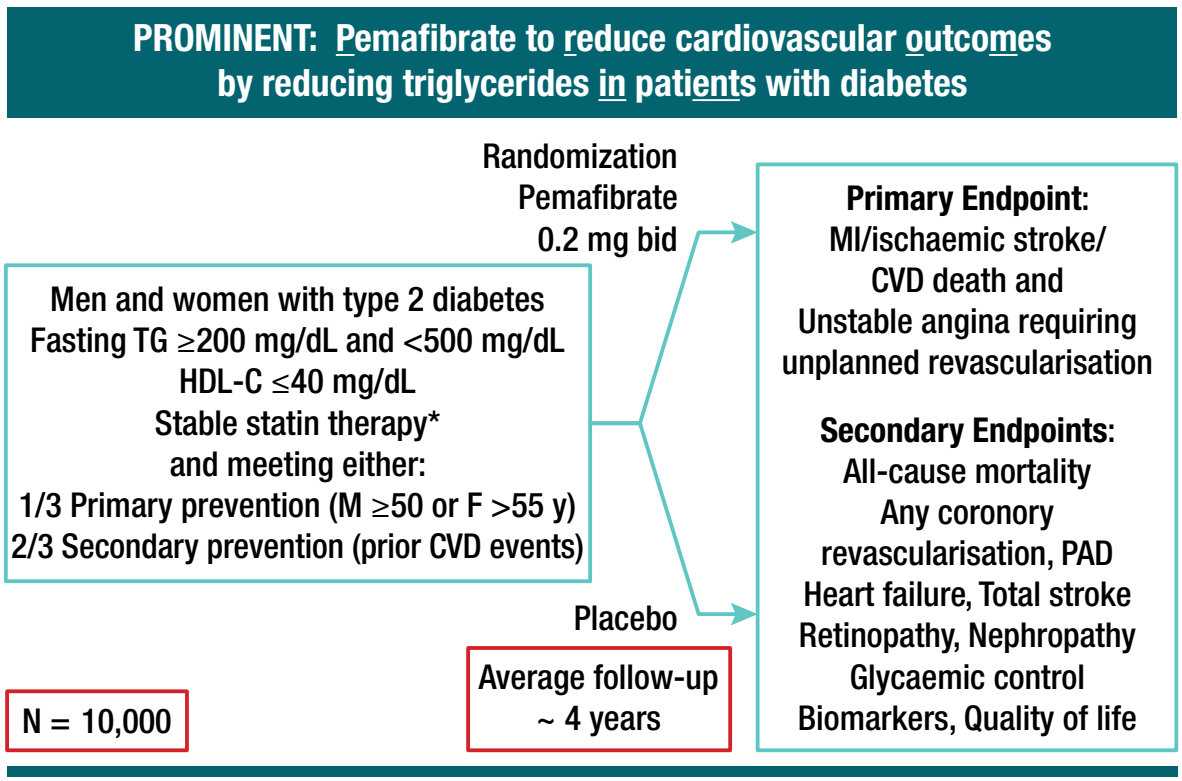
In addition, data presented by **Professor Shizuya Yamashita (Osaka University Graduate School of Medicine/Rinku General Medical Center, Japan)** showed that pemafibrate treatment resulted in enhanced HDL particle functionality, as assessed by cholesterol efflux capacity *(European Society of Cardiology Congress, London, UK, 2015)*. Pemafibrate treatment also significantly improved fasting and postprandial lipid profiles in dyslipidaemic patients *(European Society of Cardiology Congress, Rome, Italy, 2016)*, and improved hepatic insulin sensitivity in patients with elevated triglycerides, possibly via mechanisms involving increased β-oxidation of fatty acids, and fibroblast growth factor 21, which stimulates glucose uptake in adipocytes *(Matsuba et al, 2016)*.

