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New Insights Into Aortic Diseases

A Report From the Third International Meeting on Aortic Diseases (IMAD3)

Helena Kuivaniemi[1]*, Natzi Sakalihasan[2], Frank A. Lederle[4], Gregory T. Jones[5], Jean-Olivier Defraigne[2], Nicos Labropoulos[6], Victor Legrand[3], Jean-Baptiste Michel[7], Christoph Nienaber[8], Marc A. Radermecker[2], John A. Elefteriades[9]

[1]Sigfried and Janet Weis Center for Research, Geisinger Clinic, Danville, Pennsylvania; [2]Cardiovascular Surgery and [3]Cardiology Departments, University Hospital of Liège, CHU, Liège, Belgium; [4]Minneapolis Center for Epidemiological and Clinical Research, Department of Medicine (III-0), VA Medical Center, Minneapolis, Minnesota; [5]Surgery Department, University of Otago, Dunedin, New Zealand; [6]Department of Surgery, Stony Brook University Medical Center, Stony Brook, New York; [7]INSERM U698, Paris, France; [8]Heart Center Rostock, University of Rostock, Rostock, Germany; and [9]Aortic Institute, Yale University School of Medicine, New Haven, Connecticut

Abstract

The current state of research and treatment on aortic diseases was discussed in the "3rd International Meeting on Aortic Diseases" (IMAD3) held on October 4–6, 2012, in Liège, Belgium. The 3-day meeting covered a wide range of topics related to thoracic aortic aneurysms and dissections, abdominal aortic aneurysms, and valvular diseases. It brought together clinicians and basic scientists and provided an excellent opportunity to discuss future collaborative research projects for genetic, genomics, and biomarker studies, as well as clinical trials. Although great progress has been made in the past few years, there are still a large number of unsolved questions about aortic diseases. Obtaining answers to the key questions will require innovative, interdisciplinary approaches that integrate information from epidemiological, genetic, molecular biology, and bioengineering studies on humans and animal models. It is more evident than ever that multicenter collaborations are needed to accomplish these goals.

Key Words

Aortic aneurysm · Valvular disease · Epidemiology · Genetics · Surgical repair

Introduction

Aortic diseases, including aneurysms and dissections, and valvular diseases are a leading cause of morbidity worldwide. The current state of research and clinical practice on aortic diseases was discussed in a 3-day conference entitled "The 3rd International Meeting on Aortic Diseases (IMAD3)" held on October 4–6, 2012, in Liège, Belgium (Fig. 1; Table 1). The previous IMAD conferences held in 2008 and 2010, also in Liège, had attracted approximately 200 and 300 participants, respectively. The 2012 IMAD3 conference brought together ≈400 participants from 28 different countries and representing many different fields, from vascular surgery to genetics and bioengineering. The program was organized according to disease types, with day 1 devoted to thoracic aortic, day 2 to abdominal aortic, and day 3 to valvular diseases, with a total of >100 invited speakers (Table 1).

Here, we review some of the topics covered in the meeting. The conference brought up a number of opportunities for future collaborative research proj-

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http://aorta.scienceinternational.org

Fax +1 203 785 3346
E-Mail: aorta@scienceinternational.org
http://aorta.scienceinternational.org

*Corresponding author:
Helena Kuivaniemi
The Sigfried and Janet Weis Center for Research
Geisinger Clinic
100 North Academy Avenue, MC 26-10
Danville, PA 17822-2610 (USA)
Tel. +1 570 271 5593, Fax +1 570 271 6701, E-Mail: shkuivaniemi@geisinger.edu

