

# 5<sup>th</sup> International Meeting on Aortic Diseases

New insights into an old problem

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ABSTRACT BOOK

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Thursday September 15

SCIENTIFIC PROGRAM

## Extra-aortic cardiovascular features in marfan syndrome - relevance and management

Julie De Backer

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Marfan syndrome (MFS), caused by mutations in the fibrillin 1 gene has been the leading disease model for the study of genetic aortic aneurysms and dissections. Aortic root aneurysm formation at the level of the sinus of Valsalva occurs in the vast majority of patients and aortic dissection is still one of the leading causes of death in patients with MFS. With better medical and surgical management, MFS patients grow older nowadays and other cardiovascular features are now emerging and gaining more attention. Mitral valve prolapse (MVP) has been recognized as a key feature in MFS and still plays a role in the diagnostic setting. Being a benign disease in the majority of non-MFS cases, the outcome of MVP in MFS is quite different and needs careful follow-up. Timely and appropriate surgical intervention needs to be carefully considered. Heart failure in MFS has been recognized as a major cause of mortality in surgical series for several decades now, but the understanding of the pathogenesis of myocardial dysfunction is still not entirely elucidated. Related to myocardial dysfunction to some extent, arrhythmias are more frequently documented in MFS patients and sudden arrhythmic death occurs more common than in the general population. Managing these extra-aortic features in MFS requires adequate knowledge and a specific approach in some cases. These issues will be discussed in this presentation.

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## Whole blood dna methylation analysis in AAA; an epigenome-wide association study

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Abdominal aortic aneurysm (AAA) is a complex disease, with several well-established genetic and environmental risk factors having been identified, nevertheless, much remains to be understood regarding its aetiology. It is becoming increasingly clear that there are interactions between genetic and environmental risk factors. Such interactions can be detected by alterations in epigenetic markers, such as the methylation of DNA CpG sites. An epigenome-wide approach was therefore applied to an AAA case control cohort in order to identify novel disease biomarkers.

### Study Design and Methods

Whole blood methylation status of over 450,000 CpG sites was assessed in each of 961 males (488 cases and 473 AAA-free controls; mean age 72 years) using the Illumina Human Methylation450 bead chip array. Normalised methylation values were corrected for participant age and prior history of occlusive vascular disease. Results were filtered for CpGs known to be strongly associated with white blood cell composition.

### Results

In total 50 gene loci (most with multiple CpG sites) were significantly (adjusted  $P < 5 \times 10^{-8}$ ) differentially methylated in AAA. Importantly, 18 (36%) of these loci matched those previously reported as being significantly associated with smoking. These included the strongest smoking associations reproducibly reported in the AHRR, F2RL3, ALPI and IER3 genes. Approximately half of the CpG sites were also strongly associated with white blood cell composition. A pathway-based analysis implicated biological mechanisms such as interleukin signaling, vascular inflammation, T & B cell activation and blood coagulation. Protein expression of some of the genes associated with differentially expressed CpG sites was examined in aortic tissue. One such gene, YWHAQ, encodes for the 14-3-3 theta protein that was found to be significantly overexpressed within AAA-associated adventitial T-cell aggregates.

### Conclusion

Whole blood epigenome-wide association analysis identified a set of genes whose differential DNA methylation appears to be consistent with known environmental risk factors and biologically causal pathways in AAA. A large proportion of the differentially methylated signal also appeared to be strong white cell markers, suggesting that a proportion of the observed signature may be a surrogate of blood cell composition. This study demonstrates the potential utility of whole blood epigenetic studies to identify novel disease biomarkers.

## Combining Mendelian genetics and genetic epidemiology for AAA

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The pace of new genes discovery in the field of Mendelian disorders has been dramatically accelerated by the availability of the human genome sequence in the 2000s, and the next-generation sequencing technologies in the 2010s. However, a majority of the elucidated conditions so far correspond to relatively simplified situations, where the prevalence and the penetrance of the condition are high and the genetic heterogeneity is low. Nowadays, geneticists meet more and more situations where gene identification in unknown disorders can be tricky. Heritable conditions that are very rare, heterogenous or with imperfect Mendelian transmission can only be elucidated using large cohorts of patients, with a very well-characterized phenotype. Generally, using exome sequencing alone is not efficient enough to elucidate these types of conditions. On the other hand, common conditions like cardiovascular disorders have been long studied using whole genome association studies and genotyping, or sequencing tools. The efficiency of these approaches to identify strong genetic effects is globally low, and odds-ratios do not generally reach 2. The concept of hidden heritability raised from these observations, pointing to the implication of other types of variants like rare or very rare variants, in common disorders. The power of recently developed strategies comes from combining exome or genome sequencing with recently developed genetic association analysis tools, allowing for the identification of rare variants with stronger effects. These latter have been specifically developed in the context of rare, heterogenous, or polygenic disorders. We employed exome sequencing in the identification of genetic components of abdominal aortic aneurysm. This common cardiovascular disorder has a strong hereditary component and rare situations of fully penetrant, dominant inheritance. Exome sequencing was performed in a large family showing dominant inheritance, identifying only one strong candidate gene. Rare and very rare variants association analysis of the identified candidate gene was performed in a large cohort of 2500 sporadic and 500 familial AAA cases, using a recently developed association tool called SKAT-O. This combined approach allowed to characterize genetic effect of rare and very rare variants at the level of a single gene, with deleterious and protecting effect depending on the identified variants. Functional analysis of the variants and the role of the candidate gene is ongoing in cellular models.

## New Insights on genetic aspect of aortic disease

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**Background**

Hereditary factors play an important etiologic role in thoracic aortic aneurysm and dissection (TAAD), with a number of genes proven to predispose to this condition. We initiated a clinical program for routine genetic testing of individuals for TAAD via whole exome sequencing (WES). Here we present our initial results.

**Methods**

WES was performed in 102 patients (mean age 56.8 years, range 13-83, 70 males (68.6%)) with TAAD. The following 21-gene panel was tested via WES: ACTA2, ADAMTS10, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, ELN, FBLN4, FLNA, FBN1, FBN2, MYH11, MYLK, NOTCH1, PRKG1, SLC2A10, SMAD3, TGFB2, TGFB1, TGFB2.

**Results**

Seventy-four patients (72.5%) had no medically important genetic alterations. Four patients (3.9%) had a deleterious mutation identified in the FBN1, COL5A1, MYLK, and FLNA genes. Twenty-two (21.6%) previously unreported suspicious variants of unknown significance were identified in one or more of these genes: FBN1 (n=5), MYH11 (n=4), ACTA2 (n=2), COL1A1 (n=2), TGFB1 (n=2), COL3A1 (n=1), COL5A1 (n=1), COL5A2 (n=1), FLNA (n=1), NOTCH1 (n=1), PRKG1 (n=1), and TGFB3 (n=1). Identified mutations had implications for clinical management.

**Conclusions**

Routine genetic screening of patients with TAAD provides information that enables genetically personalized care and permits identification of novel mutations responsible for aortic pathology. Analysis of large data sets of variants of unknown significance that include associated clinical features will help define the mutational spectrum of known genes underlying this phenotype and potential identify new candidate loci.

## High heritability of abdominal aortic aneurysms – a population-based twin-study

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### Introduction

First-degree relatives of patients with abdominal aortic aneurysm (AAA) have an increased risk of developing AAA; however, despite intensive investigation, the specific genetic factors involved in the development of the disease are still largely unknown. In twin studies the influence of genetic and environmental factors can be assessed by comparing concordance rates between monozygotic (MZ) and dizygotic (DZ) twins. Higher phenotypic similarity between MZ than DZ twins indicates a genetic attribution to the aetiology. Overall heritability can be calculated using structural equation modelling.

### Aim

To investigate the heritability of AAA among Danish twins using concordance rates and heritability estimates.

### Materials/methods

The Danish Twin Registry was used to identify all Danish twin pairs where both twins were alive January 1, 1977. We then identified AAA-cases using the National Patient Registry and the Registry of Cause of Death. Probandwise concordance rates were calculated and heritability estimated using structural equation modelling.

### Results

We identified 414 twins with AAA; 69.8% [289/414] men and 30.2% [125/414] women. The probandwise concordance rate in MZ twins was 30% [95% CI (confidence interval):20.3;43.3%] compared with 12% [95%CI:7.0;20.1%] in DZ twins. In the heritability analysis 77% [95%CI:67;85%] of the total variance was explained by additive genetic components and 23% [95%CI:15;33%] was explained by non-shared environmental factors.

### Conclusions

We found a probandwise concordance rate 2.5 times higher in MZ twins compared with DZ twins and an overall heritability of 77% which suggests a substantial genetic component in the development of AAA.

## Global and gene specific dna methylation is associated with abdominal aortic aneurysms

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### Introduction

Abdominal aortic aneurysm (AAA) is a degenerative cardiovascular disease characterised by the gradual, irreversible dilation of the abdominal aorta. There is strong evidence of genetic predisposition in the development of AAA but only a small number of low-effect risk loci have been identified. It is feasible that DNA methylation, one cause of altered gene-regulation, may contribute to AAA. We recently identified that global DNA hyper-methylation was associated with large AAA and increasing aneurysm diameter. These associations were independent of ethnicity, gender, age and smoking, highlighting the potentially pathogenic effects of chronic inflammation on methylation<sup>1</sup>.

### Aim

To identify gene specific CpG methylation changes in the promoters of genes already known to be associated with AAA.

### Work summary

Candidate gene promoters (SORT1, LDLR, IL6R, LRP1, CDKN2B and MMP9) were isolated in DNA derived from the peripheral blood mononuclear cells of 48 people with large AAA and 48 controls using DNA bisulphite conversion and bisulphite-specific PCR, then sequenced using next-generation sequencing technology. Data was analysed using open source bioinformatics software specifically designed for methylation sequencing.

### Results

Changes in levels of CpG methylation were observed in people with large AAA vs controls. The LDLR and SORT1 promoters were consistently hyper-methylated across large sections in 48 AAA vs 48 controls. 21 individual CpGs were hyper-methylated in AAA at the LDLR promoter locus, with an average increase of 5.4% (+/-1.08) (P=0.002). 4 CpG sites were significantly hyper-methylated in AAA in the SORT1 promoter locus, with an average increase of 4.8% (+/-0.55) (P=0.004).

### Conclusion

We have now identified that global and gene specific DNA methylation is associated with AAA. Functional corroboration is needed, but it is possible that these methylation differences are biological determinants of altered gene expression, and that DNA methylation does play a role in the disease. These genes also represent viable meQTL candidates.

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## End-stage human aneurysm disease in different arterial positions is similar – aneurysm induction in mouse models however not

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### Introduction

Aneurysm disease can occur throughout the arterial tree, with abdominal aortic aneurysm (AAA) being the most frequent central - and popliteal artery aneurysm (PAA) the most frequent peripheral one. The pathology has been well examined, yet, very little is understood regarding AAA development. Leaving aside secondary vessel enlargement due to dissection, inflammation and genetic disorders, aneurysm disease has distinct features like angiogenesis and phenotypic switching of vascular smooth muscle cells (VSMC). However, little is known about these characteristics in other than AAA.

### Material and Methods

From a surgical biobank of aneurysm tissue we compared 42 AAA, 15 PAA, three ascending aortic, five iliac, three femoral, two brachial, one visceral and one carotid artery aneurysm on morphologic, protein and mRNA-expression levels. Two multi-stage mouse models of aneurysm disease, porcine pancreatic elastase infusion (PPE) and topic application of elastase (EPA), were applied to test the response to arterial aneurysm induction in different locations within the arterial system.

### Results

AAAs show a wide variety in histomorphologic appearance, which can not be detected in PAA. All investigated aneurysm entities show characteristic VSMC phenotypic switching, angiogenesis, matrix remodeling, T-cell inflammation and M1-like macrophage homing. AAA and PAA, despite being of elastic and muscular artery origin respectively, have similar involvement of key transcription factors, like i.e. Krueppel-like factor 4 or myocardin. To further investigate these conditions in inducible aneurysm models, we applied the PPE procedure to a juxtarenal aorta and the EPA model to a thoracic, abdominal and femoral location.

### Conclusion

Despite different arterial morphogenesis, advanced aneurysm disease from human intraoperative specimen shows similar characteristics of end-stage disease that are best mimicked by the murine PPE model of aneurysm induction.

## Phenotypic switching of smcs is a potential therapeutic target in popliteal aneurysms

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### Introduction

Popliteal artery aneurysm (PAA) is an individually highly fatal disease, causing ischemia and eventual major amputation, mainly in 50-70 year old males. It is the most frequent peripheral artery aneurysm and correct treatment is challenging for clinicians, since both open and endovascular repair have only modest success rates, depending on the clinical presentation. In comparison to other aneurysm entities, little is known about its specific pathogenesis.

### Material and Methods

30 Human PAA and popliteal artery samples were analyzed by immunohistochemistry, mRNA and miRNA expression analysis and protein assays on the OLink platform in order to identify key features of the disease and crucial pathways involved. Furthermore, a novel murine model of PAA is characterized for future applications in basic research.

### Results

Vascular smooth muscle cells lose their contractile phenotype along with significant inflammatory and proteolytic changes in the vessel wall architecture. Extensive tissue remodeling with high cell turnover rates is a unique feature in comparison to AAA. This correlates with highly abundant expression of the apolipoproteins E and C1 suggestive to have a pro-proliferative effect in peripheral vascular tissue. Additionally, array-based screening on gene and protein level revealed the pentraxin-related protein 3 as a potential biomarker and soluble inducer of neutrophil homing. These findings are emphasized by a specific case of a solely mechanically induced PAA in a young male. External application to the femoral artery in mice induces diameter enlargement and might thus be a potential model for further research.

### Conclusion

Pathogenesis of PAA shows similar histologic features than AAA, yet differs in potential pathways involved. Increased cell turnover in the aneurysmal neck area suggests evaluation of alternative treatment strategies, targeting key processes in its pathogenesis.



Resveratrol inhibits aortic root dilatation in the *fbn1c1039g/+* marfan mouse model

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**Objective**

Marfan syndrome (MFS) is a connective tissue disorder caused by mutations in the fibrillin-1 gene. MFS patients are at risk for aortic aneurysm formation and dissection. Usually blood pressure lowering drugs are used to reduce aortic events, however, this is not sufficient for most patients. In the aorta of smooth muscle cell-(SMC) specific sirtuin-1 (SIRT1)-deficient mice, spontaneous aneurysm formation and senescence is observed. Resveratrol is known to enhance SIRT1 activity and to reduce senescence, which prompted us to investigate the effectiveness of resveratrol in inhibition of aorta dilatation in the *Fbn1C1039G/+* MFS mouse model.

**Approach and results**

Aortic senescence strongly correlates with aortic root dilatation rate in MFS mice. However, while resveratrol inhibits aortic dilatation, it only shows a trend towards reduced aortic senescence. Resveratrol enhances nuclear localization of SIRT1 in the vessel wall and, in contrast to losartan, does not affect leukocyte infiltration, nor activation of SMAD2 and ERK1/2. Interestingly, specific SIRT1 activation (SRT1720) or inhibition (sirtinol) in MFS mice does not affect aortic root dilatation rate even though senescence is changed. Resveratrol reduces aortic elastin breaks, and decreases microRNA(miR)-29b expression coinciding with enhanced anti-apoptotic Bcl-2 expression and decreased number of TUNEL positive cells. In cultured SMCs, the resveratrol effect on miR-29b downregulation is endothelial cell- and NF- $\kappa$ B-dependent.

**Conclusion**

Resveratrol inhibits aortic root dilatation in MFS mice by promoting elastin integrity and SMC survival, involving downregulation of the aneurysm-related miR-29b in the aorta. Based on these data, resveratrol holds promise as a novel intervention strategy for MFS patients.

Is risk-factor targeted aaa screening the future?  
Data from the oxford vascular study

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**Background**

Current abdominal aortic aneurysm (AAA) screening in men aged 65 might have limited impact on overall AAA-death rates if incidence is moving to older ages. Up-to-date population-based data of age-specific incidence and outcome of acute abdominal aortic aneurysm (AAA) events are needed to understand the impact of risk factor modification and demographic change, and to inform screening policy.

**Methods**

In a prospective population-based study (Oxfordshire, UK, 2002-2014), event rates, incidence, early case fatality, and long-term outcome of all acute AAA events were determined, both overall and in relation to the four main risk factors (smoking, hypertension, male gender and age).

**Results**

Over the 12 year period, 103 incident acute AAA events occurred in the study population of 92,728 (male 72.8%, 59.2% 30-day case-fatality). Incidence/100,000/year was 55 in men aged 65-74 years, but increased to 112 at 75-85 and 298 at  $\geq 85$ , with 66.0% of all events occurring at age  $\geq 75$  yrs. Incidence at 65-74 was highest in male smokers (274), with 96.4% of events in men aged  $< 75$  years occurring in ever-smokers. Mean age (SD) (yrs) at event was lowest in current smokers (72.2 (7.2)), compared to ex-smokers (81.2 (7.0)) and never-smokers (83.7 (7.9)) ( $p < 0.0001$ ). Hypertension was the predominant risk factor in women (diagnosed in 92.9%) with 54.8% of all events in women occurring in hypertensives aged 75 and over. Extrapolating rates to the UK population, using trial evidence of screening efficacy, the current UK screening programme would prevent 5.6% of aneurysm-related deaths (315,200 scans/year: 1426/death prevented, 121/year-of-life saved). Screening only male smokers aged 65 and then all men at age 75 would prevent 21.1% of deaths (247,900 scans/year; 297/death prevented, 34/year-of-life saved).

**Conclusions**

Two-thirds of acute AAA events occurred at age  $\geq 75$  yrs and over 25% of events occurred in women. Screening non-smokers at age 65 is likely to have very little impact on AAA event rates. Risk-factor targeted screening may prevent more deaths than current strategies.



Morphology of ruptured *versus* unruptured abdominal aortic aneurysms

Janet T. Powell

on behalf of the IMPROVE trial and other collaborators at St George's (lead Alan Karthikesalingam) and Perth (lead Barry Doyle).

Currently the best metric to assess the risk of aortic aneurysm rupture is the maximum aortic diameter. Recently aneurysm volume also has been investigated. However, other morphological characteristics, readily obtainable from 3D CT reconstructions, have largely been ignored as potential prognostic indicators.

The core laboratory for admission CT scans for IMPROVE trial patients provided an opportunity to compare the morphology of ruptured and unruptured aneurysms. These have been separated into abdominal aortic and common iliac aneurysms. Proximal aneurysm neck length, diameter and angle, maximum aortic diameter, iliac bifurcation angle and iliac artery diameter were measured according to protocol, with quality control for intra- and inter-observer variability of measurements.

For abdominal aortic aneurysms we have compared 294 confirmed cases of rupture with 907 elective cases according to a prespecified analysis plan, adjusting for sex. For common iliac aneurysms the cases are fewer (and all male) and we have compared 9 cases of iliac rupture with 10 elective cases and these data will be presented.

For both types of aneurysm, the angle of the iliac bifurcation appears to be the most influential measurement after maximum aneurysm diameter which distinguishes ruptured from intact aneurysms.

## AAA rupture in Stockholm

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This population based investigation includes all patients admitted to the any of the seven emergency departments within Stockholm County diagnosed with rAAA 2009-2013. A total of 283 patients were identified, 30% (n = 85) had a previously detected AAA. Men were in majority (76% vs 24%), and four years younger than women. A majority of patients admitted to an emergency department were treated (212/283, 75%), a similar proportion of women and men. Treated patients were younger (77 vs 84 years,  $p < 0.001$ ). One third were treated with EVAR was 27%, they were older than OR treated (79 vs 76 years,  $p = 0.043$ ). Patients with a previous diagnosis of AAA, before rupture occurred, had a higher mortality, partly due to a lower intervention rate (59% *versus* 82%,  $P < .001$ ). Reasons for non-treatment when diagnosed with AAA were; denied elective surgery (36%), patient choice (18%), size-related (13%) and surveillance deficiency (31%). The majority of patients missed in surveillance were treated at rupture (85%). Overall; 47% of patients admitted with rAAA survived 30 days, and 62% of treated patients survived 30 days, similar mortality for women and men. Our results and other contemporary series show a shift towards a higher rate of patients with rAAA being treated, increasing use of EVAR and continuously improving outcomes, similarly for women and men. Improved patient-specific protocols to reduce the surveillance gaps and new methods of determining rupture risk in each individual case of AAA could be two possible future strategies to reduce the incidence of rupture, in the previously diagnosed group. Data for patients treated 2014-2015 will also be included in the presentation.