> ***"Hot off the Press: Pemafibrate has now received regulatory approval for the management of dyslipidaemia in Japan"***
>
> Professor Jean-Charles Fruchart, President of the Residual Risk Reduction Initiative

Taken together, these encouraging data imply that pemafibrate would be an appropriate candidate for testing the residual triglyceride hypothesis. **PROMINENT (Pemafibrate to Reduce cardio-vascular OutcoMes by reducing triglycerides IN diabetic patiENTs)**, an international cardiovascular outcomes study is currently being initiated. The study plans to recruit 10,000 subjects with type 2 diabetes and atherogenic dyslipidaemia (elevated triglycerides ≥200 mg/dL and <500 mg/dL, HDL-C ≤40 mg/dL) against a background of stable statin therapy. About one-third of patients will have no prior history of cardiovascular events. The primary endpoint is a composite of nonfatal MI, nonfatal ischaemic stroke, cardiovascular death or unstable angina requiring unplanned revascularization (**Figure 4**).

> ***Pemafibrate is a unique SPPARMα with the potential to supersede the fibrates in the management of atherogenic dyslipidaemia. PROMINENT will provide the first opportunity to truly test whether pemafibrate, against a background of stable statin therapy, significantly reduces residual triglyceride risk in type 2 diabetes patients***
>
> Professor Jean-Charles Fruchart, President of the Residual Risk Reduction Initiative

Figure 4. Design of PROMINENT



ClinicalTrials.gov Identifier: NCT03071692.
bid twice daily; CVD cardiovascular disease; HDL-C high-density lipoprotein cholesterol; MI myocardial infarction; PAD peripheral arterial disease; TG triglycerides

Residual microvascular risk in diabetes mellitus

While residual macrovascular risk has been the primary focus of attention, there is also a substantial burden of microvascular complications in type 2 diabetes patients, according to **Professor Michel Hermans (Cliniques universitaires St-Luc, Université catholique de Louvain, Brussels, Belgium)**. This is supported by very recent findings from the observational DISCOVER study involving 14,178 type 2 diabetes patients in 37 countries (mean age 57 years, 53% men, mean HbA1c 8.6%), with diabetes for on average 6 years. The study showed that the global burden of microvascular complications (a composite of diabetic retinopathy, nephropathy and neuropathy) was similar to that of macrovascular disease, especially in the longer-term; nearly one in five patients had microvascular complications (18% versus 13% for macrovascular disease).[29]

Data from the **REALIST-Micro** case-control study have highlighted the association between elevated triglycerides, low HDL-C and risk for diabetic retinopathy and nephropathy in patients with type 2 diabetes.[30] Given evidence of beneficial effects of fenofibrate in preventing diabetic retinopathy progression in the **FIELD (Fenofibrate Intervention and Event Lowering in Diabetes)** and **ACCORD (Action to Control Cardiovascular Risk in Diabetes)** studies,[31,32] it was announced that PROMINENT will now include a nested study to assess the efficacy of pemafibrate in preventing diabetic retinopathy.

"With the escalating diabetes pandemic, the global burden of diabetic microvascular complications is a major issue for the 21st century. We need new options beyond control of blood glucose and statin therapy. PROMINENT may offer a new therapeutic possibility"

Professor Michel Hermans, Brussels, Belgium

Implications for the management of the metabolic syndrome

There is an interplay between obesity, metabolic syndrome and related cardiometabolic conditions. Therefore the focus of current recommendations is comprehensive management strategies.

Multi-morbidity in type 2 diabetes

With this in mind, the advent of novel diabetes therapies with complementary activities, notably the glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter 2 inhibitors, has attracted much attention, commented **Professor Grineva (Federal Almazov North-West Medical Research Centre, Saint-Petersburg, Russia)**. Beyond improvement in glycaemic control, these agents also improve weight loss, systolic blood pressure, plasma lipids, and may have direct effects on the heart (increased contractility, systolic function and endothelial function), and in post-ischaemic recovery.[33] There is also emerging support for a beneficial impact on risk factors for development of heart failure, potentially via haemodynamic/metabolic-driven mechanisms of action. Such findings are highly relevant, given escalation in the prevalence and cost of care for heart failure, the latter largely driven by the cost of hospitalization.