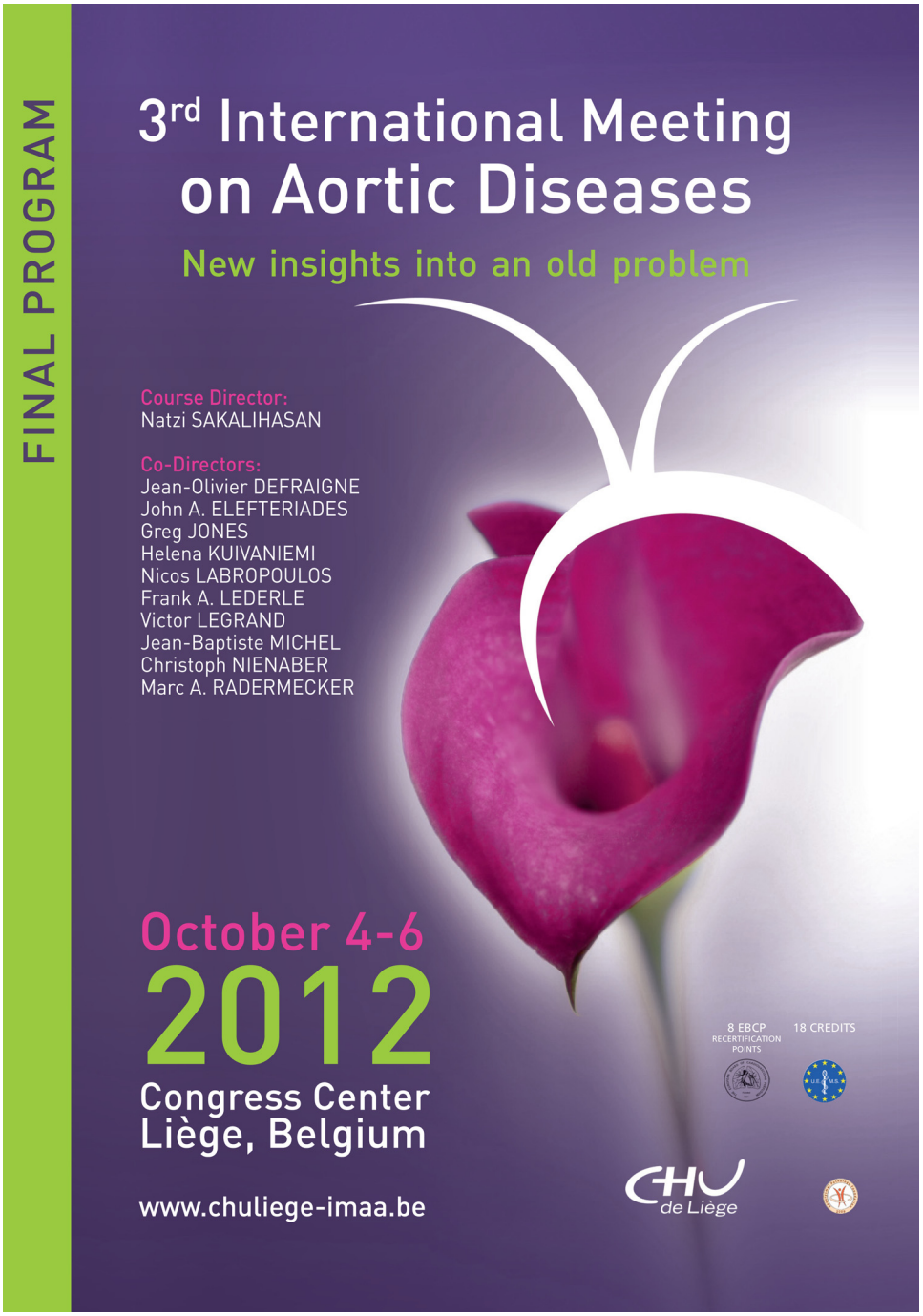

Figure 1. IMAD logo shown in the cover of the abstract booklet of IMAD3.

ects for genetic, genomics, and biomarker studies, as well as clinical trials.