## References

High proportion of known abdominal aortic aneurysm in patients with rupture indicates surveillance deficiency, Zommodi Sayid, Roy Joy, Steuer Johnny, Hultgren Rebecka, In press, JVS 2016.

## Australian trials to identify treatments to slow AAA growth

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**Background**

Currently there is no treatment for small abdominal aortic aneurysms (AAAs). Fenofibrate has been shown to limit AAA development in two studies in mouse models associated with reduction in aortic concentration of the matrix protein osteopontin and reduced aortic inflammation. Fenofibrate has also been shown to have a number of other effects which may favourably modify AAA pathology including raising high density lipoprotein and reducing matrix metalloproteinase.

**Methods**

Fenofibrate in the management of AAA (FAME-2) is a multi-centre, prospective, randomised, placebo-controlled trial to assess the effect of 24 weeks oral therapy of 145mg of fenofibrate on pathological markers of AAA. The primary endpoints are circulating biomarkers of AAA, including osteopontin. Secondary outcomes include maximum diameter assessed on ultrasound. FAME-2 is a collaboration conducted from three vascular centres in Australia.

**Discussion**

Currently, no medication has been demonstrated to limit abdominal aortic aneurysm progression. FAME-2 is a pilot study to examine whether promising results in a rodent model can be confirmed in patients.

**References**

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 Krishna SM, *et al.* Fenofibrate increases high-density lipoprotein and sphingosine 1 phosphate concentrations limiting abdominal aortic aneurysm progression in a mouse model. *Am J Pathol*. 2012;181(2):706-18.

## AAA measurement and enlargement

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**Background**

No effective treatment is currently available to prevent progression of small and medium-sized abdominal aortic aneurysms (AAAs). Identification of drugs with sufficient promise to justify large expensive randomized trials remains challenging. One potentially useful strategy is to look for associations between commonly used drugs and AAA enlargement in appropriately adjusted observational studies.

**Methods**

Potential AAA measurements were identified from abdominal imaging reports in the electronic data files of three medical centres from 1995 to 2010. AAA measurements were extracted manually and patients with an aneurysm of 3 cm or larger, who had at least two measurements over an interval of at least 6 months, were identified. Other data were obtained from the electronic data files (demographics, co-morbidities, smoking status, drug use) to conduct a propensity analysis of the associations of drugs and other factors with AAA enlargement.

**Results**

From 52 962 abdominal imaging studies, 5362 patients with an AAA of 3 cm or more were identified, of whom 2428 had at least two measurements over at least 6 months. Mean AAA follow-up was 3.4 years and the mean AAA enlargement rate was 2.0mm per year. Propensity analysis demonstrated no significant association of AAA enlargement with statins, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Diabetes was associated with a reduction in AAA enlargement of 1.2mm per year ( $P=0.008$ ), and chronic obstructive pulmonary disease was associated with increased enlargement (0.5mm per year;  $P=0.050$ ). Moderate AAA measurement variation and substantial terminal digit preference were also observed, but the digit preference became less pronounced after 2000.

**Conclusion**

This study confirms the negative association of diabetes with AAA progression. There was no evidence that commonly used cardiovascular drugs affect AAA enlargement.

## Immunopathology in patients with AAA

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Abdominal aortic aneurysm (AAA) is a serious condition with unclear pathogenetic mechanism which has a high mortality rate in case of the occurrence of the most serious complication - a ruptured aneurysm. One of the discussed pathogenic factors which might be involved in the development of AAA are immunological mechanisms. Patients and methodology: We examined a total of 58 patients with AAA requiring surgery and 20 patients treated for lipid metabolism disorder without AAA in the control group. Demographic and clinical characteristics of both groups is shown in Table 1. The following parameters were examined in both groups: IgG, IgG1-IgG4, pentraxin 3, fractalkine, IL-8, IL-10, IL-15, IL-18, IL-1b, M-CSF, MPC-1, RANTES, SAP, TNF, MMP-2, MMP-3, MMP-9, MMP-12. Results: In the AAA group of patients, statistically significantly higher concentrations of IgG4 were detected as compared to the control group. There were no significant differences in the concentration of fractalkine, IL-10, IL-15, IL-18, IL-1b, MPC-1 a TNF in both groups. RANTES concentration, as well as the concentrations of MMP 2 ( $p=0,02$ ), MMP 3 ( $p=0,04$ ) and MMP 9 ( $p=0,009$ ) were significantly higher in the group of patients with AAA ( $p=0,0004$ ). Conclusion: Significantly higher concentrations of biomarkers related to immune mechanisms and inflammatory activity were detected in the group of patients with AAA. A higher frequency of increased IgG4 concentrations in patients with AAA is a reason why some AAAs are considered to be a disease associated with IgG4. A higher inflammatory activity detected in the group of patients with AAA as compared with the control group of patients with treated arteriosclerosis provides a possibility to potentially use a targeted treatment in patients with AAA.

## How does it feel to have an abdominal aortic aneurysm – a patient-centered view

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**Aims**

An abdominal aortic aneurysm (AAA) is a potentially lethal disease, which is relatively common in elderly men. As repair has only proven benefit above 5.5cm, quite a large group of patients with smaller aneurysms do not receive specific treatment. These patients are in a watchful-waiting period and have little contact with their vascular specialist. Qualitative data from patients with small AAA's is scarce and little is known about the psychological impact of living with an aneurysm. More insights into patients' view on diagnosis and disease burden of an abdominal aneurysm is needed to provide patients with additional support in coping this disease.

**Methods**

For this purpose we perform ten in-depth semi-structured qualitative interviews with AAA patients who are in a watchful-waiting period. After the interview patients are asked to fill in a few questionnaires assessing: health related quality of life (SF-36), illness perceptions (IPQ), anxiety and depression (HADS). All interviews will be audio taped and transcribed verbatim. Interview transcripts are then coded and contents will be analyzed.

**Results**

Preliminary analyses of data derived from ten interviews shows that patients often have little knowledge on AAA-disease and treatment options. However, they accept the conservative watchful-waiting plan proposed by the surgeon. In addition, patients rated their own health and quality of life as highly positive, despite severe comorbidity and sometimes uncertain life expectancy. In these patients, the disease burden of an AAA was very low due to the absence of symptoms and active intervention. Aneurysm patients feel they have little control over their AAA and largely rely on the surgeon for judgment.

**Conclusions**

Patients with small AAA are generally content with a conservative treatment plan and consider themselves to enjoy a good health despite comorbidity. In addition, patients depend on their specialist to take control in AAA treatment.

## Meta-analysis of the current prevalence of screen-detected abdominal aortic aneurysm in women

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### Background

Although women represent an increasing proportion of those presenting with abdominal aortic aneurysm (AAA) rupture, the current prevalence of AAA in women is unknown. The contemporary population prevalence of screen-detected AAA in women was investigated by both age and smoking status.

### Methods

A systematic review was conducted, according to the PRISMA guidelines<sup>1</sup>, of studies screening for AAA, including over 1000 women, aged at least 60 years, done since the year 2000. Studies were identified by searching MEDLINE, Embase and CENTRAL databases until 13th January 2016. Study quality was assessed using the Newcastle–Ottawa scoring system for cross-sectional studies<sup>2</sup>.

### Results

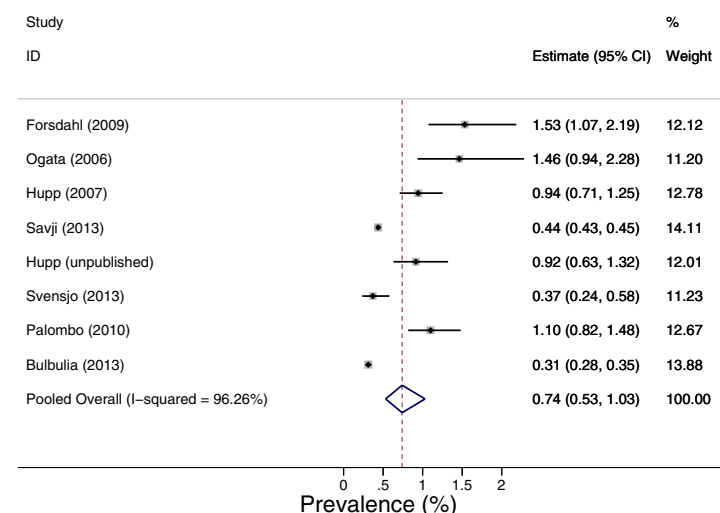
Eight studies<sup>3-9</sup> were identified, including only three based on population registers<sup>3,7,8</sup>. The largest studies were based on self-purchase of screening. Altogether 1,537,633 women were screened. Overall AAA prevalence rates were very heterogeneous, ranging from 0.37 to 1.53%: pooled prevalence 0.74% [95%CI 0.53 to 1.03]. The pooled prevalence increased with both age (>1% for women aged over 70 years) and smoking (>1% for ever smokers and >2% in current smokers).

### Conclusion

The current population prevalence of screen-detected AAA in older women is subject to wide demographic variation. However, in ever smokers and those over 70 years, the prevalence is over 1%.

### Figures

Pooled prevalence of abdominal aortic aneurysm in women aged at least 60 years: eight studies with screening performed between 2001 and 2012. Values in parentheses are 95 per cent confidence intervals



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Diameter growth rate and future indication for surgery can be predicted with finite element analysis and semi-automatic diameter measurements in small abdominal aortic aneurysms.

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### Objective

For small abdominal aortic aneurysms (AAA), it is difficult to predict which aneurysms will require surgery and which will remain stable. We aimed to evaluate if semi-automatic diameter measurements and finite element analysis were superior at predicting the four-year progression rate and indication for surgery of AAAs compared to standard diameter measurements

### Methods

Thirty-three small AAAs with a baseline diameter of 40-50 mm were identified. 'Standard diameters', measured by radiologists or vascular surgeons, were collected from patient records. The aneurysms were subsequently recreated into digital, three-dimensional (3D) models by semi-automatic segmentation from the CTAs. Maximal diameter orthogonal to the aneurysms' centerline was automatically measured and finite element analysis, yielding peak wall rupture index (PWRI), was performed. Further, growth rate between two standard diameters was studied in an overlapping group of 39 AAAs that had been measured once more after the initial CTA (baseline diameter of 40-60 mm).

### Results

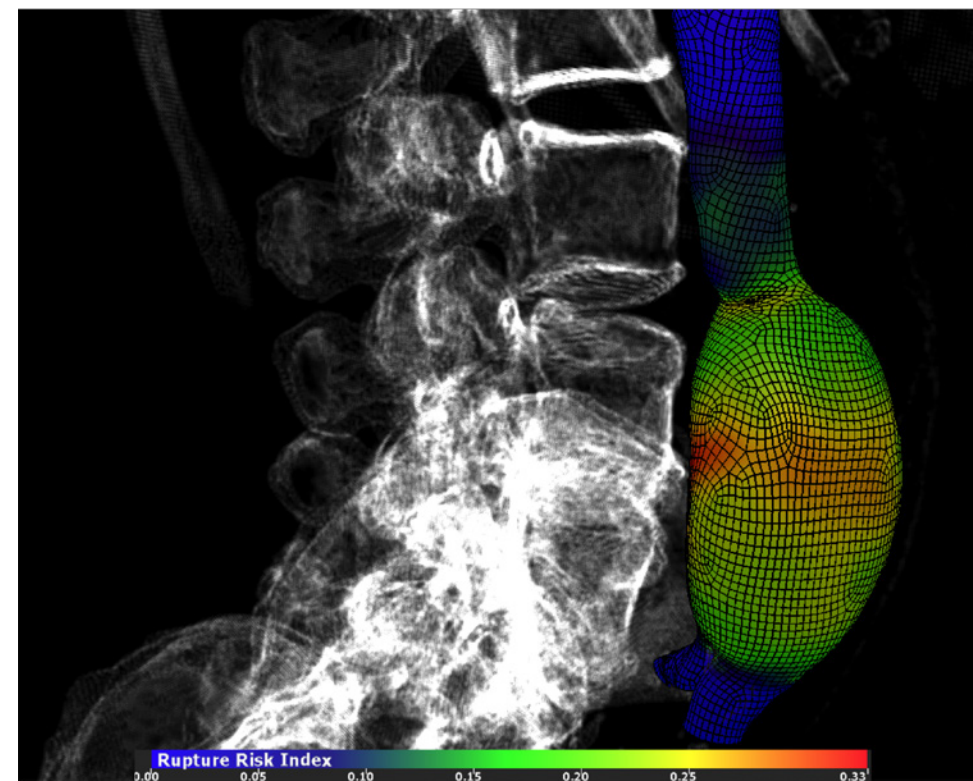
Diameter growth rate displayed a good correlation with baseline semi-automatic diameter ( $r=0.53$ ,  $p=0.0006$ ) and PWRI ( $r=0.44$ ,  $p=0.0055$ ) but only a trend could be observed for baseline standard diameter ( $r=0.31$ ,  $p=0.052$ ). After four years, 20 AAAs had received surgery or had reached indication for surgery, ie standard diameter of 55 mm, and 13 AAAs remained intact with a standard diameter of < 55 mm. Baseline semi-automatic diameter and PWRI could specifically identify aneurysms that would require surgery within four years,  $n=6$  (30%) and  $n=9$  (45%), respectively, whereas the baseline standard diameter could not ( $n=0$ , 0%).

### Conclusion

Finite element analysis and precise diameter measurements may improve AAA growth rate predictions and allow early aortic repair in selected patients with AAA.

**Figure**

Finite element analysis of an abdominal aortic aneurysm Red areas represent high and blue areas low estimated rupture risk index.



## Inward neo-angiogenesis in aortic diseases

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The medial layer of aortic wall is physiologically devoid of tissue microcirculation, whereas the external adventitial layer is rich in microcirculatory system. In contrast, aortic pathologies are all characterized by the development of an inward intramedial neo-angiogenesis, initiated from the adventitia and penetrating the media. Neoangiogenesis is always characterized by sprouting of new endothelial cells from the adventitia<sup>1</sup>. These inward cell conductances respond to the outward convective transport of angiogenic mediators, which modulate in relation to different pathologies.

In atheroma, the radial convection of intimal mediators, generated by phospholipase activities within the lipid core of the plaque initiates the angiogenic process. We identified PG-J2 as mediator, able to stimulate PPAR $\gamma$  in subjacent medial SMC, which promote VEGF release, and stimulate inward sprouting from the adventitia<sup>2</sup>. This neo-angiogenesis is the hallmark of the shift from initial stages to more vulnerable ones, in particular by promoting intraplaque hemorrhages<sup>3</sup>.

In AAA, the neo-angiogenesis is constant, linked to cyclo-oxygenase activities, but developed in the adventitia<sup>4</sup>. The limited inward penetration of neo-angiogenesis in AAA is probably related to the intensive proteolytic environment present in active ILT and media, which do not allow sprouting due to the peri-cellular proteolysis limiting the cell ability to adhere and spread on a matrix, including the fibrin matrix<sup>5</sup>. But ILT has an important impact on adventitia, including tertiary lymphoid organs<sup>6</sup> and angiogenesis. The molecular effectors involved in angiogenesis remain unknown in AAA. It has been proposed that a thick ILT provokes hypoxia in the wall<sup>7</sup>.

In TAA, inward intramedial angiogenesis is always heterogeneously present but more discrete than in atheroma. Proteomic array of the medial layer, allowed us to identify numerous mediators of neo-angiogenesis in TAA, including angiopoietin-1 and -2, Thrombospondin-1, FGF-a, etc. But VEGF expression did not differ between TAA and control normal aorta<sup>8</sup>. These angiogenic factors are counterbalanced, at least in part, by outwardly convected angiogenic inhibitors such as plasminogen-derived angiostatin, limiting the inward sprouting of new vessels. In conclusion, neo-angiogenesis is a hallmark of aortic pathologies, but the molecular mechanisms responsible of the process could be quite different.

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## Circulating miRNA associated with instable abdominal aortic aneurysm PET positive

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### Background

Prediction of abdominal aortic aneurysm (AAA) rupture is a challenging issue. Small non-coding RNAs (miRNAs) are potent regulators of gene expression and are considered as valuable circulating biomarkers. Recently, 18F-FDG uptake detected by PET in AAA was correlated with cellular and molecular alterations presaging wall instability and its potential rupture. Our study aims at identifying circulating miRNAs correlated with a positive PET that could help discriminating patients at higher risk of rupture.

### Methods

The levels of 372 miRNAs were evaluated by PCR array in plasma from 35 AAA patients displaying no FDG uptake (A0) and 22 patients with a positive PET (A+). The level of modulated miRNAs was validated by qPCR and was also measured in aneurysmal tissues.

### Results

Six miRNAs were found significantly modulated in A+ vs A0 patients. They were significantly correlated between them and with PET-positivity but only two of them were also correlated with the AAA diameter. These miRNAs displayed significant discriminating power (ROC curve) between the A+ and A0 groups. Three down-regulated circulating miRNAs, miR-99b-5p, miR-125b-5p and miR-204-5p, were also significantly reduced in the aneurysmal tissue at the FDG-uptake site compared to a negative zone in the same aneurysm and as compared to A0 aneurysms. They were further significantly inversely correlated with the expression, at the positive uptake site, of some of their potential gene targets, most notably MMP13.

### Conclusions

Six miRNAs were identified as potential new circulating biomarkers of PET+ AAA at high risk of rupture, three of them being similarly modulated in the metabolically active aneurysmal wall and might be directly involved in AAA instability.



## Transdifferentiation of human dermal fibroblasts to smooth muscle like cells: a novel method to study the effect of myh11 and acta2 variants in the aortic aneurysm wall

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### Introduction

Research on the pathogenesis of aortic aneurysms has revealed mutations in genes encoding the smooth muscle cell contractile proteins<sup>1-3</sup> as key underlying causes. Mutations associated with familial aortic aneurysms have been found in MYH11 (myosin heavy chain 11), ACTA2 (smooth muscle actin alpha 2) and MYLK (myosin light chain kinase) genes, which encode integral proteins of the contractile apparatus.

### Experimental aim/problem definition

Currently, SMC can only be obtained by an invasive aortic biopsy. Therefore, the aim of this study is to transdifferentiate skin fibroblasts into SMC-like cells to provide a less invasive diagnostic test to study SMC function and mutations.

### Work summary

Dermal fibroblasts from 7 healthy donors and 7 patients with MYH11 or ACTA2 variants were transdifferentiated into SMC-like cells within 2 weeks by using 5ng/mL TGFβ1 and a scaffold containing collagen and elastin (matrigel). As control, cells were cultured without TGFβ1. SMC-specific markers were analyzed via qPCR, western blot and immunofluorescence. To investigate and classify the pathogenicity of the variants, cDNA sequencing was performed.

### Results

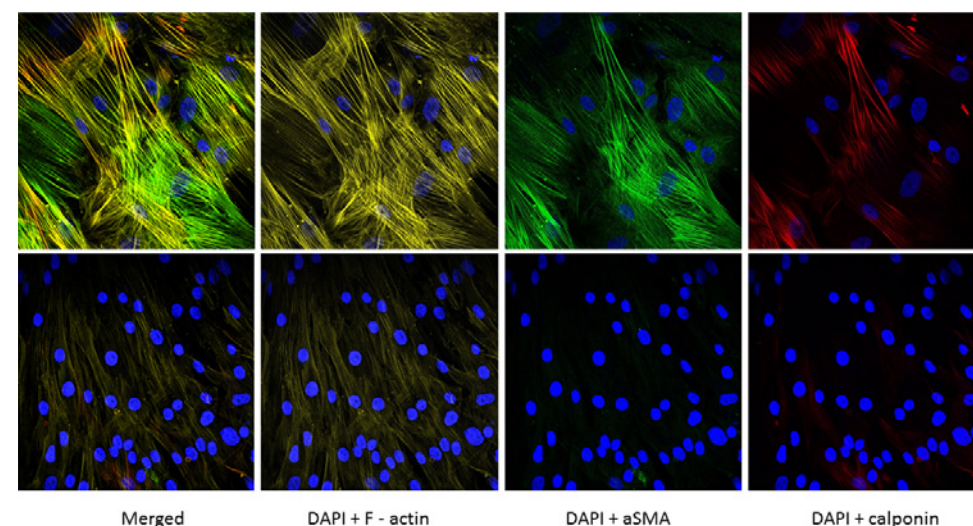
The induced SMC-like cells were comparable to primary human aortic SMC in the expression of SMC specific markers on mRNA and protein level (Fig.1): ACTA2 (αSMA), SMTN (smoothelin) and CNN1 (calponin). Importantly, in patients with MYH11 or ACTA2 variants the effect on splicing was demonstrated on the mRNA level in the induced SMC, allowing classification into pathogenic or non- pathogenic variants. Moreover, the pathogenic MYH11 variants showed overexpression of contractile proteins accompanied by defective F-actin cytoskeleton formation if compared to transdifferentiated SMC from the healthy donors.