Of course, the key question is whether such effects translate to reduction in cardiovascular outcomes. Results from major prospective outcomes studies have been variable. Some have shown proven benefit, such as the outcomes trial with empagliflozin, which significantly reduced all-cause and cardiovascular mortality,[34] as well as hospitalization for heart failure, whereas others, such as trials with the gliptins (sitagliptin, alogliptin, saxagliptin) have shown a neutral effect on cardiovascular outcomes.

> ***"The real clinical challenge, however, is to target at-risk individuals to prevent progression to type 2 diabetes and the associated cardiovascular and microvascular complications. Statistics from Russia illustrate the magnitude of this challenge: whereas 5% of people have diabetes 19% have metabolic syndrome"***
>
> Professor Grineva, Saint-Petersburg, Russia

Consider non-alcoholic fatty liver disease (NAFLD)

"With the increasing prevalence of NAFLD, and its association with cardiometabolic disease, it is clear that we need to rethink how we live our lives. We also need new therapeutic options for managing NAFLD"

Professor Raul Santos, São Paulo, Brazil

As discussed by **Professor Raul Santos (University of São Paulo, Brazil)** non-alcoholic fatty liver disease (NAFLD) is a global issue. With the escalating obesity epidemic, NAFLD now affects about one in three individuals, not only adults but also children, especially those with prediabetes and diabetes.[35] Additionally, the presence of NAFLD increases the risk of fatal and nonfatal cardiovascular events by more than 2-fold.[36]

There is some evidence to suggest a genetic predisposition to NAFLD. Half of those with NAFLD carry at least one variant (G) allele at rs738409 in the *PNPLA3* gene, which is associated with high liver fat content.[37] While some studies have shown more rapid progression of atherosclerosis and increased risk of coronary artery disease linked with carriage of this *PNPLA3* polymorphism, definitive evidence of a genetic contribution has proved difficult, given the lack of robust Mendelian randomization studies and potential pleiotropy *(Santos et al in press)*.

Irrespective of these uncertainties, the main focus of management should be early, aggressive risk factor modification. Given that a key driver of NAFLD is atherogenic dyslipidaemia, lifestyle intervention together with lipid modifying therapy are fundamental strategies. Therapeutic agents specifically indicated for NAFLD treatment are, however, lacking. With the pivotal role of PPARα in the regulation of triglyceride metabolism, together with evidence of enhanced expression in hepatocytes, PPARα may have a protective role in NAFLD pathogenesis. Yet the available PPARα agonists have limited efficacy, and there is also the risk of increased liver enzymes. As discussed by Professor Santos, the unique pharmacological profile of the SPPARMα pemafibrate suggests future therapeutic potential. In an animal models of non-alcoholic steatohepatitis, treatment with pemafibrate resulted in stimulation of lipid turnover and upregulation of uncoupling protein 3 expression in the liver;[38] however, large prospective clinical studies are clearly needed to test this.

Consider sleep apnoea

According to **Professor Konradi (Saint-Petersburg, Russia)** obstructive sleep apnoea (OSA), characterized by recurrent episodes of upper airway collapse, hypoxia and sleep fragmentation during the night, is another condition that is highly associated with the cluster of risk factors that define the metabolic syndrome. A key driver of the condition is obesity, as already described by the Wisconsin Sleep Cohort Study.[39] Obesity and OSA both appear to affect similar pathways contributing to vascular disease, including sympathetic activation, oxidative stress, inflammation and neurohumoral changes, thus providing a pathophysiological link with the metabolic syndrome.