Thoracic Aortic Diseases

The first day of IMAD3 was devoted to epidemiology, genetics, pathobiology, and different treatment modalities of both rare syndromic forms and common nonsyndromic forms of thoracic aortic aneurysms (TAAs) and dissections (TAADs). Active research continues on rare syndromic forms of TAA and TAAD, revealing mutations responsive for the phenotypes and biological pathways important for the function and structural integrity of the thoracic aorta [1]. At

Table 1. Scientific Sessions and List of Speakers at IMAD3 in Liege, Belgium, October 4–6, 2012

Session Title and Moderators	Speaker	Affiliation
Opening session	Dimitris-Solon Georgopoulos	Agia Olga General Hospital, Greece
Genetics, genomics and pathobiology of thoracic aortic diseases	Bart Loeys	University of Antwerp, Belgium
	Jean-Baptiste Michel	INSERM, France
Moderators: Eric Allaire and John A. Elefteriades	Peter N. Robinson	Charite-Universitätmedizin, Germany
	Julie De Backer	University Hospital of Gent, Belgium
	Fransiska Malfait	University Hospital of Gent, Belgium
	John A. Elefteriades	Yale University, USA
	Annette Baas	University Medical Center Utrecht, The Netherlands
	Ayako Nagasawa	Yamaguchi University, Japan
	Fabio Ramponi	University of Sydney, Australia
	Julie Faugeroux[b]	INSERM, France
	Tiwari Kausal	G. Pasquinucci Heart Hospital, Italy
	Adiguzel Zelal	Genetic Engineering and Biotechnology Institute, Turkey
Clinical management and treatment of thoracic aortic diseases	Martin Czerny	Inselspital, Switzerland
	Luigi Lovato	University Hospital S. Orsola, Italy
Moderators: Jean-Olivier Defraigne and Christoph Nienaber	Christoph Nienaber	University of Rostock, Germany
	Germano Melissano	H. San Raffaele–Chirurgia Vascolare, Italy
	Thai An Nguyen	Cho Ray Hospital, Vietnam
	Tilo Kölbel	Universitätsklinikum, Hamburg-Eppendorf, Germany
	Ian Loftus	St. George's University of London, UK
	John A. Elefteriades	Yale University, USA
	Thomas Bilfinger	Stony Brook Medical Center, USA
	Carsten Bünger	Thorax-, Gefäß- und Transplantationschirurgie Universitätsklinik, Rostock, Germany
	Stephan Kische	University Hospital Rostock, Germany
	Benjamin W. Starnes	University of Washington, USA
	Frédéric Cochennec	Centre Hospitalier Universitaire Henri Mondor, France
	Natzi Sakalihasan	University Hospital of Liège, Belgium
	Davide Patrini	Cliniche Gavazzeni-Bergamo, Italy
	Jean-Marc Alsac	Universite Rene Descartes, France
	Isabelle Bouckenooghe	OLV Aalst, Belgium
	Bart Meuris[a]	University Hospitals Leuven, Belgium
Epidemiology of AAA	Janet Powell	Imperial College, UK
Moderator: Frank Lederle	Rebecka Hultgren	Karolinska Institutet, Sweden
	Frank A. Lederle	Minneapolis VA Center for Epidemiology & Clinical Research, USA
	Paul Norman	University of Western Australia, Australia
	Soroush Sohrabi	University of Leeds, UK
	Jes Lindholt	Viborg Hospital, Denmark
	Kim Kargaard Bredahl	Rigshospital Copenhagen, Denmark
	Fredrik Lundgren	University Hospital of Linköping, Sweden
	Jordane Herail	CHU Besançon, France
	Rodolphe Durieux	University Hospital of Liège, Belgium
Genetics and genomics of AAA	Jonathan Golledge	James Cook University, Australia
Moderator: Helena Kuivaniemi	Gerard Tromp	Geisinger Clinic, USA
	Betti Giusti	University of Florence, Italy

(*table continues*)

Table 1. (*continued*)