### Conclusions

Direct conversion of human dermal fibroblasts into SMC-like cells is a highly efficient method to investigate the pathogenic effect of variants in genes encoding the proteins of the SMC contractile apparatus. Our findings suggest the role of defective cytoskeleton formation and disturbed contraction of SMC in aortic aneurysm formation.

### Figure

Representative confocal images of transdifferentiated and non-transdifferentiated cells. Upper panels: transdifferentiated SMC-like cells. Lower panels: primary dermal fibroblasts.



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## Live human arterial tissue slices for bench top research on pathophysiology of aortic aneurysms; up to 90 days ex vivo preservation

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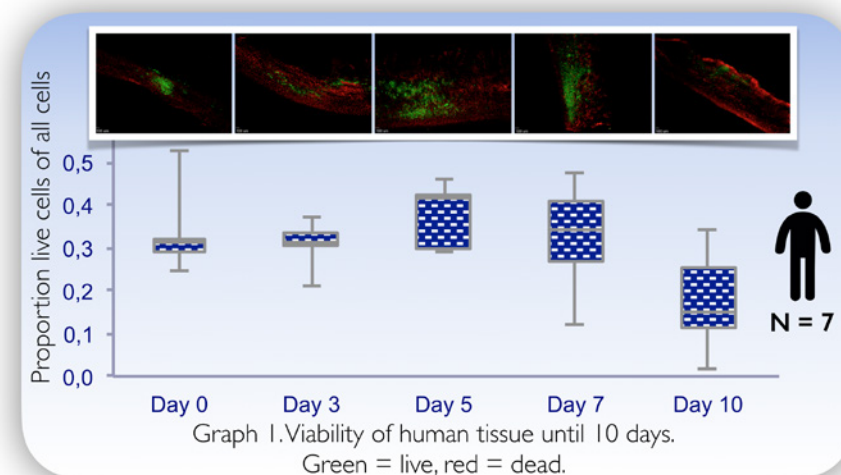
Currently, research on abdominal aortic aneurysm (AAA) pathophysiology is limited to fixated cells or isolated cell cultures<sup>1,2,3</sup>. However, due to these techniques, cell-cell interactions and communication with extracellular matrix are lost. These interactions are likely to play a role in the AAA pathogenesis<sup>4,5,6,7</sup>. We hereby present an innovative method to cut live vascular tissue slices and preserve cell viability and cellular organization for research into AAA in which anatomical, functional and microstructural characteristics are of interest.

Peroperatively harvested tissue was transported in ice-cold Custodiol and cut into cubes. Subsequently, cubes were submerged in agarose, glued on an anvil, and cut into slices of 150 µm. Slices were cultured at 37°Celsius in media supplemented with antibiotics. Viability analysis was performed up to 92 days after harvesting using LIVE/DEAD® Viability/Cytotoxicity Kit. Cell type characterization was achieved by staining for CD45, CD68, α-SMA/smoothelin to identify leukocytes, macrophages and fibroblasts/smooth muscle cells (SMC) respectively. Additionally, tissues were digested using collagenase to study individual cells and analyze cellular populations in live tissues.

Tissue slice analysis showed a stable viability of 40% until 7 days (graph. 1) and after improvement of the protocol up to 92 days after harvesting (with outgrowth of new cells). Live cells were mainly seen centrally in the tissue, while dead cells were observed at cutting edges. Live cells were differentiated by qualitative analysis based on cell morphology and specific marker expression. The majority of studied live cells were fibroblasts/SMC. Furthermore, leukocytes and macrophages were observed. These findings were in accordance with the findings in cells of digested tissues.

Vitality and organization of tissue sections of aneurysmal and non-aneurysmal vascular tissue can be preserved until 92 days after harvesting. This study provides a solid base for further experimental research on pathophysiological mechanisms underlying aneurysms and possibly other vascular diseases.

### Figures



Viability of human aortic tissue slices

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## Focal adhesion kinase is a novel target for pharmacotherapy of abdominal aortic aneurysm

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Abdominal aortic aneurysm (AAA) is characterized by chronic inflammatory cell infiltration and progressive destruction of the extracellular matrix by proteolytic enzymes. However, the molecular mechanisms that regulate chronic inflammation in AAA remain largely unknown. Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase that plays critical roles in integrin-mediated signal transduction. We previously demonstrated in vitro that FAK is involved in inflammatory responses to mechanical strain in vascular smooth muscle cells. These findings led to the hypothesis that FAK might promote AAA progression by maintaining and enhancing inflammatory responses. In this study, we found that FAK was highly activated in human AAA wall specimens compared with non-AAA walls. Activated FAK was mostly localized to macrophages within AAA tissues. FAK inhibitor, PF573228, significantly reduced secretion of monocyte chemoattractant protein-1 and matrix metalloproteinase-9 from cultured macrophages after stimulation with tumor necrosis factor- $\alpha$ . Furthermore, we created the mouse model of AAA by periaortic application of calcium chloride. Treatment of mice with PF573228 over the entire experimental period (from weeks 0 to 6 after calcium application) significantly reduced inflammatory cell infiltration and disruption of the elastic lamellae, and prevented the development of AAA. Importantly, delayed treatment with PF573228 (only from weeks 3 to 6) blocked increases in cellular infiltration and elastin disruption in aortic walls, and significantly inhibited further progression of AAA. Our findings uncover a critical role of FAK in the development and progression of AAA, indicating that FAK represents a novel therapeutic target for the treatment of AAA.

## Telmisartan in the management of abdominal aortic aneurysm (TEDY): the study protocol for a randomized controlled trial

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### Background

Experimental studies suggest that angiotensin II plays a central role in the pathogenesis of abdominal aortic aneurysm. This trial aims to evaluate the efficacy of the angiotensin receptor blocker telmisartan in limiting the progression of abdominal aortic aneurysm.

### Methods/Design

Telmisartan in the management of abdominal aortic aneurysm (TEDY) is a multicentre, parallel-design, randomised, double-blind, placebo-controlled trial with an intention-to-treat analysis. We aim to randomly assign 300 participants with small abdominal aortic aneurysm to either 40 mg of telmisartan or identical placebo and follow patients over 2 years. The primary endpoint will be abdominal aortic aneurysm growth as measured by 1) maximum infra-renal aortic volume on computed tomographic angiography, 2) maximum orthogonal diameter on computed tomographic angiography, and 3) maximum diameter on ultrasound. Secondary endpoints include change in resting brachial blood pressure, abdominal aortic aneurysm biomarker profile and health-related quality of life. TEDY is an international collaboration conducted from major vascular centres in Australia, the United States and the Netherlands.

### Discussion

Currently, no medication has been convincingly demonstrated to limit abdominal aortic aneurysm progression. TEDY will examine the potential of a promising treatment strategy for patients with small abdominal aortic aneurysms.

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## The effect of metformin on AAA

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Diabetes mellitus is negatively associated with the prevalence and progression of abdominal aortic aneurysm (AAA) disease. We investigated the possibility that the oral hypoglycemic agent metformin (Glucophage) may influence the progression of AAA disease.

### Methods

Preoperative AAA patients also noted to have diabetes were identified from an institutional database. Following assessment of individual cardiovascular and demographic risk factors and prescription drug regimens, odds ratios for categorical influences on annual AAA enlargement were calculated through nominal logistic regression. Experimental AAAs were created in normoglycemic mice to validate the database-derived observations as well to identify potential mechanisms of metformin-induced aneurysm suppression.

### Results

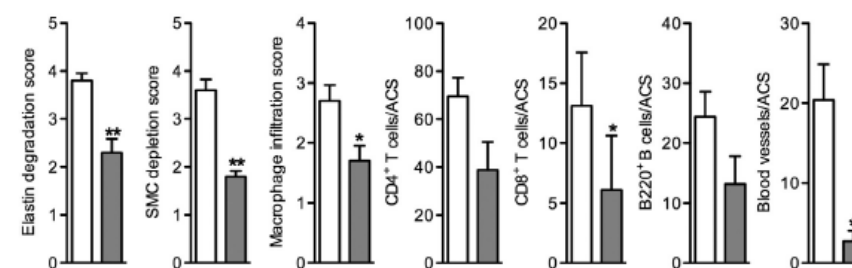
Fifty eight patients met criteria for study inclusion. Of 11 distinct classes of medications considered, only metformin use was negatively associated with AAA enlargement. This association remained significant after controlling for gender, age, cigarette smoking status and obesity. The median enlargement AAA enlargement rate in patients not taking oral diabetic medication was 1.5 mm/y; by nominal logistic regression, metformin, hyperlipidemia and age  $\geq 70$  years were associated with below-median enlargement, whereas sulfonylurea therapy, initial aortic diameter  $\geq 40$  mm, and statin use were associated with above-median enlargement. In experimental modeling, metformin dramatically suppressed the formation of AAA, with medial elastin and smooth muscle preservation and reduced aortic mural macrophage, CD8 T cell, and neovessel density.

### Conclusions

Epidemiologic evidence of AAA suppression in diabetes may be attributable to concurrent therapy with the oral hypoglycemic agent metformin.

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### Figures



**Fig 4.** Effects of metformin treatment on medial elastin and smooth muscle cell (SMC) integrity and mural inflammation in experimental abdominal aortic aneurysm (AAA). Aortic frozen sections from metformin-treated (n = 10) and vehicle-treated (n = 7) mice 14 days after porcine pancreatic elastase (PPE) infusion were stained for elastin (Verhoeff-van Gieson [EVG]), SMC (SMC  $\alpha$ -actin), leukocyte subsets (CD68 for macrophages, CD4 for CD4 T cells, CD8 for CD8 T cells, B220 for B cells), and CD31 for angiogenesis. Elastin degradation, SMC depletion, and mural macrophage infiltration were graded as score I (mild) to score IV (severe). Mural CD4 T cells, CD8 T cells, B cells, and angiogenesis were quantified as positive cells or blood vessels per aortic cross section (ACS). Nonparametric Mann-Whitney test, \* $P < .05$  and \*\* $P < .01$  compared with vehicle treatment group.

Mechanisms of experimental AAA suppression by metformin Copyright 2016 Society of Vascular Surgery/Elsevier, all rights reserved

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Fujimora N, Xiong Jiang, Kettler EB, Xuan H, Glover KJ, Mell MW, Xu B, Dalman RL. Metformin treatment status and abdominal aortic aneurysm disease progression. Journal of Vascular Surgery 2016 epub before press.

## What do we know about AAA and diabetes and does it matter

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Diabetes is generally considered to increase the risk of most manifestations of cardiovascular disease, particularly coronary heart disease and peripheral arterial disease. In contrast with occlusive arterial disease, there is a negative association between diabetes and abdominal aortic aneurysm (AAA). Several large cross-sectional studies have shown that the prevalence of AAA is 30% lower in the presence of diabetes. Cohort studies have shown that the incidence of new AAA is reduced by 60% and the expansion of existing AAAs is about 50% lower in diabetes. The underlying mechanisms for the negative association are still unclear. Whilst animal model studies and clinical observations suggest the importance of hyperglycaemia, there is also evidence that drugs used to treat diabetes, such as metformin, may play a role. One of the consequences of chronic hyperglycaemia is the increased formation of Advanced Glycation Endproducts (AGEs) due to non-enzymatic reactions between sugar metabolites and both proteins and lipids. The deposition of AGEs may result in complex changes in extra-cellular matrix, including fibrosis and resistance to proteolysis, which are compatible with reduction in AAA formation. On the other hand, binding of AGEs to a cell surface receptor (RAGE) can increase oxidative stress and inflammation – both associated with increased AAA formation. The association between AGE formation and AAAs can be assessed indirectly via biomarkers of the glycation pathway. The relationship between four of these biomarkers (glyoxal, methylglyoxal, carboxymethyllysine, and the soluble RAGE) and both aortic diameter and AAA presence in a cohort of ~900 men screened for AAA will be reported.

## Inhibition of pathological vascular smooth muscle cell remodelling as a treatment strategy for abdominal aortic aneurysm

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### Introduction

Pathological vascular smooth muscle cell (VSMC) remodelling in abdominal aortic aneurysm (AAA) drives eventual VSMC senescence, loss and luminal dilation. The VSMC have not been a major target for novel AAA treatment approaches. We hypothesise that strategies to reduce this VSMC remodelling response may be beneficial in the context of novel AAA therapeutics and provide evidence for this idea using a novel small-molecule inhibitor of VSMC remodelling in murine models of AAA.

### Methods

For the study we used a small-molecule inhibitor of PDGF induced VSMC remodelling delivered to mice via subcutaneous osmotic mini pump. In the first set of experiments, AAA was induced by AngII infusion to ApoE<sup>-/-</sup> mice, peri-aortic CaCl<sub>2</sub> or peri-aortic elastase application to C57BL6/J mice. Novel treatment was delivered at the time of aneurysm induction. In the second protocol, the novel inhibitor was given only after AAA had formed in the AngII model to investigate AAA progression. The aortic lumen was visualised with 3D in-vivo ultrasound and tissue evaluated by histology and immunohistochemistry.

### Results

Histological evidence of pathological VSMC remodelling was apparent in all three murine models investigated. Treatment of animals with the novel inhibitor throughout the experiment reduced VSMC remodelling and aneurysm size. The effect was particularly apparent on aortic lumen area. When the inhibitor was applied to ApoE<sup>-/-</sup> mice with established AAA following AngII infusion, no further aortic dilation occurred suggesting effectiveness against AAA progression and translational potential.

### Conclusion

Pathological VSMC remodelling is apparent in multiple murine models of AAA. Inhibition of the VSMC remodelling response with a small molecule inhibitor is possible and attenuates AAA progression. Translational efforts to further understand and modulate VSMC remodelling in human AAA should be explored.



Canonical tgfb $\beta$ -signaling is triggered by inflammation in human non-syndromic aneurysm disease, but is not reflected by inducible AAA mouse models

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### Introduction

Transforming growth factor  $\beta$  (TGF $\beta$ ) signaling has been demonstrated to be crucially involved in aneurysm pathogenesis since mutations in its receptors have been revealed to be responsible for multilobular aneurysm formation in patients with Loeys-Dietz syndrome. Despite TGF $\beta$ 's central role in cell signaling, its specific regulation in non-syndromic aneurysm formation is yet of unclear significance.

### Material and Methods

We explored a biobank of human AAA and popliteal artery aneurysms to elucidate the function of different components of the TGF $\beta$  pathway by immunohistochemistry, gene expression analysis and western blot. Additionally the TGF $\beta$ -connective tissue derived growth factor (CTGF) axis was analyzed in a new mouse model of inducible juxtarenal aortic aneurysm.

### Results

Canonical TGF $\beta$  signaling with increased activation of phosphorylated SMAD 2/3 was discovered independently of the grade of inflammation or the type of artery. This process was triggered by mononuclear infiltrates in the arterial media. While collagen production is increased, other downstream effects like CTGF signaling appear not elevated. Inducible murine models of AAA mimic an earlier time point of aneurysm development and demonstrate enhanced canonical TGF $\beta$  signaling in infrarenal, juxtarenal and thoracic position, as seen in two different models.

### Conclusion

Canonical TGF $\beta$  signaling is elevated in human aneurysm disease. The TGF $\beta$ -CTGF-axis seems to be of lesser importance. In vivo experiments with murine inducible models can only partly reflect these conditions due to the specific role of this pathway during aneurysm development and progression.

Phenotyping of transgenic pigs to determine the suitability of xenografts in the treatment of aortic diseases

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Abdominal aortic aneurysm and aortoiliac occlusive disease are the two most common vascular diseases in which surgical treatment requires the implantation of aortic prosthesis. The synthetic materials can cause graft infection, a distal potentially fatal complication of surgical treatment. This is connected with the necessity of patient re-operation and the replacement of prosthesis with biological material, such as auto- or allografts. Due to the shortage of multiorgan donors, many patients with infection of the prosthesis cannot be treated successfully. The domestic pig may be the perfect donor of easily accessible blood vessels for transplantation. Under the MEDPIG project a series of „humanized” pigs were generated by genetic engineering and breeding, to omit species incompatibility.

We focus on the ex vivo studies of biological material harvested from several genetic variations of humanized pigs. Tissue samples are tested to identify modification the least immunogenic to human. We established over 20 primary endothelial aortic cells lines, isolated from thoracic aorta of transgenic pigs and comparable number of cell lines from control, wild type animals. In vitro studies include several cytotoxicity assays to evaluate response to the human complement and other components of human immune system. Biomechanical properties studies focus on comparative analysis of a transgenic pig and human vessels, in order to identify anatomical resemblance and ability to function in different hemodynamic conditions. Biomechanical, histological and molecular evaluation of arteries were performed before and after cryopreservation. The level of inbreeding of pigs was also evaluated genetically. In a pilot study functionality of the aortic grafts was tested in vivo through cross transplants. Our studies demonstrate the application of transgenic pig tissue in modeling and therapy of human aortic diseases. Funded by The NCRD (grant n. INNOMED/I/17 /NCBR/2014) from the Innovative Economy Operational Programme funds, in the framework of the ERDF.

## Imaging alternatives in order to prevent rupture (volume vs diameter)

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**BACKGROUND**

The diagnosis and management of abdominal aortic aneurysms (AAA) currently relies on the aortic maximal diameter, which, however, is the subject of increasing discussion. Specifically the threshold diameter criterion lacks a sound patient-individual assessment, is already about 20 years old, and may no longer adequately reflect current treatment options. Most important, AAA rupture is a complex event and a better understanding requires a multi-disciplinary approach<sup>1</sup>.

**METHODS**

All AAA patients at Karolinska University Hospital, Stockholm, Sweden who had undergone two Computed Tomography Angiographies (CTA) with roughly one year's interval (8-17 months) were retrospectively identified. Forty-one patients (9 female, 32 male) were included and digital three-dimensional reproductions of the aneurysms were segmented and analyzed from the 82 CTAs (A4clinics Research Edition, VASCOPS GmbH, Austria). Specifically, AAA diameter, AAA volume were measured from 3D reconstructions, while Peak Wall Rupture Index (PWRI) was calculated based on a Finite Element Analysis (FEA)<sup>2</sup>.

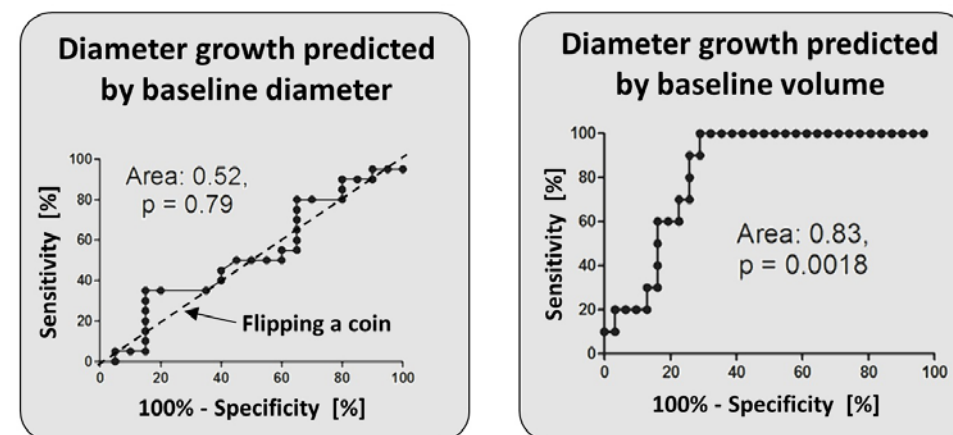
**RESULTS**

Diameter growth rate did not correlate with baseline diameter ( $r=0.15$ ,  $p=0.34$ ) or with increasing PWRI ( $r=0.17$ ,  $p=0.30$ ). Volume growth rate correlated with baseline volume ( $r=0.56$ ,  $p=0.0001$ ) and volume growth rate higher than or equal to the sample median could be predicted with 90% sensitivity and 85% specificity, see Figure 1. Volume growth rate correlated with increasing PWRI ( $r=0.75$ ,  $p=0.0001$ ) and further results are reported elsewhere<sup>3</sup>.