More than half of individuals with the metabolic syndrome have moderate to severe OSA; elevated blood glucose, triglyceride levels and markers of inflammation and arterial stiffness are also prevalent, predisposing to increased subclinical atherosclerosis, and potentially, cardiovascular events.[40] There is also evidence that OSA is a trigger for atrial fibrillation, independent of obesity, which is not surprising, given the common profile of risk factors and pathogenic mechanisms activated by OSA.

For clinicians, weight loss is recommended as the first step in management for all overweight or obese patients with OSA. In combination with continuous positive airway pressure (CPAP), there was incremental improvement in insulin resistance and reduction in serum triglycerides, compared with either intervention alone.[41] Whether CPAP has favourable effects on blood pressure, and reduces the recurrence of atrial fibrillation, beyond the effects of weight loss, has yet to be established definitively.

"With the interplay between obesity, metabolic syndrome and sleep apnoea, lifestyle intervention aimed at better control of metabolic function, is as important as CPAP treatment for management of OSA"

Professor Konradi,
Saint-Petersburg, Russia

Translating the evidence to everyday practice

While clinical trials are essential for investigating therapeutic approaches to the management of metabolic syndrome and related co-morbidities, translating the evidence to routine practice can often be problematic. **Professor Richard Ceska (Center of Preventive Cardiology, School of Medicine and University Hospital, Charles University, Prague, Czech Republic)** discussed findings from the **ATTRACTIV study**, reporting real life experience of implementation of lifestyle management in patients with the metabolic syndrome.

ATTRACTIV included 4,427 (47% male) subjects recruited by 464 centres, predominantly general practitioners. The study evaluated the effects of lifestyle counselling and pharmacotherapy for dyslipidaemia (atorvastatin), hypertension (amlodipine ± an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) and glycaemic control (metformin) over 12 months. Overall, subjects were older (mean age 63 years), and either overweight/obese, with a high prevalence of risk factors: 97% were hypertensive, 47% had type 2 diabetes, 99% had dyslipidaemia (predominantly elevated LDL-C and triglycerides), and 35% were smokers.

Intensive treatment resulted in improvement in the risk profile of subjects, with significant reduction in blood pressure, atherogenic lipoproteins (notably reduction in LDL-C and triglycerides, a marker of triglyceride-rich lipoproteins), glycaemia and waist circumference and BMI. Summing up, Professor Ceska commented: ***'ATTRACTIV has shown that implementation of a comprehensive risk factor management programme in individuals with metabolic syndrome is feasible in routine practice, and results in halving of global cardiovascular risk. Despite this, only one-third of patients attained recommended goals for LDL-C and triglycerides, emphasizing the importance of measures to improve adherence.'***

Does subclinical imaging have a role?

Imaging has application in the research setting to identify subclinical atherosclerotic vascular disease – but is it feasible for use in the management of metabolic syndrome in routine practice? According to **Professor S. Lale Tokgözoğlu:** ***'Imaging may have a number of potential uses: to identify patients with metabolic syndrome but without diabetes who may be candidates for more aggressive risk factor modification; to aid in reclassification of risk; and to improve patient adherence. The downsides, however, are the lack of randomized controlled trial data to support these approaches and cost.'***

Professor Tokgözoğlu overviewed the evidence for the use of different imaging approaches to assess risk in the metabolic syndrome. Carotid intima-media thickness (CIMT), assessed by B-mode ultrasonography, has been shown to worsen as the number of components of the metabolic syndrome increases, but does not improve risk prediction over available risk scores and is highly operator-dependent.[42] Non-invasive coronary artery calcium (CAC) score is correlated with the number of metabolic syndrome components, can aid in reclassification of risk, and can help in ensuring treatment adherence. There are, however, a number of disadvantages, notably the need to consider the risk due to low-dose radiation, the inability of this technique to show noncalcified plaque, and cost. Computed tomography angiography may offer advantages over CAC given that the metabolic syndrome is associated with more mixed and noncalcified plaques,[43] although once again there are issues due to radiation dose and cost. Furthermore, while magnetic resonance imaging and more advanced imaging technologies can be used to identify plaque burden and vulnerability, their use is restricted to specialized centres. Finally, Professor Tokgözoğlu stressed that imaging the plaque is not enough, as it is also important to consider what causes risk, by assessment of markers of endothelial function, coagulation status and even, potentially, genetics.