Session Title and Moderators	Speaker	Affiliation
Pathophysiology and biomarkers of AAA	Jose Luis Martin Ventura	Autonoma University, Spain
	Gillian Cockerill	St. George's University of London, UK
Moderators: Gillian Cockerill and Jes Lindholt	Joel Pincemail	University Hospital of Liège, Belgium
	Koichi Yoshimura	Yamaguchi University, Japan
	Joost A. Van Herwaarden	University Medical Center in Utrecht, The Netherlands
	Jesper Swedenborg	Karolinska Institutet, Sweden
	Andrea Ascoli Marchetti	University of Rome, Italy
	Marc A Bailey	University of Leeds, UK
	Melina Vega de Céniga	Hospital de Galdakao-Usansolo, Spain
	Osamu Yamashita	Yamaguchi University, Japan
	José Monteiro	University of Sao Paulo, Brasil
Tips and tricks for better management in aortic surgery: team building	Francine Blaffart	University Hospital of Liège, Belgium
	Filip De Somer	University Hospital Gent, Belgium
	Marc Schepens	AZ Sin. Jan Brugge, Belgium
Moderators: Francine Blaffart and Filip De Somer	John Murkin	University of Western Ontario, Canada
	Niels Rahe-Meyer	Hannover Medical School, Germany
	Marc G Lagny	University Hospital of Liège, Belgium
Creating standards for measuring AAA growth	Henrik Sillesen	Rigshospitalet, Denmark
	Timothy Baxter	University of Nebraska, USA
Moderator: Eric Allaire	Anders Wanhainen	Uppsala University Hospital, Sweden
Clinical management and treatment of distal arch, thoraco-abdominal and abdominal aortic aneurysms: Part I	Furuzan Numan	Istanbul University, Turkey
	Eric Verhoeven	Klinikum Nürnberg Süd, Germany
	Michael Jacobs	Maastricht University Medical Center, The Netherlands
Moderators: Nicos Labropoulos and Eric Verhoeven		
Clinical management and treatment of distal arch, thoraco-abdominal and abdominal aortic aneurysms: Part II	Hence Verhagen	Erasmus University Medical Center, The Netherlands
	Jason Lee	Stanford University, USA
	Athanasios Giannoukas	University Hospital of Larissa, Greece
	Nicos Labropoulos	Stony Brook University Medical Center, USA
Moderators: Nicos Labropoulos and Hendrik Van Damme	Frank Veith	New York University, USA
	Frank Vermassen	Universitair Ziekenhuis Gent, Belgium
	Gilberto Boselli	Reggio Emilia Public Hospital, Italy
	Bertrand Saint-Lèbes	University Hospital of Toulouse, France
	V.A. Piccone	Staten Island University Hospital, USA
	Sebastien Deglise	CHUV, Switzerland
	Roberto Gattuso	University Sapienza, Italy
AAA Genetics	Matthew Bown	University of Leicester, UK
Moderators: Matthew Bown and Gregory Jones	David Carey	Geisinger Clinic, USA
	Daniel Swerdlow	University College London, UK
	Anna Helgadóttir	deCODE Genetics, Iceland
	Gregory Jones	University of Otago, New Zealand
	Per Eriksson	Karolinska Institutet, Sweden
	Grisha Pirianov	St. George's University of London, UK
	Mohamed Salah	UK SH-Campus Lübeck, Germany
	Rebecka Hultgren	Karolinska Institutet, Sweden
	Ewa Strauss	Polish Academy of Sciences, Poland
	Irene Hinterseher	Charite-Universitätmedizin, Germany
	Viviane Kokje[b]	Leiden University, The Netherlands
	Fernando Rodríguez-Pascual	Centro de Biologia Molecular Severo Ochoa, Spain

(*table continues*)

Table 1. (*continued*)