**CONCLUSION**

Our study clearly demonstrated that aneurysm volume, compared to its maximum diameter, better predicts aneurysm growth rate and correlates stronger with increasing biomechanical rupture risk. Our results support the notion of monitoring all three dimensions of an AAA.

Figures



Baseline diameter *versus* baseline volume as growth predictor Receiver Operator Characteristics (ROC) curves for baseline diameter (left) and baseline volume (right) to predict Abdominal Aortic Aneurysms diameter growth. Data is based on following-up 41 patients over approximately one year and demonstrates that aneurysm diameter growth can be reasonably predicted by baseline volume but not by baseline diameter. Dashed line in the left image represents flipping a coin, i.e. represents the ROC curve of no predictive information at all.

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Is the risk different for female or male fdrs to AAA patients?

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Although family history is well known as a risk factor for development of AAA, the problem is not systematically addressed in clinical practice. The prevalence of AAA is higher in persons with a family history than in smokers. Guidelines suggest selective screening of First Degree Relatives (FDRs) (regardless of sex) in the US at one time, and the ESVS guidelines at age 50-55 years, although the level of evidence is low. Male relatives, but not female, will however be invited within the population-based screening programs for elderly men in Sweden and the UK. Previous studies have reported contradictory findings regarding prevalence of AAA in FDRs, but most reports show an increased prevalence, approximately 10%. The prevalence in female FDRs is always lower, but this mainly reflects the lower prevalence overall in women in the population as compared to men (0.5-1% vs 1.5-4%). The risk for a male FDR (brothers) to develop an AAA is 20% compared to 6% in a female FDR, as reported from the Liege AAA Family study. In the Swedish Sibling study; 17% vs 6% prevalence in brothers and sisters was found; however this should be compared with the prevalence in the population, which gives a 12 times increased prevalence in female FDRs compared to women in the population, and 8-9 times in male. The age at which screening of FDRs could be adequate, has recently been investigated in our Swedish Sibling cohort. Our results, and others support a selective screening program for all FDRs (male and female at 50 and 55 years) supporting the ESVS guidelines. The population based screening at 65 could be too late for all FDRs, a finding supported by several reports on the increased diameter at diagnosis, growth rate and rupture risk in patients with AAA and a family history compared to non-familial AAA. The risk for the FDR to develop disease if the proband is a male or female has also been investigated, and quite contradictory findings from an increased risk to a similar risk are found (Darling, Mejnert, Larsson, Blanchard).

In conclusion, the risk for all FDRs to develop AAA is high compared to the population, even when smokers are analyzed separately. One should possibly compare the AAA prevalence in female FDRs with that of women in the population, rather than with male FDRs when developing selective screening programs. The male FDRs also have an increased chance of detection due to the ongoing population based screening programs.

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## Keynote lecture. Lessons learned from the IMPROVE trial

Janet T. Powell

for the IMPROVE trial investigators

The Immediate Management of the Patient with Rupture: Open *Versus* Endovascular repair (IMPROVE) trial randomised 613 patients with an in hospital diagnosis of ruptured abdominal aortic aneurysm to either a strategy of endovascular first (with open repair as the default) *versus* open repair between 2009 and 2013.

The trial reported its primary outcome, 30-day mortality, early in 2014<sup>1</sup> and 1-year outcomes in Spring 2015<sup>2</sup> and now is poised to complete analysis of the final 3 year follow up. There was no difference in either 30-day or 1-year mortality between the randomised groups, although subgroup analyses at both timepoints were consistent with women having a survival advantage from an endovascular strategy. The 1-year results also reported quality of life, costs and cost-effectiveness, which were all better in the endovascular first strategy group<sup>2</sup>. Since this is perhaps the largest prospective series of patients with ruptured abdominal aortic aneurysm, we have been able to learn about other important aspects too, including the impact of pre-operative blood pressure, type of anaesthesia, aortic morphology and abdominal compartment syndrome<sup>3,4</sup>. We also have collaborated with 2 smaller European trials to publish individual patient data meta-analyses, which strengthen all the main observations of the IMPROVE trial<sup>5</sup>.

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## Management of visceral artery aneurysms: a 20-year single centre experience

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Visceral artery aneurysms (VAA), including renal and splanchnic lesions, are rare (0,01% up to 2% in general population) but life-threatening disease. The natural history is unknown but rupture occurs frequently particularly when vessel dimension exceeds 2 cm that, to date, represent the threshold to intervene in asymptomatic patient. Unfortunately, when rupture occurs, mortality rate is consistent ranging from 21% when the complication is located at the hepatic artery site up to 100% when is located at the celiac artery site. Objective of this study is to review our experience with VAA treatment. Between January 1995 and August 2015, 28 VAA were treated, (21 males, 7 females) with mean age of 56 years (range 25-87). Intraoperative data included surgical approach, type of reconstruction and associated procedure. N=19 patients were asymptomatic, n= 6 symptomatic and n=3 presented on emergency due to rupture. The most common locations were renal artery (n=10), splenic artery (n=8), hepatic artery (n=4), celiac trunk (n=3). Four patients underwent endovascular treatment (1 on emergency), 23 patients underwent open surgery (2 on emergency) and 1 patient was operated on in Minimally Invasive approach. Overall early mortality was 7.14% (2 patients in surgical group operated on emergency due to the rupture of renal aneurysm). Perioperative morbidity was 3,5% (1 patient operated on splenectomy). Late mortality was 25% (1 patient in endovascular group). We believe that surgical VAA treatment is a safe and effective procedure irrespective if it will be done open or percutaneous, mortality and morbidity are low outweighing dismal expectancy of life in untreated patients.

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## Aortic size index could improve surveillance of women and men with abdominal aortic aneurysm

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### Background

Abdominal aortic aneurysm (AAA) predominantly affects men, however the risk of rupture is higher in women resulting in a poorer outcome. Recent studies have shown that the correlation between body surface area and aortic diameter (aortic size index) could be a better predictor than aortic diameter for rupture in women, however there is a lack of knowledge within the field. This study aims at investigating the correlation between body surface area and aneurysm diameter in women and men with non-ruptured AAA.

### Methods

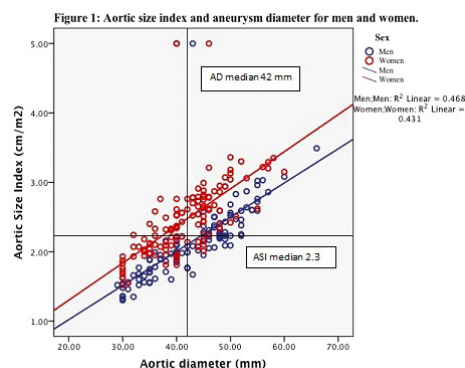
A retrospective population based cohort study. Patients with AAA followed at the Karolinska University Hospital in Stockholm, Sweden between January 2012 and December 2014, with at least two imaging examinations performed were eligible for inclusion, 120 women and 120 men were included in the study. Data was collected through review of medical records. Means were compared using independent t-test and Mann Whitney test for continues variables. Pearson's chi-square and Fischer's exact test was used for categorical variables.

### Results

Women had a higher mean age, but did not differ from men regarding comorbidities. The aortic diameter was similar between women and men (41.5mm *versus* 43.0mm,  $p=0.21$ ). Women had a smaller body size area and a larger aortic size index (2.4 *versus* 2.1,  $p<0.05$ ). Older patients had a higher aortic size index compared to younger patients. The median growth rate for the cohort was 2.2 mm per year. No difference in growth rate was shown between women and men. Larger aneurysms (median 45.0 mm) had a higher growth rate compared to smaller aneurysms (2.7 mm *versus* 1.6 mm,  $p<0.05$ ).

### Conclusion

The results supports previous reports showing that aortic size index, combined with aortic diameter could be a useful tool for improved surveillance, especially in women and older patients with small AAA. Further prospective analysis must be performed in order to define the predictive value of ASI for rupture risk.



## How common is the classic triad of symptoms in patients with ruptured abdominal aortic aneurysm?

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### Introduction

Ruptured abdominal aortic aneurysm (rAAA) is a life threatening condition with mortality around 70-90%. Diagnostics is still depending on identification of a classic diagnostic triad of pain, hypotension and pulsatile mass. The literature is scarce regarding the true occurrence of the classic triad of symptoms in patients with RAAA.<sup>1-3</sup> Primary Aim: To investigate how many of admitted patients with rAAA that had the classic triad. Secondary Aim: To investigate whether a correlation between number of triad-symptoms and time to treatment and outcome can be found.

### Material and Methods

Records of 283 patients with ICD code 171.3 (RAAA) diagnosed between 2009-2013 in the Stockholm County has been identified, for this analysis only patients subjected to the Karolinska University Hospital in Stockholm were reviewed retrospectively, 52 were included.

### Results

The classic triad was present in 13 (25%) of the patients with RAAA. Back or abdominal pain was present in 49 (94%) and hypotension in 43 (83%). Pulsating mass was found in 14 (27%), but only in one (4%) of the overweight patients ( $p=0.004$ ). Patients with 3 out of 3 symptoms of the classic triad did not have shorter time to treatment ( $p=0.72$ ) or lower 30 day mortality ( $p=0.41$ ) compared to patients with less than 3 symptoms.

### Conclusions

Only one fourth of the patients with RAAA have the classic triad of symptoms, which correlates with the few reports within the field. The diagnostic value of the classic triad can be discussed in the present form, however adding ultrasound for evaluation of aortic diameter would probably increase the validity.

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## Survival disparity following aaa repair highlights inequality in socioeconomic status

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### Background

Determinants of survival following abdominal aortic aneurysm (AAA) repair are well documented and are predominantly co-morbidity driven. Other patient factors such as socioeconomic status (SES) have also been suggested as factors influencing mortality. The aim of this study was to report if deprivation influences survival after AAA repair.

### Methods

Consecutive patients undergoing AAA repair between July 2000 and December 2013 were identified from the national database. SES was defined as recorded on health records. A score of 1 indicates those least deprived and 10 representing the most deprived. Multivariate logistic regression model was used along with confounders included as independent variables to calculate odds ratios (OR) and survival analysis using cox proportional model to report adjusted hazard ratios (HR).

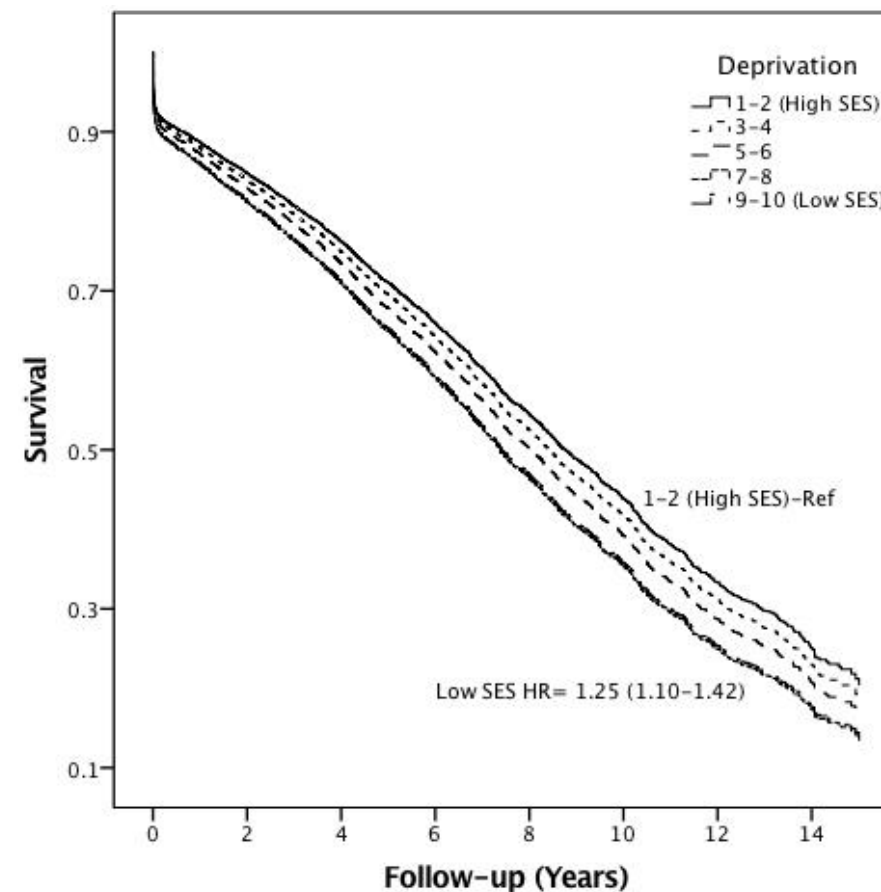
### Results

5824 patients with a mean age (standard deviation, SD) of 74 (7.7) years and 78.7% males were included. The mean (SD) deprivation score was 6.1 (2.7). Deprivation categories 7-8 and 9-10 were associated with OR 1.54 (95%CI: 1.07-2.23) and 1.61 (95%CI: 1.10-2.36) respectively. The median survival follow up period was 5 years and after adjusting for confounders, deprivation categories 9-10 was associated with a higher risk of death HR=1.25 (95%CI: 1.10-1.42).

### Conclusions

Patients with a lower SES have an independent risk of reduced short and long-term survival. Identifying deprivation status may represent a mechanism through which cardiovascular risk modification is initiated and maintained during follow-up. This may help reduce outcome disparities for people with lower SES and highlights the need for more emphasis on targeting at-risk groups.

Figure



Adjusted Survival of deprivation categories

## Patient reported quality and functional life after AAA repair

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### Introduction

Patient reported outcomes are becoming an important health measure. Long term results from the DREAM trial shows that patients that underwent open aneurysm repair (OAR) have an improved quality of life (QOL) compared to patients that received EVAR. The aims of this study were to assess the QOL and functional outcomes for patients that underwent AAA repair in the clinical setting.

### Methods

Consecutive patients who have undergone AAA repair between January 2009 and December 2014 were identified from a prospective maintained database. A questionnaire relevant for post AAA patients was developed from a literature review and the Short Form Health Survey (SF-12) was used. Patients were invited to attend a 30-minute clinical assessment appointment or a phone interview.

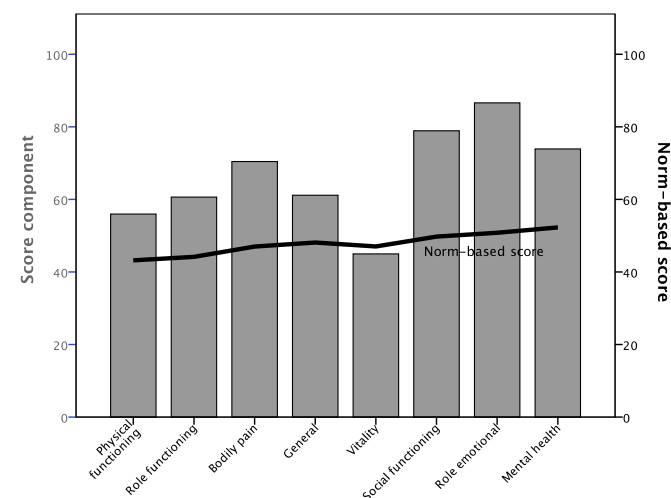
### Results

There were 381 patients that had an AAA repair, of which 101 (26.5%) were not alive and were excluded from further analysis. Of the 280 eligible patients, 228 (85.7%) were males, 229 (74.3%) were elective procedures and 134 (43.5%) were EVAR. The minimum and median follow-up period was 12 and 42 months. In all, 223 patients were recruited and completed follow-up (inclusion rate 80%). There was no difference in SF-12 components between patients receiving OAR and EVAR. The percentage of patients that were living independently, driving and working preoperatively was 99, 93 and 27 respectively and corresponding percentages following AAA repair were: 98, 86 and 18. There was no difference between any of the SF-12 components within an age-sex matched population.

### Conclusions

There were no perceived differences in QOL of patients receiving OAR or EVAR and the majority still enjoy a good QOL and have returned to their baseline activities without considerable limitations. These results may help clinicians inform realistic expectations to patients, not only on 5-year survival but also on functional outcomes when consenting or offering AAA repair.

Figure



SF-12 components compared to the normal based score



Friday September 16

SCIENTIFIC PROGRAM

## Diagnostic algorithm for acute aortic dissection – imaging and biomarkers

Toru Suzuki

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Diagnosis of acute aortic dissection still remains a challenge.

Effective use of available diagnostic technologies including imaging and biomarkers is critical for immediate decision making.

Recent developments in biomarkers such as D-dimer have established a potential role for biomarker-assisted diagnosis.

Coupled with rapid imaging such as a triple rule-out CT would provide for a diagnostic algorithm of acute aortic dissection.

Protocol-based diagnostic algorithms are helpful in the emergency setting and integration with available pathways such as for STEMI will be a topic that needs to be addressed.

Current thinking on diagnostic algorithms based on biomarkers and imaging will be discussed.

## Individualized risk assessment in type B aortic dissection

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Thoracic endovascular aortic repair is considered to be the first-line treatment for patients with complicated type B aortic dissection. Decision making is often based on physician experience and subjective clinical judgment and therefore the management of type B aortic dissection is complex. The long-term benefits of endovascular repair to prevent aortic-related mortality has been demonstrated in randomised controlled trials however recently attention has been turned to whether endovascular repair should be performed in uncomplicated cases. Pre-emptive surgery may not be the solution for all patients because of the occurrence of adverse events such death, stroke and paraplegia. A number of groups have undertaken studies to investigate morphological and false lumen characteristics that may be able to identify patients with uncomplicated type B aortic dissection at high risk of complications that would benefit from early endovascular intervention. Characteristics investigated include aortic diameter, the position, size and number of entry tears and false lumen thrombus volume. Functional imaging methods such as magnetic resonance and echocardiography are able to provide clinically relevant structural, hemodynamic and biomechanical information, which could be used for risk stratification of individual patients. A patient-specific approach designed to intervene only in patients that are at high risk of developing complications should improve the long-term outcome of these patients.



## Can we predict aortic size prior to dissection? Yes!

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**Objectives**

Multiple studies have quantified the relationship between aortic size and risk of dissection. However, these studies estimated the risk of dissection without accounting for any increase in aortic size from the dissection process itself. This study aims to compare aortic size before and after dissection and to evaluate the change in size consequent to the dissection itself.

**Methods**

Fifty-five consecutive patients (29 Type-A; 26 Type-B) with aortic dissection (AoD) and incidental imaging studies prior to dissection were identified and compared to a control group of aneurysm patients (n=205). Average time between measurement at and prior to dissection was  $1.7 \pm 1.9$  years ( $1.9 \pm 2.0$  years mean inter-image time in control group). A multivariate regression model controlling for growth rate, age and gender was created to estimate the effect of dissection itself on aortic size.

**Results**

Mean aortic sizes at and prior to dissection were  $54.2 \pm 7.0$  mm and  $45.1 \pm 5.7$  mm for the ascending (AA), and  $47.1 \pm 13.8$  mm and  $39.5 \pm 13.1$  mm for the descending aorta (DA), respectively. Multivariable analysis revealed a significant impact by the dissection itself ( $p < .001$ ) and estimated an increase in size by 7.65 mm (AA) and 6.38 mm (DA). Thus, a proportional estimate of 82.8% (AA) and 80.8% (DA) dissect at a size lower than the guideline recommended threshold (55 mm).

**Conclusions**

Aortic diameter increases substantially due to aortic dissection itself and thus, aortas are dissecting at clinically meaningfully smaller sizes than natural history analyses have previously suggested. These findings have important implications regarding at what size to intervene surgically (suggesting a shift toward smaller aortic sizes).

## Initial experience in dissection of aorta in Nepal

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**Introduction**

Interventional cardiology including cardiovascular surgery is in its early phase of development in Nepal. Sahid Gangalal National Heart Centre is the only cardiology dedicated government hospital in Nepal and therefore, the main tertiary cardiac patient referral centre for the whole country. Surgery for aortic dissection has recently started in the country. We present our early experience with aortic dissection cases in the hospital.