Novel targets for the future?

Cardiovascular calcification

Cardiometabolic disease accelerates atherosclerosis and cardiovascular calcification, the latter implicated as a contributor to plaque rupture. While conventional imaging modalities clearly have a role in the detection of advanced calcification, these cannot be used in the early stages of disease. Originally considered a passive degenerative disease, cardiovascular calcification is now thought to be an active process, with mechanism similar to that of bone formation, driven by inflammation as discussed by Professor Elena Aikawa, Brigham and Women's Hospital, Boston, USA. Smooth muscle cells become modified to acquire the expression of osteogenic proteins, and release calcifying extracellular vesicles, precursors of microcalcification, which contribute to plaque instability. Matrix vesicles released by macrophages are also implicated in this process.

Genetic and mechanistic studies have provided evidence that sortilin plays a key role in lipid metabolism, inflammation, and vascular calcification. Sortilin appears to act as a regulator of smooth muscle cell calcification via its recruitment to extracellular vesicles. In preclinical studies, sortilin-deficient mice developed less arterial calcification without any changes to bone structure and function, implying that its mechanism is specific to the vasculature. Added to this, observational studies have indicated a direct association between serum sortilin levels and risk for major adverse cardiovascular events which is independent of levels of CRP and LDL-C.[44] Statins have failed to show benefit in slowing the progression of valve calcification, possibly due to initiation of treatment at more advanced stages of atherosclerotic vascular disease. Instead, targeting atherogenic factors and/or pro-inflammatory pathways at an earlier stage of calcification may offer potential.

Macrophage activation

An alternative strategy has been to focus on novel mechanisms for macrophage activation, beyond the known modifiable risk factors as discussed by **Professor Masanori Aikawa, Brigham and Women's Hospital, Boston, USA**. Of targets investigated to date, Poly (ADP-ribose) polymerase (PARP), a family of proteins involved in a number of cellular processes such as DNA repair and programmed cell death, indicate promise. Notably, preclinical studies suggest that PARP14 and PARP9 may cross-regulate macrophage activation; inhibition of PARP9 and/or activation of PARP14 may attenuate macrophage-mediated atherosclerosis.[45]

In addition, preliminary studies have shown that pemafibrate can reduce macrophage accumulation and activation in various *in vitro* models of atherosclerosis, suggesting the possibility of shifting the balance between pro- and anti-inflammatory subsets of macrophages. Although at an early stage, these findings infer a role for pemafibrate in the management of inflammatory disease, highly relevant in the light of increasing evidence that inflammation is a contributor to residual vascular risk.

"With an aging population, the global health burden of vascular calcification will increase, highlighting the need for novel therapeutic approaches; sortilin may represent a valuable diagnostic biomarker of subclinical calcification"

Professor E. Aikawa,
Boston, USA

"Identification of novel targets involved in macrophage activation may offer future therapeutic potential for addressing residual vascular risk"