Session Title and Moderators	Speaker	Affiliation
Epidemiology, genetics and pathophysiology of valvular diseases	Per Eriksson	Karolinska Institutet, Sweden
	Alessandro Della Corte	Second University of Naples, Italy
	Anders Franco-Cereceda	Karolinska Institutet, Sweden
Moderators: Per Eriksson and Victor Legrand	Jean Dumesnil	University Institute of Cardiology and Pneumology of Quebec, Canada
	Mohamed Salah	UK SH-Campus Lübeck, Germany
	M. Buonocore	Second University of Naples, Italy
	V. D'Oria	Second University of Naples, Italy
	Laure Gilis	University Hospital of Liège, Belgium
Clinical management and treatment of valvular diseases	Luc Pierard	University Hospital of Liège, Belgium
	Carlo Di Mario	Royal Brompton Hospital, UK
Moderators: Victor Legrand and Marc A. Radermecker	Gebrine El Khoury	Clinique Universitaire de Saint-Luc, Belgium
	Vitalii Kravchenko	M. Amosov National Institute of Cardiovascular Surgery, Ukraine
	K.J. Griffin	University of Leeds, UK
	Victor Legrand	University Hospital of Liège, Belgium
	Inez Rodrigus	University Hospital of Antwerp, Belgium
Perceval™ S. the truly sutureless valve: 5-year clinical results and first BeNeLux results	Bart Meuris	University Hospitals Leuven, Belgium
	Jean-Marc Marnette	CHR Namur, Belgium
	Suzanne Kats	University Hospital Maastricht AZM, The Netherlands
Moderator: Jean-Olivier Defraigne	Mattia Glauber	G. Pasquinucci Heart Hospital, Italy
Recent advances and future directions of aortic diseases	Frank Veith	New York University, USA
	Eric Allaire	Centre Hospitalier Universitaire Henri Mondor, France
Moderator: Frank Lederle	Jan Lindeman	Leiden University, The Netherlands
	Frank Lederle	Minneapolis VA Center for Epidemiology & Clinical Research, USA
	Natzi Sakalihasan	University Hospital of Liège, Belgium
	Christian Gasser	The Royal Institute of Technology, Sweden
	Tim McGloughlin	University of Limerick, Ireland
	Jes Lindholt	Viborg Hospital, Denmark
	Giampaolo Martufi	The Royal Institute of Technology, Sweden
	Alain Nchimi	University Hospital of Liège, Belgium
	Arend-Jan Nieuwland	Leiden University, The Netherlands
	Badri Vijaynagar[a]	University of Leicester, UK
	Nicoletta Charolidi	St. George's University of London, UK
	Laurence Rouet	MediSys, France

[a]Received the Raymond Limet Prize given to the 2 best posters/short communications on natural history and/or pathophysiology of abdominal aortic aneurysms.

[b]Received the Camillo Di Croce Prize given to the 2 best posters/short communications on familial and/or genetic aspects of aneurysms.

For details on the program, visit the conference Web site at http://www.chuliege-imaa.be/.

least 15 distinct, rare diseases with vascular manifestations such as arterial tortuosity and dilatation or dissection of the aorta have been characterized in detail on the molecular level, and genetic defects have been identified [2–11]. The diseases include the arterial tortuosity syndrome, vascular type of the Ehlers-Danlos syndrome, cutis laxa (multiple subtypes), Loeys-Dietz syndrome (multiple subtypes), Marfan syndrome, multisystemic smooth muscle dysfunction syndrome, type 5 of the Moyamoya disease, periventricular heterotopia, and Shprintzen-Goldberg craniosynostosis syndrome. In most of these syndromes, the vascular manifestations occur in the aortic arch or the ascending or descending thoracic aorta, and it is rare to see aneurysms in the abdominal aorta. At least 13 different genes harbor mutations causing these 15 syndromic forms of aortic aneurysms and dissections [2–11]. Mutations in *ACTA2* (smooth muscle alpha ac-

tin) can lead to either the multisystemic smooth muscle dysfunction syndrome or the type 5 subtype of the Moyamoya disease [12]. Similarly, mutations in the *TGFβR1* and *TGFβR2* (transforming growth factor, beta receptor) genes can lead to phenotypic heterogeneity and classification of the patient into different subtypes of the Loeys-Dietz syndrome [13]. Because the number of patients studied for most of these conditions is small, it is difficult to make generalizations about genotype-phenotype correlations. What can be concluded, however, is that many of the genes encoding members of two biological pathways, the transforming growth factor-β (TGFβ)–signaling pathway and the contractile apparatus of the smooth muscle cell, are mutated in these patients. The proteins of the extracellular matrix constitute the third important category of proteins defective in some of the patients. Future research efforts will include development and refinement of animal models for these conditions and the testing of different pharmaceutical compounds as medical treatment options [1,4,6].