**Method**

We did a retrospective descriptive analysis of aortic dissection cases requiring surgery over a period of 26 months between February 2014 and April 2016.

**Results**

Altogether 20 cases of dissection of aorta were operated during the period. Thirteen (65 %) patients were males. Average age of the patients was 54 years (range: 25 to 81 years). Eighteen cases (90%) were of type A dissection: 17 with acute and 1 with chronic dissection, while the remaining two (10%) had type B dissection and required surgery because of complications like leak or rupture. Of the 18 type A dissection cases, two-third (12/18) underwent M Bentall's procedure while 3 underwent Bentall's with hemi arch replacement, 2 underwent ascending aortic replacement, and 1 underwent Bentall's with proximal arch replacement. In addition, one of these patients had right coronary artery unroofing while another one had coronary artery bypass graft. Five of these 18 patients (27.8%) died. The two cases of type B dissection underwent surgery in an emergency basis due to ongoing leak and both expired post-operatively.

**Conclusion**

Our early experience with aortic dissection management shows a success rate of 65%. Studies that look into details of patient characteristics and health-provider related parameters can help improve success rate, and reduce mortality.

## Positive family history of aortic dissection dramatically increases dissection risk in family members

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### Objective

Although family members of patients with aortic dissection (AoD) are believed to be at higher risk of aortic dissection, the prognostic value of a positive family history (FH) of aortic dissection (FHAD) in family members of patients with AoD has not been studied rigorously. We seek to examine how much a positive family history of aortic dissection may increase the risk of developing new aortic dissection among first-degree family members.

### Methods

Patients with AoD treated at our institution between 1983 and 2015 were contacted to complete a questionnaire on FHAD. A family history was considered positive if AoD occurred in the index patient and one or more family members. The age at AoD, exposure years in adulthood before AoD, and annual probability of AoD among first-degree relatives were compared between patients with negative and positive FHADs.

### Results

A total of 100 patients with AoD were identified. Mean age at dissection was  $59.9 \pm 14.7$  years. FHAD was positive in 32 patients and negative in 68. Compared to patients with negative FHAD, patients with positive FHAD dissected at significantly younger age ( $54.7 \pm 16.8$  vs  $62.4 \pm 13.0$  years,  $P = 0.013$ ), had more AoD events in first-degree relatives ( $2.3 \pm 0.6$  vs  $1.0 \pm 0.0$ ,  $P < 0.001$ ), and shorter exposure years per AoD event ( $18.3 \pm 6.7$  vs  $43.1 \pm 8.5$ ,  $P < 0.001$ ). The annual probability of AoD per first-degree relative was 2.77 times higher in patients with positive than negative FHADs ( $0.0100 \pm 0.0057$  vs  $0.0036 \pm 0.0014$ ,  $P < 0.001$ ).

### Conclusions

A positive FHAD confers a significantly increased risk of developing AD on family members.

## Open surgical conversion after TEVAR: incidence and treatment options

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### Background

To analyze indications, describe different approaches and report outcomes of patients undergoing late open conversion (LOC) after thoracic endovascular aortic repair (TEVAR).

### Methods

From 1999 to 2015, 65 patients at our Institution underwent redo procedures after TEVAR. Thirty of them underwent LOC. Average time from the index TEVAR to LOC was 57 months (range 2-98 months), indication to LOC was progression of distal aortic disease in nine patients (30%), stent-graft infection/fistulization in 10 (33.3%), retrograde dissection in 6 (20%), endoleak in 3 (10%), device migration/failure in 2 (6.7%). In 17 patients (56.6%) thoracic stent-graft was only partially removed and the proximal anastomosis was performed including native aorta, stent-graft and surgical graft. Left heart bypass and cerebrospinal fluid drainage were used in 22 (73.3%) and 16 (53.3%) cases, respectively. Biological flap coverage with intercostal muscle flap was used in 6 of infected cases.

### Results

Overall perioperative mortality rate was 16.6% (5 patients) – 20% in the subgroup of patients with stent-graft infection/fistulization (2 patients) and 33% in the subgroup with retrograde dissection (2 patients). The most common postoperative complication was respiratory failure with seven cases (23.3%). Paraplegia was observed in 1 patient (3.3%). During a mean follow-up of 19 months (range, 5-63) was registered only one aortic-related death for aorto-esophageal fistula.

### Conclusions

Open conversion after TEVAR is a technically demanding procedure but feasible leaving in site the proximal segment of thoracic stent-graft in most of the cases. Morbidity and mortality rates were higher in case of infection, fistula and retrograde dissection.

## Neuromonitoring using motor and somatosensory evoked potentials in aortic surgery

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### Background

Motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP) are established methods of neuromonitoring aimed at preventing paraplegia after descending or thoracoabdominal aortic repair. However, their predictive impact remains controversial. The aim of this study was to evaluate our single center experience using this monitoring technique.

### Methods

Between 2009 and 2014, 78 patients (mean age  $66 \pm 12$ , 53% male) underwent either descending or thoracoabdominal aortic repairs. Of these, 60% had an aortic aneurysm, 30% dissection and 10% other etiologies. Intraoperatively, MEPs and SSEPs were monitored and, if necessary, clinical parameters (blood pressure, hematocrit, oxygenation) were adjusted in response to neuromonitoring signals. This analysis is focused on the neurological outcome (paraplegia, stroke) after the use of intraoperative neuromonitoring.

### Results

Thirty-day mortality was 10 (12.8%). All patients with continuously stable signals or signals that returned after signal loss developed no spinal cord injury, whereas 2/6 of the evaluable patients with signal loss (without return) during the procedure suffered from postoperative paraplegia (one transient and one permanent). Sensitivity and specificity of use of MEP and SSEP were 100% and 94.20% regarding paraplegia, respectively.

### Conclusions

1. Preservation of signals or return of signals is an excellent prognostic indicator for spinal cord function.
2. Intraoperative modifications in direct response to the signal change may have averted permanent paralysis in the patients with signal loss without neurologic injury. We have found MEP and SSEP neuromonitoring to be instrumental in the prevention of paraplegia.

## Radiation protection for patient and staff during routine EVAR and TEVAR procedures

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Endovascular aortic aneurysm repair require extended fluoroscopy guidance for the manipulation of endovascular devices, which is associated with biological risks for both physicians and patients. Potential consequences range from skin injuries to the development of solid cancers and leukemia. There is no absolutely safe amount of ionizing radiation and protection must be a priority for the endovascular therapist. When following good practices it is possible to keep the risks as low as reasonably achievable to commensurate with the medical purpose. Radiation protection can be achieved with the use of appropriate protective equipment and the reduction of the radiation dose. The use of shielding devices (lead aprons, thyroid shields, table suspended lead shields) is mandatory. The use of tables with a carbon fiber top instead of regular surgical tables is preferable. The distance between the patient's body and the image receptor should always be minimized to avoid beam energy dispersion and the screen should always be collimated vertically and horizontally to the area of interest. Radiation dose reduction requires a strict application of the "as low as reasonably achievable" principle. The x-ray system should be by default set to low dose program and pulsed mode, while the pedal should be engaged only when information is required. Magnification should be avoided, while digital subtraction angiography should be replaced by fluoroscopy runs in most instances possible. Extreme angulations of the x-ray equipment should be avoided. Image fusion can facilitate endovascular navigation and reduce the dose needed, although have not been widely applicable. All interventionists should receive appropriate radiation protection training and always audit and review the outcomes of each procedure. The application of specific regulation of radiation protection during routine EVAR and TEVAR is mandatory. Optimized set-up of the fluoroscopy system, adherence to good clinical practice and adequate training are key points to ensure safety for both the patients and the staff during the procedure.

## Management aortic coarctation in 2016: surgery vs endovascular treatment

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Coarctation of the aorta is one of the commonest congenital cardiac conditions - a narrowing of part of the thoracic aorta, most commonly of the isthmus around the insertion of the arterial duct. This condition accounts for 7-10% of all congenital heart lesions<sup>1</sup>.

Before the advent of balloon angioplasty and stenting, repair was first described in 1945<sup>2</sup>, usually performed through a left lateral thoracotomy. Three standard surgical approaches dominated the approach to repair, resection and end-to-end anastomosis; subclavian flap repair and Dacron patch aortoplasty.

There are however, a number of reports describing the long-term complications of surgery. The largest series (891 patients) which analysed patients with 1-24 years of follow up revealed 5.4% developed pseudo-aneurysms at the site of repair; 89.6% in those undergoing patch aortoplasty, 8.3% after end-to-end anastomosis, and 2.1% after prosthetic graft replacement<sup>3</sup>.

Standard open repair of these post coarctation repair aneurysms involves redo sternotomy and careful dissection with interposition grafting most commonly. This redo surgery is challenging. There is a significant rate of recurrent laryngeal nerve damage, bleeding and a mortality rate quoted of up to 14%<sup>4</sup>. In addition, these patients often have associated congenital cardiac defects, and convincing these patients that surgery is a durable option is not always easy.

With the advent of endovascular techniques and in particular the new stent grafts available on the market the options for these patients have increased, We have had significant success in the endovascular treatment of these patients over the last six years.

A report from our unit<sup>5</sup>, which has been replicated by others describes a series of thirteen patients from 27-66 years of age. Utilising current generation stent grafts the initial technical success was 100% with all aneurysms excluded entirely in 10/13. Early CT scans showed type II endoleaks in two patients and a single type 1b endoleak that required successful distal stent extension.

In our series, we have a median of three years follow up. Except for the one initial distal extension needed for a type 1b endoleak noted at the time of initial CT evaluation, we have had no patients that have required further intervention of any type. Careful planning to achieve adequate seal and fixation at landing zones with newer generation stent grafts, selected on a case by case basis is essential for success. The majority of the saccular aneurysms have regressed to an impressive degree with no measurable sac.

One significant concern with endovascular stent graft repair in these patients is durability. However, it is not a valid argument to compare the results of thoracic stenting for aneurysmal disease with localised pathologies. Careful follow up and assessment will allow a robust comparison between surgery and stenting in the future.

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## Keynote lecture. Medical errors during endovascular treatment for aortic diseases. How can we avoid them?

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A significant number of patients come to harm while in hospital<sup>1</sup>. The highest rate of adverse events is in patients undergoing intervention, most commonly in patients undergoing vascular procedures<sup>2</sup>. Endovascular techniques are associated with a significant advantage in terms of morbidity and mortality when compared to open surgical procedures as most vascular patients are elderly patients with major comorbidity, however the potential for error may be increased using these techniques<sup>3</sup>.

It is important to map the pattern of error and determinants. The Landscape of Error in Aortic Procedures (LEAP) study ran between 2010-2014 and involved collaboration from twenty vascular teams at ten English hospitals trained in self-reporting (phase I) who then participated in structured post-operative debriefs, reporting system errors in open/endovascular aortic procedures (phase II).

In phase I, teams recorded errors using a self-report collection tool<sup>4</sup>, which was validated in 88 cases. Intraoperative errors were identified through trainer observation and team self-reporting. There was a strong correlation between observer and team number/type of errors identified per procedure.

Subsequently (phase II), in 185 aortic cases, operating teams self-reported a median of 3 errors/procedure (interquartile range 2-6). There was a wide range of categories of error reported. The most frequently reported errors related to equipment (unavailability/ failure/ configuration/ decontamination-33.9%). The most frequent major or harm-producing errors were communication failures.

Importantly, fourteen errors directly harmed twelve patients (6.5% of the cohort). In addition, there were a significant number of major errors that either delayed proceedings in theatre or were likely to cause patient harm in the majority of cases. The potential for significant harm as a result of avoidable error appears to be a real and prominent risk for many vascular patients.

Further analysis of the data showed significant predictors of increased error rate were: open repair *versus* endovascular (Incidence Rate Ratio (IRR) 0.71; 95% confidence interval (CI) 0.57-0.88,  $p=0.002$ ); thoracic/arch aneurysms relative to other aortic pathologies (IRR 2.07; CI 1.39-3.08,  $p<0.001$ ); equipment unfamiliarity (IRR 1.52; CI 1.20-1.91,  $p<0.001$ ). Unfamiliarity with equipment was associated with increased major error rate (IRR 2.59; CI 1.51-4.28,  $p=0.001$ ). Major intra-operative error total was associated with reoperation ( $p=0.01$ ), major complications ( $p=0.03$ ) and death ( $p=0.03$ ).

We have also examined the safety events listed in the National Reporting and Learning System (NRLS) to study the pattern of reports in elective aortic surgery [unpublished data]. Between 2003-2013, the UK National Reporting and Learning System (NRLS) has collated almost 6 million safety reports. We have interrogated elective aortic vascular surgery

incidents to quantify incident patterns and prioritize safety improvements.

A systematic search of the NRLS was performed and following duplicate removal, narratives were scrutinized and inclusion criteria applied. Independent researchers- both experienced in vascular surgery and human factors, reviewed elective aortic reports and categorized validated safety incidents according to category (WHO classification) and harm (modified medication error index). Thematic analysis of harming events was performed to identify process and problem modes. In this research 6,750 reports were retrieved following term search and duplicate removal. We identified 2,698 aortic surgery safety incidents, of which 1,126 were elective- 448 preoperative, 302 intraoperative, 376 postoperative.

The dominant five categories account for 80.0% of all reports- medical devices (22.1%), resources/ organizational management (20.4%), clinical process/ procedure (17.1%), medication 10.5% and documentation 9.9%. Of the 1126 reports- 885 reached the patient (78.6%), 307 caused harm (27.3%). Severe harm or death occurred in 7.3% of reports.

From these studies we have been led to understand the key features in the generation of error in the vascular operating pathway. It also has convinced us that these errors contribute to direct harm and adverse patient outcomes. Decreasing the number of avoidable intraoperative errors may well lead to improvements in patient outcomes, particularly in endovascular surgery, which consistently has a higher rate of intraoperative error compared to open surgery. Important in complex vascular surgery is the careful preparation and utilisation of equipment, with appropriate training and accreditation in the use of unfamiliar devices. Communication and collaboration between operating team members is essential to reduce major and harm producing errors. We have instituted a leadership and team-training programme to attempt to reduce errors occurring in surgery. This appears to be effective in reducing error when assessed adequately<sup>5</sup>. Pre-procedural, patient specific rehearsal may also be effective in reducing errors made by teams<sup>6,7</sup>.

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## Incidence, treatment and long-term clinical outcome in patients with aortic graft infections

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### Introduction

Aortic graft infections are relatively rare, with an incidence of 0.6-3%<sup>1</sup>. High mortality rates continue to be a major concern in this patient category. The primary aim of this study was to identify the incidence of postoperative aortic graft infection and assess the long-term clinical outcome of different treatment modalities in a population-based cohort.

### Methods

Using the in-hospital electronic patient registry and the Swedish Vascular Registry (Swedvasc), 2026 patients treated for aortic aneurysms and aortoiliac occlusive disease in Stockholm county region (pop. 2.2 million) during the period 2005-2015 were identified. Review of the patients' records provided information on type of infection, treatment and outcome.

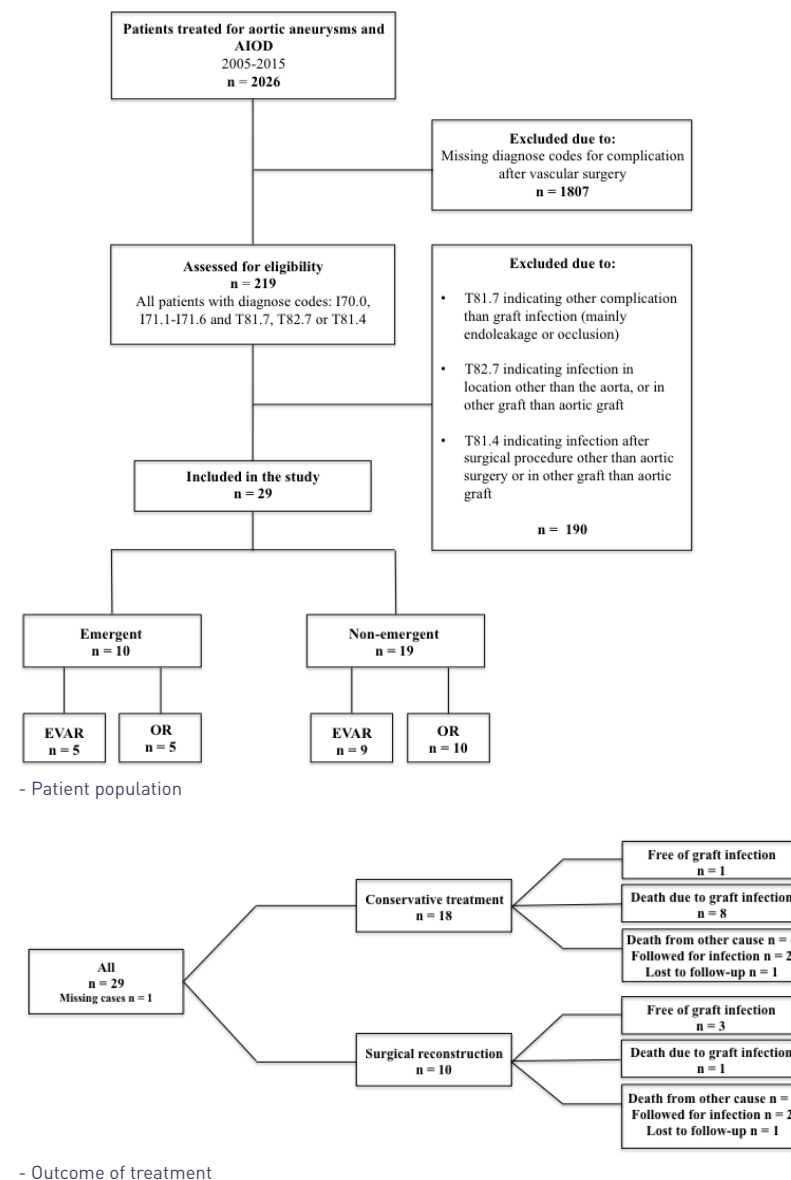
### Results

219 suspected cases of infection were reviewed, yielding 29 patients (26 males, 3 females) with aortic graft infections. The mean age was  $68.9 \pm 10.7$  years. Mean follow-up time was  $81.4 \pm 66.3$  months from primary surgery (EVAR  $51.3 \pm 44.7$ ; open repair  $98.6 \pm 71.8$ ). The overall incidence of graft infection was 1.4% (29/2026). Ten patients had emergency surgery at the time of primary intervention (EVAR  $n = 5$ ; open repair  $n = 5$ ). Nineteen patients had non-emergent surgery (EVAR  $n = 9$ ; open repair  $n = 10$ ). The incidence of graft infection for both non-emergent and emergent cases was 1.4%. In the non-emergent group ( $n = 19$ ), 11 patients were treated conservatively, seven patients underwent surgical reconstruction and there was one missing case. In the emergent group ( $n = 10$ ), seven patients were treated conservatively and three underwent surgical reconstruction. There were five deaths due to graft infection in the conservatively treated group but none in the surgically treated group. All-cause mortality for the non-emergent group was 53% and for the emergent group 80%. Mortality rates based on treatment method were 78% for conservatively treated patients and 40% for surgically treated patients. In the conservatively treated group 5.6% were free of infection compared to 30% in the surgically treated group.

### Conclusion

There were no significant differences between the emergent and non-emergent groups in terms of incidence of graft infection or time to infection. Surgically treated patients had better rates of eradication of infection and survival than the conservatively treated patients.

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## Sex differences in outcomes after AAA repair in the United Kingdom

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**Introduction**

AAA screening in men is cost-effective and reduces mortality. There is no evidence that screening women is effective. However, women are four times more likely to rupture and account for 33.6% of all ruptured AAA deaths, therefore may be disadvantaged by current policies.

**Problem Definition**

Peri-operative risk is critical in determining the effectiveness of screening and contemporaneous estimates of these risks are lacking. We therefore aimed to compare outcomes for men and women undergoing AAA in the UK.

**Work Summary**

Anonymised individual data from the UK National Vascular Registry for patients who had undergone AAA repair 2010-2014 were analysed. Relevant covariates were extracted for further analysis by sex. Analyses were stratified by 5-year age bands and the primary outcome measure was in-hospital mortality by gender, indication and operation. Multivariate regression was performed to adjust for co-morbidities.