Professor M. Aikawa,
Boston, USA

References

1. Heymsfield SB, Wadden TA. *N Engl J Med* 2017; **376**:1492.
2. Antonopoulos AS, Antonopoulos AS. *J Physiol* 2017; **595**: 3907-17.
3. Secnik J *et al. Diabetes Care* 2017 [Epub ahead of print].
4. Sjostrom L. *JAMA* 2012; **307**:56-65.
5. Nilsson SK *et al. Atherosclerosis* 2011; **219**:15-21.
6. Pennacchio LA, Rubin EM. *Arterioscler Thromb Vasc Biol* 2003; **23**:529-34.
7. Khera AV *et al. JAMA* 2017; **317**:937-46.
8. Triglyceride Coronary Disease Genetics Consortium *et al. Lancet* 2010; **375**:1634-9.
9. Jørgensen AB *et al. N Engl J Med* 2014; **371**:32-41.
10. TG and HDL Working Group of the Exome Sequencing Project *et al. N Engl J Med* 2014; **371**:22-31.
11. Dewey FE *et al. N Engl J Med* 2016; **374**:1123-33.
12. Stitziel NO *et al. J Am Coll Cardiol* 2017; **69**:2054-63.
13. Graham MJ *et al. N Engl J Med* 2017 [Epub ahead of print].
14. Novartis Phase III study shows ACZ885 (canakinumab) reduces cardiovascular risk in people who survived a heart attack https://www.novartis.com/news/media-releases/novartis-phase-iii-study-shows-acz885-canakinumab-reduces-cardiovascular-risk
15. Voight BF *et al. Lancet* 2012; **380**:572-80.
16. Lincoff AM *et al. N Engl J Med 2017*; **376**:1933-42.
17. Klempfner R *et al. Circ Cardiovasc Qual Outcomes* 2016; **9**:100-8.
18. Bittencourt MS *et al. Am J Cardiol* 2017; **119**:1352-8.
19. Varbo A *et al. J Am Coll Cardiol* 2013; **61**:427-36.
20. Bernelot Moens SJ *et al. Arterioscler Thromb Vasc Biol* 2017; **37**:969-75.
21. Sabatine MS *et al. N Engl J Med* 2017; **376**:1713-22.
22. Fruchart JC *et al. Am J Cardiol* 2008; **102**(10 Suppl):1K-34K.
23. Bohula EA *et al. Circulation* 2015; **132**:1224–33.
24. Ridker PM. *Circ Res* 2017; **120**:617-9.
25. Duewell P *et al. Nature* 2010; **464**:1357-61.
26. Fruchart JC. *Cardiovasc Diabetol* 2013; **12**:82.
27. Hennuyer N *et al. Atherosclerosis* 2016; **249**:200-8.
28. Arai H *et al. Atherosclerosis* 2017;Epub ahead of print.
29. Kosiborod MN, *et al.* 303-OR. American Diabetes Association 77th Scientific Sessions; June 9-13, 2017; San Diego. https://www.healio.com/endocrinology/diabetes/news/online/%7B202ca9c8-679d-4d15-b2b2-8434dc8a412f%7D/global-burden-of-diabetes-complications-substantial-continues-to-grow
30. Sacks FM *et al. Circulation* 2014; **129**:999-1008.
31. Keech AC *et al. Lancet* 2007; **370**:1687-97.
32. ACCORD Study Group *et al. N Engl J Med* 2010; **363**:233-44.
33. Sattar N *et al. J Am Coll Cardiol* 2017; **69**:2646-56.
34. Zinman B *et al. N Engl J Med* 2015; **373**:2117-28.
35. Newton KP *et al. JAMA Pediatr* 2016; **170**:e161971.
36. Targher G et al. *J Hepatol* 2016; **65**:589-600.
37. Yki-Järvinen H. *Lancet Diabetes Endocrinol* 2014; **2**:901-10.
38. Honda Y *et al. Sci Rep* 2017; **7**:42477.
39. Peppard PE *et al. JAMA* 2000; **284**:3015–21.
40. Drager LF *et al. J Am Coll Cardiol* 2013; **62**:569-76.
41. Chirinos JA *et al. N Engl J Med* 2014; **370**:2265-75.
42. Tzou WS *et al. J Am Coll Cardiol* 2005; **46**:457-63.
43. Lim S *et al. Radiology* 2011; **261**:437-45.
44. Goettsch C *et al. Arterioscler Thromb Vasc Biol* 2017; **37**: 1005-11.
45. Iwata H *et al. Nat Commun* 2016; **7**:12849.