Dr. Julie De Backer presented a comprehensive review of the treatment of Marfan syndrome. β-Blockers, although the standard of therapy, are largely unproven in effectiveness. Many promising clinical trials of TGFβ antagonism by losartan (an angiotensin receptor blocker) will come to fruition within the next few years. New information on molecular mechanisms of aortic disease in Marfan syndrome could lead to new treatment options in the future. For example, experiments performed in a mouse model in Dr. Peter Robinson's laboratory showed that treatment with the BA4 antibody neutralized fibrillin fragments and ameliorated aortic pathology [14].

The myocardium appears to be adversely affected, in both its systolic and diastolic function, in patients with Marfan syndrome. Fibrillin-1 is expressed in myocardium [15].

Vascular Ehlers-Danlos syndrome continues to elude preventative therapy, with most patients presenting with catastrophic arterial hemorrhage, usually in the abdomen or head or neck region. Empirical therapy with the particular β-blocker celiprolol can be considered [16]. A new animal model developed by Dr. Fransiska Malfait will enable advances in this syndrome.

The Yale group is accumulating evidence that patients with aortic root aneurysm are protected from systemic arteriosclerosis. Comparative studies found lower total-body arterial calcium (a late arteriosclerotic indicator) and lower carotid intima-media thickness (an early arteriosclerotic indicator) [17,18]. These clinical observations are consistent with the earlier findings by Grainger that indicated that TGFβ has antiatherogenic properties [19].

The quest for clinically useful biomarkers of aortic disease has largely run fallow [20]. Although D-dimer is 100% sensitive for aortic dissection, it rises after dissection has occurred and therefore has no utility in prediction. A Yale "RNA signature" holds promise to provide a general diagnostic test and a real-time indicator ("virtual biopsy") of aortic molecular biology [21].

In the session on how to improve management of aortic surgery, the importance of achieving optimal brain protection to avoid ischemia by use of systemic hypothermia was discussed by Dr. Filip De Somer. A surgical approach to visceral, spinal cord, and cerebral protection has been developed by Dr. Marc Schepens. The spinal cord protection, achieved by use of a left-left bypass, permissive hypothermia, evoked potential monitoring, reimplantation of critical arteries, and cerebrospinal fluid drainage, can greatly reduce the risk of neurological deficits after thoracoabdominal aortic surgery with or without bypass. Deep hypothermic circulatory arrest with or without antegrade selective cerebral perfusion can be useful for cerebral protection during arch surgery.

Transcranial Doppler and cerebral oximetry are technologies helpful in avoiding intraoperative desaturation. Dr. John Murkin described an algorithm for intraoperative use of cerebral near-infrared spectroscopy (NIRS) and low cerebral saturation. Dr. Niels Rahe-Meyer discussed coagulation management during and after complex cardiovascular surgery. The amount of blood loss during the surgery and preoperative fibrinogen levels were correlated. Fibrinogen infusion successfully reduced the rate of bleeding and allogeneic blood transfusion in the postoperative period. Despite recent improvements in prevention, medical treatment [22], and endovascular aortic repair, invasive surgery associated with cardiopulmonary bypass remains the best option for treatment of some patients. Dr. Marc Lagny discussed cardiopulmonary bypass procedures and aortic surgery. Arterial cannulation requires special attention because of the possibility of local dissection, malperfusion, or embolic events. Strategies to achieve good cerebral protection include hypothermia with or without selective cere-

bral perfusion [23,24]. Perfusion plays an important role in blood management [25] during the potentially hemorrhagic surgery.

Pathophysiology of TAADs is Complex

The TGFβ signaling pathway plays a critical role in TAAs [6]. Activation of the TGFβ/SMAD2 pathway is characterized by accumulation of activated phosphorylated SMAD2 (pSMAD2) [26]. The amounts of TGFβ1 protein retained within and released by aneurysmal tissue were greater than for control aortic tissue, contrasting with unchanged *TGFβ1* mRNA levels. Increased stored TGFβ1, TGFβ binding protein-1 (LTBP1) protein and mRNA, phosphorylated SMAD2, and *SMAD2* mRNA levels were detected in the ascending aortic wall from all types of TAAs. In addition, a complex dysregulation of SMAD2 signaling, independent of TGFβ1, was observed in TAA-derived cultured vascular smooth muscle cells. The cell specificity of this overexpression strongly implicated epigenetic control of SMAD2 expression [27], and an increase in H3K9/14 acetylation and H3K4 methylation was detected by chromatin immunoprecipitation in a cell-specific and transcription start site-specific manner.