**Results**

33,069 patients were included. For elective open surgical AAA repair, in-hospital mortality was 4.0% in men and 6.9% in women (OR 1.77, 95%CI 1.33-2.35,  $P=0.0001$ ) whilst for EVAR in-hospital mortality was 0.7% in men and 1.7% in women (OR 2.51, 95%CI 1.57-4.03,  $P=0.0001$ ). No differences were seen in mortality after ruptured AAA repair. Elective morbidity was higher in women who were more likely to develop cardiac complications (4.3% *versus* 5.7%, OR 1.34 95%CI 0.99-1.82,  $P=0.04$ ) and renal failure (7.0% *versus* 9.3%, OR 1.37, 95%CI 1.07-1.75,  $P=0.007$ ) after OSR and haemorrhage (1.0% *versus* 1.7%, OR 1.70, 95%CI 1.07-2.71,  $P=0.02$ ) and cerebral complications (0.2% *versus* 0.5%, OR 2.53, 95%CI 1.01-6.36,  $P=0.05$ ) after EVAR. Female gender remains a significant risk factor for death ( $P=0.028$ ) after adjustment.

**Conclusion**

Women have worse outcomes after elective AAA repair. This highlights the need for sex-specific pre, peri and post-operative strategies to reduce the differences seen and may erode any benefit of screening for AAA in women.

## Explantation of a fenestrated abdominal endograft with autologous venous reconstruction for infection

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**Case report**

A 72-year old man underwent a three-vessel FEVAR for an asymptomatic thoraco-abdominal aneurysm of 64 mm. The immediate postoperative course was favorable. One month postoperatively he was re-admitted for urosepsis, treated with IV antibiotics. A CT scan for ongoing fever showed infection of the stentgraft with multiple intra-abdominal abscesses. The largest abscess was drained percutaneously and antibiotic therapy stabilized the patient. Revision surgery was refused at that moment. After two months the patient was discharged with lifelong oral antibiotics.

During the next eight months the patient was re-admitted four times. CT imaging was always reassuring. Ten months postoperatively CT imaging showed new periaortic abscesses. Percutaneous drainage of the abscesses and IV antibiotics were applied. Then the patient agreed with revision surgery as only chance for some durable quality of life. Meanwhile, he was completely exhausted.

A staged procedure was performed: First, an axillobifemoral bypass was performed to reduce cardiac afterload during clamping of the aorta and to guarantee perfusion of the legs. Two days later the endograft was explanted and an autologous in situ venous reconstruction was performed using both superficial femoral and great saphenous vein. An aortoduodenal fistula was closed and the axillobifemoral bypass was broken down. Two revisions for bleeding were needed. During the second revision colon and small bowel ischemia was present despite patent bypasses. A subtotal colectomy and segmental enterectomy was performed. Finally the patient developed myocardial infarction and eventually multiorgan failure. The patient died three days postoperatively.

**Discussion**

Infectious complications after FEVAR cause a major problem. Radical surgical management is seen as last rescue if maximal conservative measures fail. Mortality and morbidity rates are very high in these ill patients. Maybe, earlier decision for radical revision surgery could improve survival rates. We demonstrated that in situ autologous venous reconstruction is technically feasible.



## Patients' compliance with post-EVAR follow-up and its impact on the outcome

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Lifelong follow-up after Endovascular Aortic Aneurysm repair (EVAR) is recommended to monitor the effectiveness and durability of the treatment. Nevertheless, patients' compliance with follow-up protocol is an important element that may be related to the outcome. We conducted a study to assess patients' compliance with the follow-up imaging protocol, the presence of any factors associated with the patients' compliance and the potential influence of imaging-protocol adherence on outcomes. This study was a systematic review of the existing literature by searching the MEDLINE, CENTRAL, and Cochrane databases and the related keys references.

One randomized control and nine retrospective studies were identified reporting on post-EVAR follow-up compliance. The studies included 36,119 patients with mean age of  $76 \pm 3.1$  years and the mean follow-up ranged from 25 to 73 months. Most of the patients were males (51%- 89%), white (51%- 97.7%) and the majority of them were living  $\leq 100$  miles from the treatment center. The data were too heterogeneous to perform a meta-analysis. Incomplete follow-up and complete loss of follow-up were ranging from 15% to 65% and 22% to 56%, respectively. Advanced age, symptomatic or ruptured aneurysm, history of chronic diseases, and social-economic issues were associated with poor follow-up compliance. Five of these studies suggested that complete follow-up did not offer any survival benefit, while only one study suggested that incomplete follow-up was associated with higher fatal complication rates.

Patients' compliance with a post-EVAR follow-up imaging protocol is poor while patients' age, social-economic issues, chronic comorbidities and operation undertaken as emergency appear to be factors associated with poor patients' compliance. However, there is lack of solid evidence to show that this poor compliance results in worse outcomes. Prospective studies focused on the impact of follow up adherence on the EVAR outcomes are needed.

## Early and long-term outcomes after open or endovascular repair for abdominal aortic aneurysms in high-risk patients

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### Introduction

The aim of this study was to evaluate the short and long term results of surgical or endovascular treatment for abdominal aortic aneurysms (AAA), stratifying patients according to preoperative risk.

### Methods

A retrospective, observational study was performed. Data on preoperative risk factors were analyzed to stratify patients according to the SVS / ISCVS score. The patients were then classified in two groups according to the surgical risk (Group A SVS score 0-10, Group B SVS score 11-22). In the two groups of patients were evaluated postoperative complications, 30-day mortality and survival during follow-up.

### Results

From July 2011 to November 2014 at our unit were treated electively 374 patients with AAA. The analysis of the results was carried out only in 212 cases (24 females and 188 males) in which it was possible to collect clinical data. The mean age was 76.5 years (range 56-93 years); 135 (63.7%) patients underwent OR treatment, 77 (36.3%) underwent EVAR. The medium follow-up was 685 days (0-1420 days range). Open repair performed out in 75 and 60 patients in group A and B respectively. EVAR was done in 43 and 34 of the group A and B respectively. Mortality at 30 days was 1.7% and 3.2% in group A and B respectively. During follow-up the median survival was 91.9% for patients in the OR group, and 98.3% for patients undergoing EVAR in group A and 98.3% for patients subjected to OR and 79.4% for patients undergoing EVAR.

### Conclusions

The results of our study showed a lower 30-day mortality in high-risk patients undergoing surgical or endovascular treatment. Analysis of the results showed that survival in high-risk patients during follow-up does not seem to be affected by the type of treatment and in fact was higher in patients undergoing OR compared with patients undergoing EVAR.

## Renal function is the main predictor of acute kidney injury after endovascular abdominal aortic aneurysm repair

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### Background

Postoperative acute kidney injury (AKI) may occur in up to 20% of elective endovascular abdominal aortic aneurysm repairs (EVAR)<sup>1-3</sup> and has been associated with poor outcome<sup>1-4</sup>; however, it is not clear which patients are at highest risk, to target renoprotection effectively. We sought to determine the predictive factors of AKI after elective EVAR.

### Methods

Overall, 947 patients undergoing elective EVAR between January 2004 and December 2014 were analyzed, using prospectively collected data. Postoperative AKI was defined by serum creatinine change within 48 hours, using the latest validated criteria (Acute Kidney Injury Network and Kidney Disease Improving Global Outcomes). Cardiovascular and kidney-disease risk factors were entered in univariate and multivariate analyses to assess influence on AKI development. Associations between AKI and long-term mortality, morbidity and cardiovascular events were sought using multivariate models.

### Results

Overall, 167 (17.6%) patients developed AKI but only 2 patients required dialysis perioperatively. At multivariate analysis, adjusted for established AKI-risk factors and parameters that differed between groups at baseline, preoperative estimated glomerular filtration rate (eGFR; as per the chronic kidney disease epidemiology [CKD] formula); odds ratio (OR): 1.02 (per unit decrease); 95% confidence interval (CI): 1.003-1.041;  $P = 0.025$ ; and chronic kidney disease (CKD) stage  $> 2$  (OR: 1.28; 95% CI: 1.249-2.531,  $P = 0.001$ ) were associated with development of AKI. During a median follow-up of 62 months, AKI was associated with CV events on adjusted analyses [Hazard Ratio (HR): 1.73, 95% CI 1.06-3.39,  $p=0.03$ ] and mortality (HR: 1.84, 95% CI 1.01-4.22,  $p=0.01$ ).

### Conclusions

AKI was common after elective infrarenal EVAR and preoperative renal function was the main predictor. Patients with a low eGFR need to be targeted with more aggressive renal protection, since AKI development is associated with poor outcomes.

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Saturday September 17

SCIENTIFIC PROGRAM

## Genotype-based risk stratification of bav disease: dream or reality?

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There is considerable heterogeneity in long-term valvular and aortic morbidity in patients with a bicuspid aortic valve (BAV) <sup>1,2</sup>. We are markedly hindered in our dissection of this heterogeneity by the most-common presentation of BAV being only when the patient has symptomatic valvular or aortic disease with impending surgery, as it hinders the conduct of long-term observational studies of early BAV. Even when BAV is identified without symptomatic disease, we currently lack the understanding of the role of altered blood flow patterns across the individual's aortic valve and in the ascending aorta. Further, we lack a detailed understanding of the biological mechanisms of both bicuspid and tricuspid calcific aortic valve disease (CAVD) and aortic dilation.

BAV occurs more frequently in a diverse range of rare recognizable genetic diseases such as Turner, Loays-Dietz, DiGeorge, Kabuki and Anderson-Tawil syndromes, amongst others <sup>1</sup>. These genetic variants, along with others such as ACTA2 mutations, are highly penetrant but make up a very small proportion of the 0.5 – 2% of individuals with BAV in the general population. Although ~10% of individuals with BAV report a first degree relative with BAV or TAAD, it is clear that BAV is not a single gene defect. Investigation has thus far revealed numerous loci with weak and unreplicated association on chromosomes 3p22 (*TGFBR2*), 5q15-21, 9q22.33 (*TGFBR1*), 9q34-35 (*NOTCH1*), 10q23.3 (*ACTA2*), 13q33-qter, 15q25-q26.1, 17q24 (*KCNJ2*), and 18q22.1 (13,15,16, 17). Despite strong evidence for BAV association with NOTCH1 variants in a few families, NOTCH1 appears to have little role in sporadic BAV and its role in presentation with CAVD is unreported.

For the aortic valve, the multitude of types and severity of cusp fusion, leaflet size and number of leaflets yields a wide array of potential leaflet strain and shear forces upon the multiple layers of the aortic valve itself. How these hemodynamic stresses are translated into early initiation and development of CAVD, or leaflet dysfunction, are still obscure <sup>2</sup>. Although CAVD has been strongly and mechanistically associated with apolipoprotein-a (LPA) genetic variation <sup>3</sup> and Lp(a) levels <sup>4-7</sup>, treatment with statins in the latter stages of CAVD – after identification of CAVD, has failed to reverse or attenuate disease <sup>8-10</sup>. To date, in BAV patients, we have failed to identify any relationship between LPA variants and the onset or severity of aortic stenosis. This is in marked contrast to TAV patients. We will present data that expands upon this observation and provides potential targets for further studies.

For aortic disease, the crux of the issue is whether the high propensity of aortic dilation and aneurysm seen in BAV reflects a property of altered flow patterns in the aorta or whether these it reflects a genetic defect related to the embryonic development of BAV that is also related to a fundamental “weakness” of the aortic wall, or both. 30-40% of patients with BAV will develop a dilated thoracic aorta over their lifetime. We identified 203 patients from 404 (~50%) who had a largest aortic dimension >40 mm in our cohort. We identified four GWAS

level loci in 1q25.1, 1q41, 6p21.1 and 9q22 associated with aortic dimension. Two additional loci in 9p21.3 and 17q25.3 were identified at lower levels of significance. The findings seem to indicate that there is a genetic component, that may work in concert with the hemodynamic and flow disturbance generated by the bicuspid aortic valve.

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## Implementing phenotype-based risk stratification of bav aortopathy in surgical practice

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Phenotypic heterogeneity of bicuspid aortic valve (BAV) disease and associated aortopathy has emerged as a relatively new concept in the last decade. Distinct BAV phenotypes have been identified, which may have different pathogenetic background of associated bicuspid aortopathy and therefore may require tailored surgical strategy. Increasing evidence suggests that the BAV stenosis phenotype is predominantly secondary to deleterious hemodynamic patterns of transvalvular flow and is associated with a more benign long-term prognosis once the stenotic aortic valve is replaced. In contrast, the BAV root phenotype- which is associated with a significant aortic valve annular dilatation and resultant aortic insufficiency- is suggested to have a predominantly genetic origin and may be associated with a significantly higher risk of adverse aortic events, irrespective of the treatment of aortic valvular disease. In accordance with these findings, recent meta-analysis demonstrated a 10-fold increased risk of post-AVR aortic dissection in BAV patients presenting with an aortic insufficiency as compared to those with aortic valve stenosis. Although prospective data demonstrating the effectiveness of such a phenotype-specific surgical treatment strategy are still lacking, more aggressive management of concomitant aortopathy seems to be justified in patients presenting with root phenotype BAV disease.

## Structural finite element modelling of the bicuspid root to understand disease progression

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Bicuspid aortic valve (BAV) is a congenital aortic valve disease where two out of the three leaflets are fused together. BAV is a recognized risk factor for pathologies affecting the aortic valve and the ascending aorta. Despite the genetic origin of BAV, the associated alterations in aortic root structural mechanics and fluid dynamics may play a relevant role in the progression of the mentioned degenerative processes, and hence in the timing for surgery. Currently, the evaluation of the progression of the disease, and hence prognosis and decision for surgery, largely rely on purely geometrical criteria, i.e. on the measurement of some key dimensions of the aortic root (AR) from clinical images. These criteria are empirical and sub-optimal; complementing them with new and biomechanically-driven ones could allow for more reliable prognosis and aid the decisional process. On this basis, we developed computational tools to assess the in vivo fluid dynamics and structural mechanics of the AR, aimed to the quantification of the biomechanical anomalies characterizing BAV disease. Here we focus on the finite element analysis of AR structural mechanics in presence of BAV through a novel approach that exploits the anatomical information yielded by magnetic resonance imaging and that allows for consistency between the image-based AR geometry and the pressure loads acting on it. We simulated AR function throughout the cardiac cycle for two preliminary cohorts of healthy volunteers (n=4) and BAV patients with normo-functional valves (n=3), and compared the corresponding biomechanical variables. Namely, we analyzed two features of potential clinical relevance in BAV patients. First, the increase in diastolic leaflet strains and stresses characterizing the abnormal closed valve configuration, which may impact on the differentiation of valvular interstitial cells (VICs) and promote aortic valve calcification. Second, the increase in systolic aortic wall stresses in BAV patients in the tubular ascending aorta, which may be linked to aortic wall remodeling and to an increased risk for wall dilation and coarctation. Despite the inter-subject variability within each cohort, differences were evident between healthy ARs and BAV-affected ones. When compared to healthy ARs, BAV-affected ones were characterized by i) altered diastolic leaflet stretches, which were notably reduced in the commissure-commissure direction and increased in the annulus-to-free margin direction, ii) increased diastolic leaflet stresses, and iii) aortic wall regions affected by elevated stresses in systole, which run from the sino-tubular junction to the convex side of the ascending aorta.

When applied to a sufficiently wide and statistically robust population of subjects undergoing proper follow-up, our approach may yield detailed biomechanical data whose prognostic value could be evaluated, paving the way towards sounder criteria for the prognosis of BAV disease.

## Identifying circulating biomarkers of bav aortopathy risk

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The current knowledge of bicuspid aortic valve (BAV)-related aortopathy is recognized to be inadequate<sup>1</sup>, especially in its pathogenetic and prognostic aspects. Patients are usually operated on electively, to prevent the risk of acute aortic events, namely aortic rupture and aortic dissection, on the basis of “dimensional” criteria of indication, i.e. aortic diameter and size progression rate<sup>2</sup>. However, it is now understood that dimensional criteria alone are not enough to adequately manage such a heterogeneous disease as BAV aortopathy, especially in terms of prognosis<sup>3</sup>: thus additional “non-dimensional” criteria for risk stratification are needed to the purpose of developing personalized medicine strategies<sup>4,5</sup>. The search for putative risk markers of BAV aortopathy is particularly lively, however most studies have addressed imaging-based markers<sup>6</sup>, while only few focused on the identification of biochemical markers<sup>7-9</sup>. Indeed, a biomarker of aortopathy should have pathogenetic significance, and ideally it should have limited correlation with aortic diameter, to provide additional information for prognostic stratification alongside this parameter. The issue of identifying possible biomarkers of BAV aortopathy has been addressed by few studies, with different approaches. Tzemos *et al.* previously reported higher MMP-2 serum concentration in BAV patients with aortopathy than in BAV patients without aortopathy (defined by aortic diameter >40mm and <35mm respectively)<sup>10</sup>. Later on, unique profiles of plasma MMPs, tissue inhibitors of MMPs and microRNAs were revealed in TAV *versus* BAV patients with aortic aneurysm<sup>7</sup>, showing the possibility to predict the presence of specific etiologic subtypes (i.e. TAV or BAV) of aneurysm disease using a plasma multi-analyte regression strategy. Others<sup>8</sup> reported significant correlation between serum levels of the receptor for advanced glycation end-products (sRAGE) and its tissue expression, that was in turn associated with disrupted elastin and proteoglycan deposition, irrespective of the diameter. Hillebrand *et al.*<sup>11</sup> recently assessed the serum levels of TGF- $\beta$ 1 in an etiologically heterogeneous population, also including BAV patients: total serum TGF- $\beta$ 1 was higher in patients with aortic dilatation, however the only independent predictor in multivariable analysis was the presence of a genetic syndrome, and non-syndromic BAV patients had lower serum levels of TGF- $\beta$ 1 compared to the reference controls. The growing body of information on this topic will be systematically reviewed in this presentation and the unmet needs in the search for prognostically relevant biomarkers in BAV aortopathy will be appraised.

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## How to integrate imaging and biochemistry into risk stratification of bicuspid aortopathy

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Efforts over the past few years have focused on defining individual risk factors for disease progression in patients with bicuspid aortic valve (BAV) and aortopathy. The risks associated with BAV aortopathy may be less than previously believed. This statement is based on contemporary natural history studies and key comparisons to those with tricuspid aortic valve disease and genetic connective tissue aortopathies. More conservative and selective approaches to prophylactic aortic resection may be indicated, particularly in patients with BAV stenosis. Using newer state-of-the-art imaging modalities (4D-flow MRI) with tissue correlation of molecular biomarkers, novel data supports valve-mediated hemodynamics as a critical mediator of disease progression in BAV aortopathy. Recent studies by us and others indicate that altered aortic hemodynamics in BAV patients are directly associated with regional degradation of the aortic wall and the BAV aortopathy phenotype. Findings based on 4D flow MRI, which allows for the in-vivo measurement of aortic blood flow with full volumetric coverage of the aorta, have documented changes in transvalvular blood flow and their downstream impact on regional aortic wall shear stress (WSS) even for BAVs without valve dysfunction. WSS is a known stimulus for arterial mechanotransduction and can alter endothelial cell function resulting in outward vascular remodeling (e.g. dilation). A recent study from our group provides strong evidence for this proposed mechanism via the use of in-vivo 4D flow MRI and aortic tissue resection in BAV patients undergoing aortic repair. Correlation of aortic 4D flow MRI hemodynamics with resected aortic tissue histopathology showed that regionally elevated WSS patterns were closely associated with the severity of aortopathy. There remains a substantial gap in knowledge with respect to BAV aortopathy in the pathophysiology and molecular mechanisms of disease progression. There is a critical need to develop individualized risk assessments beyond size and growth criteria to offer more precise and individualized strategies for surgical resection of the aorta in BAV patients. The integration of novel imaging and biomolecular markers of BAV aortic disease progression and severity may improve our management of individual patients who need prophylactic aortic resection.

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## Aortopathy in patients with a bicuspid aortic valve: a process beyond normal cardiovascular ageing

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## Introduction

Patients with a bicuspid aortic valve (BAV) carry an increased risk for aortic dilation as compared to patients with a tricuspid aortic valve (TAV). During cardiovascular development the second heart field (SHF) and neural crest progenitor cells (NCC) guide and contribute to numerous processes such as semilunar valve formation and differentiation of vascular smooth muscle cells (VSMCs). It is therefore plausible that an altered NCC and/or SHF contribution not only can lead to the development of a BAV but is also associated with a structurally different aortic wall leading to pathology.