Another interesting pathophysiological question studied by Dr. Jean-Baptiste Michel's laboratory is whether aneurysms in the thoracic ascending aorta induce platelet activation and thrombin formation [28,29]. The amounts of P-selectin and platelet-bound fibrinogen were increased, demonstrating platelet activation. Transparietal concentration and activation (thrombin formation) of prothrombin was enhanced in TAA wall compared with healthy aortas [29]. Thrombin/antithrombin complex formation was also increased through the TAA wall. Moreover, prothrombin/thrombin was retained in areas of mucoid degeneration.

Because activation of the pericellular fibrinolytic system leads to degradation of adhesion proteins, activation of matrix metalloproteinases, loss of vascular smooth muscle cells [30], and an increase in the bioavailability of TGFβ, the ability of the plasminergic system to be activated in TAAs was also investigated [31]. Immunohistochemical staining showed accumulation of tissue (tPA) and urokinase (uPA) plasminogen activators and plasmin in TAAs, associated with residual vascular smooth muscle cells. Plasminogen was present on the surface of smooth muscle cells and inside cytoplasmic vesicles, but plasminogen mRNA was undetectable in the TAA medial layer, which suggests that plasminogen originates from plasma. Fibronectin-related material was detected immunohistochemically in dense clumps around smooth muscle cells and colocalized with LTBP1.

Diseases of the Abdominal Aorta

The second day of IMAD3 was devoted to epidemiology, genetics, pathobiology, and different treatment modalities of abdominal aortic aneurysms (AAAs).

Decreasing Trends in AAA Prevalence and Mortality

In the past few years, studies from around the world have described a marked decline in AAA prevalence and mortality. Smoking is perhaps the strongest predictor of AAA, and the temporal pattern of the rise and fall of smoking rates roughly parallels the changes in AAA mortality. To gain insight into this and other explanatory factors, the Charing Cross group combined the strength of risk factors as judged from multivariate regression models with the change in their prevalence over time to try to estimate the contribution of each to the decline in AAA mortality [32]. Their modeling suggested that in addition to smoking, increased use of elective repair and of statins and antihypertensive drugs all likely contributed to the decline in AAA mortality.

Unlike cerebral and thoracic aneurysms, AAAs are much less common in women than in men. The reasons for this difference have been difficult to pin down. A protective effect of female sex hormones has been postulated and demonstrated in animal models, but studies of hormone use and biomarkers in humans have been inconclusive [33]. Also unexplained are the apparently higher rupture rate of AAAs in women and the more frequent finding of concurrent aneurysms in the thoracic aorta [34]. With few answers available, gender differences remain an important area of AAA research.

Another topic discussed at IMAD3 involved factors that contribute to AAA enlargement. Large data sets have been examined looking especially for evidence of reduced enlargement rate associated with use of common drugs such as statins, angiotensin-converting enzyme (ACE) inhibitors, and calcium blockers. These have been difficult to identify, and one reason

may be what has been termed *index event bias* [35]. This describes a phenomenon whereby risk factors that contribute to a patient being diagnosed with a disease continue to operate in that individual but do not stand out as being predictive of progression compared with other risk factors that continue to operate in other diagnosed individuals.

In addition to their intended purpose of identifying AAAs, data from large screening studies have allowed assessment of the relationship of aortic diameter to various outcomes. Several studies have found that an aortic diameter larger than normal but still well below the range of an AAA may be predictive of cardiovascular mortality and of peripheral artery disease [36]. Further research is needed to determine whether individuals with above-normal aortic diameters might benefit from more intensive risk identification and modification.