## Methods

Ascending aorta biopsies of BAV (n=36) and TAV (n=23) both with and without dilation were investigated with classical stainings (MOVAT pentachrome, resorcin fuchsin and hematoxylin eosin). Differentiating and mature VSMCs, lamin A/C, and progerin were studied by immunohistochemistry and with western blot. A pathology score was developed based on seven histopathological criteria: mucoid extracellular matrix accumulation, inflammation, loss of smooth muscle cell nuclei, smooth muscle cell differentiation, intimal thickness, elastic fiber degradation and atherosclerosis.

## Results

We found a significant difference in the structure and maturation of the aortic wall in BAV, persisting in the dilated aortic wall, presenting with a thinner intima, lower expression of several VSMC markers ( $p < 0.05$ ) and lowered lamin A/C expression in BAV ( $p < 0.05$ ) as compared to TAV. The dilated TAVs showed significantly increased progerin expression ( $p < 0.05$ ) as well as increased periaortic inflammation ( $p < 0.01$ ).

## Conclusion

Our findings indicate that the structure of the non-dilated and dilated aortic wall in BAV and TAV is intrinsically different, with the latter having more aspects of ageing. In BAV there is a VSMC differentiation defect possibly linked to an altered NCC and/or SHF contribution to the aortic wall. These findings are clinically relevant, indicating the requirement for different treatment modalities for aortic dilation in TAV and BAV patients.

## The role of hemodynamics and shear stress on the ascending aortic wall in patients with a bicuspid aortic valve

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### Background

A bicuspid aortic valve (BAV) is the most common congenital cardiac malformation and is associated with ascending aortic dilation in 60-80%. Structural differences have earlier been noted between patients with BAV and a tricuspid aortic valve (TAV). The purpose of this study was to analyze the correlation between hemodynamics and shear stress on aortopathy in BAV patients.

### Methods

BAV (n=36) (mean age 55.8 ± 8.7 years, 72% male) and tricuspid aortic valve (TAV) (n=17) (mean age 60±9 years, 82% male) patients undergoing aortic valve replacement underwent pre-operative cardiac phase-contrast cine magnetic resonance imaging (4D flow MRI) assessment to detect the area of maximal flow-induced stress in the proximal aorta. Based on these MRI data paired aortic wall samples (i.e. area of maximal shear stress [jet sample] and the opposite aortic wall [control sample]) were collected during surgery. The jet and control sample were graded by histopathology in the tunica intima, media and adventitia for the pathology score features: mucoid extracellular deposition, inflammation, elastic fiber fragmentation, smooth muscle cell differentiation, loss of smooth muscle cell nuclei, intimal thickness and atherosclerosis.

### Results

Earlier described differences in the pathology score between all BAV and TAV patients were confirmed in this study<sup>1</sup>. Comparing the jet and control samples in both BAV and TAV, regions of maximal shear stress did not show any difference in the pathology score in the tunica media and adventitia even if corrected for aortic stenosis/regurgitation, aortic dilation and raphe position. At the jet side all BAV and TAV patients, however, showed changes in endothelial phenotype from squamous to cuboid, an increase of the subendothelial elastic lamellae and intimal elastin filaments and increased intimal extracellular matrix deposition.

### Discussion

Increased wall shear stress leads to intimal pathology with observed activation of the endothelium in both BAV and TAV patients.

### Reference

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## Twenty-five year outcome of composite graft aortic root replacement: near "curative" impact on aortic root disease

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### Background

Operative choices for aortic root disease abound. We report our experience with traditional composite graft replacement in 449 patients focusing on long-term survival and freedom from late reoperation and adverse events.

### Methods

The coronary button technique was used. Mean age was 56.1±14.0 years (range 14-87) with 83% males (373/449). Valve prosthesis was mechanical in 343 (76%) and bioprosthetic in 106 (24%). A modified Cabrol procedure (Dacron coronary graft) was employed in 10% (45/449) and concomitant CABG 10.9% (49/449). There were 15.8% (71/449) urgent/emergent and 8.2% (37/449) redo procedures. Survival follow-up was 100% averaging 7.0±5.1 years (range 0.1-24.8).

### Results

Operative mortality occurred in 14 patients (3.1%) and was 2.2% (9/418) in non-dissection and 1.9% (7/361) in elective first-time operations. Stroke and re-exploration for bleeding occurred in 9 (2.0%) and 20 (4.5%) patients, respectively. Major late events included bleeding in 2.5% (11/435) and thromboembolism in 1.1% (5/435). At 5, 10 and 20 years, freedom from major events and reoperations on the root were 97.8%, 95.4% and 94.39%, and 99.0%, 99.0% and 97.9%, respectively. Survival in patients aged <60 years was 92.0%, 90.1% and 79.8% at 5, 10 and 20 years versus 88.4%, 67.9% and 42.6% in patients aged ≥60 years. Compared with age- and gender-matched controls, survival was not significantly different (p = 0.20).

### Conclusions

Composite graft aortic root replacement is associated with low operative risk, excellent long-term survival, and low incidence of reoperation and late events. The favorable long-term results indicate an almost "curative" impact on aortic root disease.

## Is there really research-based evidence for a guideline dimension for ascending aortic aneurysm repair?

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### Introduction

Bicuspid aortic valve (BAV) is the most common congenital valvular abnormality, with prevalence of 0.5–2%. Single-center studies focusing on the long-term risk for dissection after isolated AVR in patients with bicuspid aortic valves have yielded conflicting outcome data<sup>1-3</sup>, so the indications for concomitant intervention on the thoracic aorta at the time of AVR are controversial<sup>4,5</sup> but are embodied in a single Guideline recommendation "Replacement of the ascending aorta is reasonable in patients with BAV undergoing AVR because of severe aortic stenosis or aortic regurgitation when the diameter of the ascending aorta is greater than 4.5 cm"<sup>6</sup>.

We therefore sought to test the hypothesis that concurrent repair of dilated or aneurysmal aortic disease during aortic valve replacement (AVR) in patients with BAV substantially improves morbidity and mortality outcomes, and there is an aortic dimension, above which aortic repair yields improved patient outcomes. We tested this hypothesis by comparing long-term outcomes of mortality and reoperation, for adult patients with bicuspid aortic valves undergoing primary AVR, with or without aortic repair over ranges of aortic dimension, aortic dimension Z-score, and age, while accounting for other causes of mortality and reoperation.

### Methods

From two Boston institutions, 1,879 adults with a BAV undergoing first aortic valve surgery occurring between 1/1/2002 – 6/30/2014 were identified. We examined survival and reoperation outcomes in patients with dilated aortas defined by largest aortic dimension >40mm or aortic Z-score >1.96.

### Results

There were no significant differences in reoperation or mortality outcomes between surgeons, hospitals or the operation performed between the two cohorts. Event rates were low, with reoperation and death within one year being <2% and 6%, respectively. Cox proportional hazards modeling of the mortality or reoperation outcome in both the aortic dimension and Z-score based cohorts was primarily driven by mortality, not reoperation. Censoring events occurred more frequently in the elderly, and patients with COPD, renal failure, cancer and those with low ejection fraction. Overall, there was no significant difference in outcomes between the AVR-only and AVR-AR procedures, nor across aortic dimensions or Z-scores. Sub-categories of aortic dimensions and ages showed weak association of operative strategy with morbidity and mortality for younger patients with largest aortic Z-score between 1.96 and 3.0.

### Conclusion

In this two-institution large cohort of BAV patients undergoing AVR there was not strong association between aortic dimension, age and aortic repair with mortality and reoperation outcomes. These results do not provide support of the currently guidelines, as stated, but may provide limited guidance for some sub-groups.

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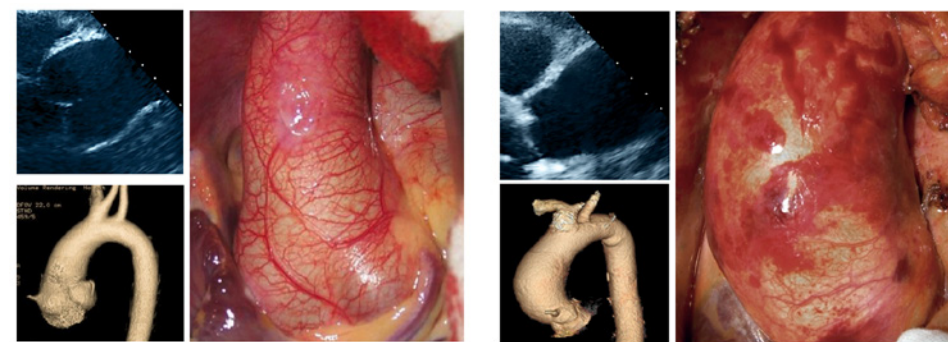
## How to classify the dilatations of the ascending aorta?

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While classification systems are available and currently used in the terminology to define aortic dissection and thoraco-abdominal aortic aneurysms, there is no such established method to classify the dilative aortopathies that affect the ascending aorta. Several types of classifications have been proposed, in particular applied to the setting of bicuspid aortic valve-related aortopathy. They are based on different criteria for classification, including: 1) the pattern of dimensions (one segment relative to another); 2) the presence of dilatation in absolute terms (need for a cut-off); 3) the combination of both the previous criteria. These will be appraised in this presentation and their respective potential for a clinical usefulness will be commented. The hypothesis will also be issued that bicuspid aortopathy might be the testing ground for the identification of the best criterion to be then applied to all other tricuspid-aortic-valve-associated dilatations of the proximal tract of the aorta.

### Figures



Root Phenotype

Ascending Phenotype

Several evidences in the literature suggest that the classification distinguishing between a "root phenotype" and an "ascending phenotype" may have both descriptive significance and prognostic meaningfulness.

## Update On Total Arch Endovascular Repair

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Complete replacement of the aortic arch remains one of the most complex vascular operative procedures. Open surgical repair is the reference standard but despite advances in surgical technology and techniques the mortality and neurological complication rates remain high. The arch branch endograft has been used in selective centers since 2009 and despite an initially steep learning curve, 30-day mortality rates are now similar to traditional open repair, despite taking on a significantly more morbid patient population. There are many challenges associated with this procedure, such as the integrity of the seal zones, the correct method for alignment of the device intra-operatively and consideration of the aortic valve. These will have an effect on the ease of implantation, the morbidity and mortality associated with the procedure and the long-term durability of the repair.

## Deep hypothermia with retrograde cerebral perfusion – as method of brain protections in ascending aorta and arch aneurysms surgery

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**Introduction**

Antegrade and retrograde perfusion for cerebral protection are controversial approaches in the surgery of ascending aorta and arch. In some cases retrograde cerebral perfusion (RCP) is preferable because of technical simplicity and it allows to reach a good result.

**Aim**

Selection of efficient technology for RCP on the basis of clinical experience, instrumental and laboratory researches.

**Materials and methods**

253 patients with ascending aortic and arch aneurysms were operated on during 1994 - 2015 (205 (81,0%) males, 48 (19,0%) females), age ranged 27 – 79 years, mean 53,4±8,2; acute (subacute) dissection took place in 224 (88,5%), chronic – in 12 (4,8%), without dissection – 17 (6,7%) pts. The main reason of aneurysms forming was: arterial hypertension, atherosclerosis – in 151 (59,7%); Marfan syndrome – 32 (12,6%); bicuspid aortic valve disease – 26 (10,3%); cystomedioneclerosis – 22 (8,7%); lues – 12 (4,7%); Takajasu arteriitis – 3 (1,2%); falling from height – 2 (0,8%); unknown – 5 (2,0%). Operations` were fulfilled with heart-lung bypass, deep hypothermia and RCP through superior vena cava (SVC). Femoral artery was utilized for arterial cannulation. The following methods were used for correction: supracoronary grafting of ascending aorta with hemiarch(arch) – 179(4) (70,8%); Bentall`s operation with hemiarch (arch) – 56(4) (22,1%); isolated arch grafting – 9 (3,5%); Wheat operation with arch grafting – 5 (2,0%); aortic arch plastic – 4 (1,6%).

**Results**

Group I (1994-2001) – 25 operations with deep hypothermia (16-18°C), perfusion blood flow – 500-750 ml/min, pressure in SVC – 15-25 mmHg. Mortality – 7 (28%) pts., in 2 cases the cerebral complications were the cause of death. Group II – 63 operations fulfilled in 2002-2007 yy., with deep hypothermia (12,5-14°C), blood flow rate – 250-500 ml/min, pressure in SVC – 10-12 mmHg. Mortality – 11 (17,4%) pts. Pulmonary complications were in 5 cases, 3 (4,8%) of them died. Lethal brain injury were 1 pts (1,6%). Group III – 125 operations fulfilled in 2008-2015 yy., with deep hypothermia (18-20°C), blood flow rate – 250-500 ml/min, pressure in SVC – 10-12 mmHg. Perfusion through femoral artery during the RCP stage was maintained permanently in group II and III. 30-day mortality – 9 (7,2%) pts. Pulmonary complications was lethal in 1 (0,8%) patient and brain lesion – 1 (0,8%) pts. Overall 30-day

mortality composed 10,7%. Better clinical results in Group III were confirmed by analysis of arterial and venous blood, thermography, EEG and MRI of the brain.

### Conclusion

RCP with deep hypothermia (18-20°C), pressure in SVC – 10-12 mmHg, blood flow rate – 250-500 ml/min with continually perfusion through femoral artery is safe method of brain protection during ascending aortic and arch correction.

**Aneurysm at the site of repair of coarctation of aorta: frequency, methods of treatment, results.**

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### Objective

Remote period after coarctation of aorta (CoA) repair is accompanied with risk of descending thoracic aorta (DTA) aneurysm development. AIM. To inform about frequency, methods and results of treatment of aneurysms, which developed after CoA repair?

### Materials and methods

4234 patients with CoA were operated in the Institute during 1960-2015. Aneurysms after CoA repair took place in 165(3.9%) patients in period till 1 months to 38 years. Mean term from CoA repair till operation on the reason of developed aneurysm composed 16 years. Aneurysms developed in 16 (0.6%) patients after CoA repair by end-to-end anastomosis, in 17(5.7%) patients after aorta grafting with vascular graft and in 114(9.5%) cases after patch aortoplasty. Aneurysm diagnosis was established by TTETO and verified by CT. 131(79.3%) patients were operated on, 34(20.7%) patients abstained from surgical treatment of developed aneurysms. Visceral organs protection from hypoxia was accomplished in 124(94.6%) patients by use of passive shunt from ascending to descending aorta, in 5(3.8%) patients artificial blood circulation was used. After aneurysms resection, aorta grafting was performed-in 128 (97.7%) cases, aortorrhaphy-in 3(2.3%).

### Results

Hospital mortality composed 14 (10.6%). There were no renal and spinal cord complications. Out of 34 patients, who abstained from operation on different reason, 26 patients died during 7 years after diagnosis of aneurysm was established.

### Conclusions

1. Coarctation of the aorta repair by patch aortoplasty is inexpedient.
2. Lifelong dispensary supervision of operated on patients is necessary for timely detection and treatment of aneurysms after coarctation of the aorta repair.

## Critical analysis of recent registries and randomized trials

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Clinical studies and registries supporting the safety and efficacy of Transcatheter Aortic Valve Implantation (TAVI) have been accumulated for the last two years. Additionally, randomized trials comparing TAVI with Surgical Aortic Valve Replacement (SAVR) showed non inferiority and even superiority of TAVI over SAVR in moderate and high risk patients as defined by STS or Euroscore II scores. Results of four randomized trials comparing SAVR and TAVI are reviewed. Patient's characteristics, early and late clinical outcomes of each trials are presented and discussed. TAVI was associated with a significant 13% reduction in mortality at 2 years, as compare to SAVR. Survival benefit of TAVR was significant for female patients ( $p=0.01$ ) and for patients undergoing transfemoral access ( $p=0.004$ ). The TAVI survival benefit was consistent across high-risk and lower-risk groups and was independent of device type. Of note that TAVI is not associated with survival benefit in male patients ( $p=0.95$ ). TAVI procedures were associated with fewer kidney injury, new onset atrial fibrillation and major bleeding. Conversely, fewer major vascular complications, fewer new PCMK implantation and paravalvular regurgitation occurred among SAVR patients. Large US and European registries not only confirm the increasing use of TAVI for the treatment of aortic valve stenosis, but also aim to better define patients in whom the procedure may be futile. Patients with severe kidney or lung dysfunction, those with poor LV function (LF/LG stenosis, NYHA class IV) have worse outcomes. Presence of 3 or more major organ system compromises should be considered at prohibitive risk. Additionally, frailty index and cognitive functions should also be considered in decision making. Above all, it is now clear that the best treatment of aortic valve stenosis should be discussed by a valvular heart team which goal is to confirm the indication and decide the best procedure [TAVI or SAVR], according to clinical status of the patient and local experience.

## Choice of the best transcatheter site for TAVI implantation

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The least invasive access for the TAVI procedure is via the common femoral artery. However, among the patients actually referred for this procedure, this route is either impracticable or unwise in approximately 15-20% of the patients. Indeed, vascular complications and haemorrhage have a major negative impact on the outcome following this procedure.

We present the experience of the CHU of Liège over 215 cases of TAVI procedure using the Corevalve Medtronic(r)device. Our strategy implies the decision for the therapy and the selection of the vascular access in heart team. The past history of the patient, angio-CT data and the arteriography performed during the catheter evaluation are integrated.

The left axillary artery (20/215) and the right carotid artery (15/215) have been used successfully in our practice as respectively second and third choice options. This versatility enabled us to treat in a antegrade or minimally invasive fashion virtually every patient.



## e Posters abstracts

## Adventitial adipogenic degeneration: an unidentified contributor to aortic wall weakening in the abdominal aortic aneurysm

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### Objectives

To determine additional pathophysiological mechanisms driving AAA growth.

### Background data

The processes underlying abdominal aortic aneurysm (AAA) growth and ultimate rupture are complex and poorly understood. AAA is accepted as an inflammatory response with an accompanying proteolytic imbalance, however clinical intervention studies consistently fail to show a benefit from interference with these processes. There are striking associations between AAA and popliteal artery aneurysms (PAA); yet while AAAs will eventually rupture, PAA's have a low propensity for rupture. We reasoned differences between AAA, PAA and normal aorta's provide critical clues towards other processes involved in critical debilitation of AAA's.

### Methods

Tissue was harvested during elective open aneurysm repair or kidney transplantation for control aortas. Tissue was handled correctly and used for qPCR, microarray, IHC and in vitro studies.

### Results

Histological evaluation of AAA, PAA and control aorta showed extensive fibrous changes in AAA and PAA and identified presence of large adventitial adipocyte aggregates as a unique and consistent feature of AAA ( $P < 0.01$ ). The combination of fibrosis and adipogenic degeneration characterize AAA as dystrophic disorder. Adipogenic differentiation is controlled by transcription factors from C/EBP family, KLF5 and PPAR $\gamma$ . Immunohistochemistry revealed abundant expression of these factors in AAA disease indicating the transcriptional machinery required for adipogenic differentiation is present. qPCR data confirms upregulation of KLF-5 ( $P < 0.05$ ) and PPAR $\gamma$  ( $P < 0.05$ ), two factors crucial in the final stages of adipogenic differentiation. Furthermore, microarray analysis between ruptured and stable AAA's reveals upregulation of both adipogenesis ( $P < 0.001$ ) and PPAR ( $P = 0.002$ ) pathways. Adipogenic potential of AAA and control adventitial cells were underwent adipogenic differentiation in vitro showing the capability of normal cells adapt an adipogenic phenotype. AAA cells have a higher propensity to do so ( $P < 0.05$ ).

### Conclusions

Systemic evaluation of AAA and PAA tissues shows adventitial fatty degeneration in the context of dystrophy as an additional pathophysiologic mechanism. These results should be considered in the light of failing pharmaceutical therapies and provide new avenues for pharmaceutical AAA stabilization.

## Pet-tc utility to assess the abdominal aortic aneurysm growth and its relationship with changes in energetic metabolism

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### Introduction

PET-CT utility to assess AAA growth remains controversial. Factors involved in the increased metabolic activity that leads to its inflammatory activity remain unknown.

### Experimental aim

To check the 18-FDG uptake by PET-CT in AAA, evaluate its correlation with diameter and growth and determine differences in those processes involved in the energetic metabolism.

### Work summary

The 18-FDG PET-CT was performed in 20 patients with AAA before elective open surgery. A SUVmax  $> 2.5$  was considered as increased 18F-FDG uptake. The aneurysmal aortic wall samples collected during surgery (in case of increased uptake, two sample were collected, one of them from the highest uptake site). The expression of following proteins involved in the cellular metabolism were analyzed: aerobic (lactate-dehydrogenase, pyruvate-dehydrogenase), anaerobic (malate- dehydrogenase), beta-oxidation of fatty acids (acetyl-coenzyme-A-dehydrogenase [acilCoADH], carnitine-palmitoyltransferases [CPTs]), oxidative phosphorylation (uncoupling-protein 1 [UCP-1]), ATP-synthase.

### Results

5 patients showed an increased uptake. Therefore 25 samples were collected. There was a statistical significant difference regarding demonstrated growth of the AAA (80% in uptake group vs 20%,  $p = 0.018$ ) with a RR 7.4 [CI 95% (1.02-54.31)]. The uptake group showed a lower aortic diameter without statistical significance ( $53.80 \pm 9.09$  mm vs  $60.87 \pm 8.48$  mm). We observed no differences regarding to the expression of proteins related to aerobic or anaerobic metabolism. Levels of expression acilCoADH ( $32.80 \pm 8.05$  UA vs  $55.58 \pm 4.28$ ,  $p = 0.049$ ) and CPT-II ( $12.68 \pm 4.73$  UA vs  $38.30 \pm 3.78$ ,  $p = 0.001$ ) were significantly lower in the uptake group. Significantly higher levels of expression of UCP-1 were observed in the uptake group ( $138.64 \pm 26.57$  UA vs  $55.05 \pm 11.12$ ,  $p = 0.005$ ), with lower levels of ATP synthase ( $10.17 \pm 2.67$  UA vs  $20.11 \pm 4.01$ ).

### Conclusions

Metabolic changes in AAA with increased 18-FDG uptake is related to an uncoupling of the oxidative phosphorylation chain and a diminished ATP synthesis. PET-CT could be considered a potential bio-marker to detect those AAA with recent growth, but further studies are required to confirm its validity.

## Evidence of intimal tear in aortic intramural hematoma

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Aortic Intramural Hematoma (IMH) represent Class II of Acute Aortic Syndrome (AAS); this group of virulent lesions share the presence of an intimal tear but original description of IMH is reported as a "dissection without intimal tear" due to vasa vasorum rhesis. Moreover, as per Acute Dissection (AD) timing of surgery is well codified, for IMH this issue is controversial ranging from watchful waiting, eventual surgery up to emergency. Related to this the natural history described IMH as a dynamic entity with associated tendencies (regression, progression to AD, expansion or rupture) that vary geographically. To date only sporadic reports emphasize the prevalence in IMH of a tear, lesion that may contribute to justify a change in the policy protocol considering the causative role of vasa vasorum as questionable because the pressure generated by the rupture is too low to overcome the counterpressure exerted from the inner lumen. We review retrospectively our data on a group of patients with diagnosis of AAS during a period between July 2013 to March 2016 focusing on natural history, radiographic follow-up and intraoperative findings of subset of patients (12,12%) affected by IMH. All IMH patients, both type A-type B, were operated on as eventual surgery, except one IMH type A that was operated on as emergency. Pre-operative and/or intraoperative findings showed in one-third of all cases the evidence of an intimal lesion. There was no intraoperative death, one patient was complicated with retrograde TAAD during Tevar procedure and was the one that suffered for permanent neurologic disorder and account for late death. Our data review, due to IMH high rate of worsening during follow-up, the coexistence of an intimo-medial tear and the favourable surgical results, led us to consider for IMH a more aggressive timing for intervention.

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## The application of metabolic profiling to aneurysm research

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### Background/Objective

Metabonomics is a top-down systems biology approach<sup>1</sup> involving high resolution spectroscopic profiling of small (<1kDa) molecules (representing endpoints of metabolism) combined with computational data modeling that may be used to determine biomarkers of disease presence, unravel pathophysiological pathways, confer prognostic information, or map response to treatment. There is considerable uncertainty regarding the aetiological development and optimal management of aneurysmal disease. This study aimed to explore the diversity and outcomes of existing metabonomic research as applied to the clinical challenges for patients with abdominal aortic aneurysm (AAA).

### Method

A systematic review has been performed adhering to PRISMA guidelines. All original research articles applying metabolic profiling to samples collected from patients with aneurysms were included. Non-human studies and reviews were excluded.

### Results

Seven articles relevant for inclusion were identified<sup>2-8</sup> examining plasma/serum or tissue. All studies utilised mass spectrometry (MS) and one additionally incorporated Proton Nuclear Magnetic Resonance Spectroscopy (1H-NMR)<sup>5</sup>. Aminomalonic acid (GC-MS)<sup>5</sup>, guanidosuccinic acid (HPLC-MS)<sup>2</sup> and glycerol (1H-NMR)<sup>5</sup> emerge as biomarkers of large aneurysm presence. Results from targeted metabolic lipid profiling suggest that preferential incorporation of adipocytes into aneurysm adventitia may occur, decreasing tensile strength, thereby increasing the risk of rupture. Temporal relationships between chemical mediators of inflammation and resolution in patients undergoing open AAA repair imply differential responses in early and late healers, generating hypotheses for targeted perioperative adjunctive therapy. Limitations encountered include small study sizes, single time-point sampling, and lack of statistical correction for the likelihood of false positive discovery.

### Conclusion

Current studies demonstrate the utility of metabonomic science in identifying potential biomarkers of aneurysm presence and elucidating mechanisms underlying dilating arterial disease. Further translational longitudinal studies incorporating larger, matched cohorts are required for validation of the metabolites identified, to determine metabolic variations associated with aneurysm growth and generating targets for drug design and development.

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## Preoperative fibrinogen levels and early outcome following endovascular repair of ruptured abdominal aortic aneurysms

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### Aim

To investigate the potential association between preoperative levels of fibrinogen and early outcome following endovascular aortic repair (EVAR) of ruptured abdominal aortic aneurysms (RAAAs).

### Methods

Consecutive patients undergoing EVAR for RAAA between March 2010 and May 2016 were recruited from a single vascular centre. Patient details including fibrinogen levels on admission were extracted from case files and 30-day mortality was recorded. Fibrinogen levels were compared between survivors and fatal cases using the independent samples t-test.

### Results

Twenty-one patients (20 males, median 71 years) with a RAAA receiving EVAR and available preoperative fibrinogen levels were included in this study. There were 16 patients with a de novo RAAA and 5 with free rupture after a previous EVAR. Of these, 3 patients died within 30 days (14.3%), one intra-operatively and two within 24 hours due to multiple organ failure. Fibrinogen levels on admission were significantly higher in the group of survivors when compared to those who died (mean  $\pm$  standard deviation 456.36 $\pm$ 183.72 versus 192.57 $\pm$ 52.26; p=0.026).

### Conclusion

This study suggests a possible relationship between fibrinogen levels on admission and early mortality in patients undergoing EVAR for a RAAA. Higher fibrinogen levels, which may indicate a preoperative hypercoagulable profile, seemed to be associated with better chances of early survival in our small series. Further and larger studies are needed to clarify this issue and possible future therapeutic implications.

## Inflammation as a predictor of abdominal aortic aneurysm growth and rupture: a systematic review of imaging biomarkers

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### Background

Methods are required to identify abdominal aortic aneurysms (AAAs) at increased risk of rupture. Inflammatory characteristics of AAA can be visualised using advanced imaging techniques and have been proposed as potential predictors of aneurysm progression. The objective of this review was to determine which inflammatory imaging biomarkers are associated with AAA growth and rupture.

### Methods

A systematic review was carried out in accordance with the PRISMA guidelines. The electronic databases of Medline (PubMed), Embase, and the Cochrane Library were searched up to January 1, 2016 for studies to determine the potential association between inflammatory imaging biomarkers and AAA growth or rupture.

### Results

Seven studies were included, comprising 202 AAA patients. 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG PET-CT) was evaluated in six studies. Magnetic resonance imaging with ultrasmall superparamagnetic particles of iron oxide (USPIO-MRI) was evaluated in one study. Two of six 18F-FDG PET-CT studies reported a significant negative correlation ( $r = .383$ ,  $p = .015$ ) or a significant negative association ( $p = .04$ ). Four of six 18F-FDG PET-CT studies reported no significant association between 18F-FDG uptake and AAA growth. The single study investigating USPIO-MRI demonstrated that AAA growth was three times higher in patients with focal USPIO uptake in the AAA wall compared to patients with diffuse or no USPIO uptake in the wall (0.66 vs. 0.24 vs. 0.22 cm/y,  $p = .020$ ). In the single study relating 18F-FDG uptake results to AAA rupture, the association was not significant.

### Conclusions

Current evidence shows contradictory associations between 18F-FDG uptake and AAA growth. Data on the association with rupture are insufficient. Based on the currently available evidence, neither 18F-FDG PET-CT nor USPIO-MRI can be implemented as growth or rupture prediction tools in daily practice. The heterogeneous results reflect the complex and partially unclear relationship between inflammatory processes and AAA progression.

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## The association of mmp9 and mmp13 functional genetic polymorphisms and abdominal aortic aneurysm in a greek population

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### Background

An imbalance between extracellular matrix (ECM) production and degradation, towards the degradation has been importantly related with AAA. Metalloproteinases (MMPs) are principal enzymes of ECM remodeling and their proteolytic activities have been related with the pathophysiology of AAA. Genetic variations can influence the transcription of genes coding MMPs and the function of coding proteins. This case-control study was designed to investigate the possible association of genetic polymorphisms of the MMP9 and MMP13 genes in the etiology of AAA.

### Material and Methods

A prospective non-randomized case control study was undertaken including AAA patients from a tertiary center and controls from a AAA screening program, assessing differences in genotype and allele frequencies of the MMP9 (-1561C/T) and MMP13 (-77A/G) single nucleotide polymorphisms (SNPs). The selected SNPs were genotyped using standard polymerase chain reaction and restriction-fragment-length polymorphism methods. Clinical characteristics of the patients and controls were collected.

### Results

The SNP MMP9 (-1561C/T) was analyzed in a sample of 182 AAA patients (mean age 72.9±7.5) and 166 controls (mean age 71.5±7.1), whereas the SNP MMP13 (-77A/G) was analyzed in a sample of 171 AAA patients (mean age 72.6±7.6) and 161 controls (mean age 71.2±9.3). Statistical difference was reached in genotype ( $p=0.034$ ) and allele frequencies for SNP MMP13 (-77A/G). The G allele was more frequent in patients with AAA than in control group [142 vs. 108,  $p=0.034$ , OR (95% CI) 1.41 (1.03–1.93)]. No significant differences in genotype or allele frequencies for the MMP9 polymorphism were detected.

### Conclusion

Significant genotypic and allelic associations were observed between MMP13 (-77A/G) polymorphism and AAA in a Greek population, supporting its potential involvement in AAA pathogenesis, while no correlation was identified between MMP9 and AAA.

## Can aortic root replacement with a graft affect cardiac function in patients with marfan syndrome?

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### Background

Marfan syndrome (MFS) is a hereditary connective tissue disorder characterized by skeletal, ocular and cardiovascular manifestations. The most known and life-threatening cardiovascular condition is aortic root dilation and dissection. Different surgical techniques to replace the aneurysmatic or dissected aorta with a graft are possible. Recently, decreased left ventricular function, leading to cardiomyopathy in some cases, and arrhythmias have also been identified as an important cause of mortality in these patients. Furthermore, abnormal myocardium has been shown in different mice models of MFS. Nevertheless, risk factors favouring the development of ventricular dysfunction and arrhythmias are not well known. We, therefore, wanted to investigate the effect of aortic surgery by inserting a rigid graft on cardiac function in patients with MFS.

### Methods

We selected all patients from our cohort who underwent aortic root replacement (AoRR). We retrospectively collected demographic and clinical data and we reviewed systolic and diastolic parameters on echocardiography at 3 different time points: before surgery, 6 months after surgery and during the last follow up.

### Results

Thirty-three MFS patients underwent AoRR. Twenty-eight patients (84.9%) had an aortic valve sparing surgery (6 of which with associated aortoplasty). The rest underwent a Bentall procedure. Median aortic root before surgery was 52.5mm (IQR 49–56) and 13 patients (39.4%) had at least moderate aortic regurgitation. Median time of follow up was 5 years (IQR 2–10.5). Left ventricular end diastolic and systolic diameters (LVEDD, LVESD) decreased significantly during the first 6 months after surgery (56.75 vs 52.75mm;  $p<0.001$  and 37.16 vs 32.16mm;  $p=0.018$  respectively). At the last follow-up, LVEDD was similar to 6 months after surgery, but LVESD significantly increased (36.1mm,  $p=0.02$ ). Increase of LVESD led to decreased left ventricular ejection fraction (LVEF) (59.57 at 6 months vs 52.86% at follow-up,  $p=0.016$ ). No changes in diastolic parameters were observed.

Right ventricular function was also affected by AoRR: TAPSE decreased after surgery to a suboptimal value and remained like this during follow-up (22.3mm before surgery, 17mm at 6m and 16.52mm during last FU,  $p<0.001$ ).



## Conclusion

these results support the hypothesis that the placement of a rigid graft might influence cardiac function on long term. Our study is limited in the fact that it was retrospective and that no comparison group has been used.

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## Cholesterol precursors in patients with AAA

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## Introduction

Abdominal aortic aneurysm (AAA) is a serious condition with unclear pathogenetic mechanism. One of the discussed factors involved in its pathogenesis is arteriosclerosis. We focused in our study on the detection of biomarker concentrations which are far more precise in monitoring the balance between cholesterol synthesis and absorption, namely campesterol, sitosterol and lanosterol as markers of cholesterol absorption, and desmosterol and lathosterol as markers of cholesterol synthesis.

## Patients and methods

We examined a total of 58 patients with AAA requiring surgery and 20 patients treated for lipid metabolism disorder without AAA in the control group. Demographic and clinical characteristics of both groups is shown in Table 1. The following parameters were examined by means of mass spectrometry: campesterol, sitosterol, lanosterol, desmosterol, and lathosterol. In addition, lipoprotein-associated phospholipase A2 (Lp-PLA2) and hsCRP serum concentrations were examined.

## Results

The difference of Lp-PLA2 concentrations in both groups was not statistically significant. hsCRP concentration was significantly higher in the group of patients with AAA ( $p=0.007$ ). No differences between both groups were found for cholesterol absorption markers - campesterol and sitosterol ( $p=0.96$  and  $0.65$  respectively). By contrast, cholesterol synthesis markers - lanosterol, desmosterol and lathosterol - were significantly higher in the AAA group of patients as compared to the control group ( $p=0.004$ ;  $p=0.0005$  and  $p=0.0002$  respectively, Table 1).

## Conclusion

In the AAA group of patients, statistically significantly higher concentrations of hsCRP were detected as compared to the control group. Cholesterol synthesis markers were statistically significantly higher in the AAA group while cholesterol absorption markers were not statistically significantly different in both groups. It suggests an imbalance in cholesterol synthesis in patients with AAA and a potential possibility of targeted adjustment of hypercholesterolemia therapy in patients with AAA who are treated with statins.

## Gene expression signature in patients with abdominal aortic aneurysm

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### Introduction

Abdominal aortic aneurysm (AAA) is a serious condition with unclear pathogenetic mechanism and progression. Etiology is clearly multifactorial in nature and is being further investigated. In our study, we compared gene expression in abdominal aortic aneurysm tissue and unaffected tissue of the same patient.

### Patients and methods

A total of 48 patients with AAA in whom surgery was necessary were included into the study. Two samples (5x5 mm) of the entire arterial thickness were collected from each patient during AAA surgery. One sample was collected from the aneurysm at the site with the largest dilation seen macroscopically while the second sample was collected from the aneurysm neck where the tissue had no aneurysm changes. Subsequently, the gene expression profiles using microarrays (Illumina) were compared in RNA extracted from samples. Demographic and clinical characteristics of the patients is seen in Table 1.

### Results

Altogether, 2185 genes were found to be upregulated and 2100 downregulated. Analyzing the gene list based on the biological pathways they belong to and using Panther and Nature pathway revealed that regulation of „Inflammation mediated by chemokine and cytosine signaling pathway“, „integrin signaling pathway“, „T and B cell activation“ were the most important pathways.

### Conclusion

We demonstrated different gene expression in the tissue with aneurysm changes and the sample of healthy vessel. The changes related to inflammation regulation by means of immunity mechanisms comprising T and B lymphocyte subpopulations. Understanding these mechanisms may potentially aid in better understanding etiopathogenetic mechanisms of aneurysm and its treatment.

## The natural history of a large aorta is greater cardiovascular risk

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### Introduction

Ultrasound screening for AAA is cost effective and reduces AAA related mortality. Excess cardiovascular morbidity and mortality is well recognised in patients with AAA, however, AAA screening has no formal role in cardiovascular risk reduction which may be an opportunity missed.

### Problem Definition

The aim of this study is to characterise the association of cardiovascular mortality with aortic diameter utilising a single screening cohort.

### Work Summary

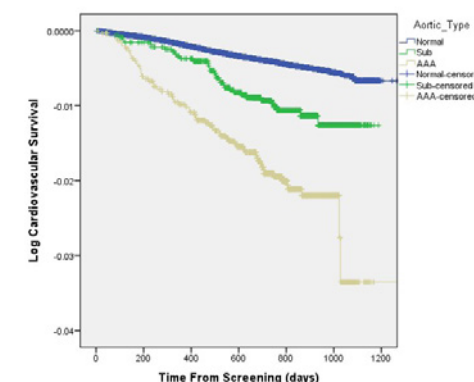
Consent was gained to analyse the NHS AAA screening cohort (2013-2014) and the UK Health Episode Statistics/Office for national statistics deaths dataset. Patients who did not attend screening were excluded. Data relating to maximum AP aortic diameter, study date, date of death and cause of death (ICD-10) were extracted. Cardiovascular death included those ICD codes pre-specified by the Global Burden of Disease studies. Relative risks were calculated to compare groups and log-rank survival analysis performed.

### Results

240,954 patients were included and mean aortic diameter was 18mm (SD 3mm). 3,235 patients (1.34%) had a sub-aneurysmal aorta (25-29mm) and 2,981 (1.24%) had an AAA (>30mm). At three years 34 patients in the sub-aneurysmal group (1.1%, RR 2.25, 95% CI 1.61 – 3.14, P=0.0001) and 61 in the small AAA group (5.3%, RR 4.2 95%CI 3.34-5.47, P=0.0001) had a cardiovascular related death compared to those with a normal aorta (<24mm). Overall cardiovascular survival decreased with progressive aortic dilation (Figure 1, Log Rank P=0.0001).

### Conclusion

The natural history of an enlarging aorta is progressive cardiovascular risk. Aortic screening is currently an opportunity missed to address this risk in those with and without AAA.



## Overview about the value of functional imaging in the management of aortitis

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### Background

Aortitis is defined as an abnormal inflammatory condition of infectious or non infectious origin involving the aortic wall. Aortitis may be related to multiple causes with variable prognoses. Because of the nonspecific clinical presentation, aortitis is often overlooked and patients frequently undergo multiple tests and imaging to reach the final diagnosis. However, it is important to establish an early diagnosis as soon as possible. Indeed, this inflammatory process may deteriorate the aortic wall, resulting in potentially life-threatening vascular complications. Compared to conventional imaging tools that provide anatomical and morphological information, Positron Emission Tomography/Computed tomography (PET/CT) provides important additional information.

### Methods and Results

During a 4-year period, 428 consecutive patients referred to our cardiovascular surgery department for aortic diseases underwent FDG PET/CT examinations. Among these, 19 (4.4%) patients with suspected to have aortitis. All of them had an initial positive FDG PET/CT uptake occurring in the aorta and major branches as evaluated by visual analysis of images and assessed with the final diagnosis of aortitis. During follow up, after surgery and/or starting immunosuppressive treatment, each patient undergoes PET/CT which was compared with the initial evaluation. In all cases, normalisation of FDG uptake was correlated with clinical improvement.

### Conclusions

Our experience, insight this observational study, aim to illustrate the interest and the various aspects of functional monitoring with PET/CT in the management of aortitis. PET/CT constitutes a valuable imaging modality to assess the diagnosis, monitoring and planning aortitis treatment. We confirmed the importance of an early detection of inflammatory large-vessel pathology, which can constitute an important threat.



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