AAA is a Complex Disease with Multiple Genetic Risk Factors

AAA has a significant genetic component, with twin studies reporting heritability of ≈70% [37]. The pattern of inheritance appears to be autosomal, although evidence for both recessive and dominant models has been suggested [38].

Although numerous candidate gene associations have been published [38,39], only three large-scale genome-wide association studies (GWAS) have been reported for AAA [40–42]. To date, only four genetic associations, the *CDKN2BAS1* locus (9p21) [43], *DAB2IP* (9q33) [42], *LRP1* (12q13) [41], and *IL6R* [44], have reached genome-wide significance ($P < 10^{-8}$) and have been replicated in different populations. Although some of these markers (*CDKN2BAS1* and *DAB2IP*) appear to have concurrent associations with other forms of arterial disease, *LRP1* may represent an AAA-specific association. Another highly significant ($P = 0.00006$) association was found recently with AAA and single-nucleotide polymorphisms (SNPs) in the apolipoprotein(a) (*LPA*) gene [45].

Future genetic discovery in AAAs is likely to be made via two complementary strategies. First, meta-analysis of GWAS data sets will significantly improve the statistical power to detect disease-associated SNPs. The largest AAA GWAS reported to date included 1866 cases [41]; however, meta-analysis of all currently existing GWAS, from the United Kingdom, the Netherlands, Iceland, New Zealand, and the United States, would combine >5,000 cases and >60,000 controls. This approach has been shown to be an effective discovery tool in other cardiovascular phenotypes, such as coronary artery disease (CAD) [46] and dyslipidemia [47]. A strategy to combine all published and unpublished AAA GWAS data and perform a meta-analysis with follow-up replication was discussed and endorsed at IMAD3.

The second alternative SNP discovery strategy is to utilize prior knowledge of biological associations, such as CAD and dyslipidemia, to facilitate analysis of GWAS data sets [48]. For example, because >100 loci have been convincingly associated with CAD or dyslipidemia in large-scale meta-analyses, these regions may also be risk loci for AAA, as is the case for the chr9p21 *CDKN2BAS1* locus. Investigation of AAA GWAS data sets by use of a "focused" set of SNPs with prior knowledge significantly reduces the multiple testing correction requirements typically associated with whole-genome analysis.

Regardless of the approach to genetic discoveries, it is clear that there is potential overlap between genetic risk for concurrent vascular diseases, such as AAA, CAD, and peripheral artery disease, and associated risk factors, such as dyslipidemia and smoking [49]. It will therefore be important that future genetic studies be able to statistically model these interactions. The eMERGE Network, organized by the National Human Genome Research Institute, is one example of a study group that has recognized the need for integrated genetic, demographic, and clinical data analysis [50]. Such studies will be vital if genetic risk is to be successfully integrated into the demographic and clinically based risk models that are currently in clinical practice.

Finally, although these approaches are capable of identifying independent genetic risk factors, the biological mechanisms underpinning these associations are not always clear. Functional studies linking SNP genotypes with tissue-specific gene expression profiles by Folkersen and colleagues [51] demonstrated that approximately half of the 166 cardiovascular risk SNPs investigated influenced expression of genes in close proximity. A smaller number of SNPs, however, appeared to influence genes that were not in the immediate vicinity of the risk SNP, nor were these variants in linkage disequilibrium with another SNP near the gene. In addition, SNP-associated gene effects were tissue specific, and tissue specificity was

phenotype dependent (for example, lipid metabolism SNP-gene effects were predominantly liver-specific). This suggests that SNP–gene expression mechanisms are complex, and considerable caution is needed when interpreting possible pathological mechanisms underpinning SNP-phenotype associations.

Inflammation and Oxidative Stress Play Key Roles in AAA Pathophysiology

On the basis of histological and molecular studies, the aortic wall tissue from human AAAs large enough to be repaired shows extensive inflammation, vascular smooth muscle cell loss, and extracellular matrix degradation, as well as increased amounts of matrix metalloproteinases and oxidative stress [1,52–54]. These features have also been key findings in recent unbiased genomic and proteomic studies, which confirms their relevance to the disease pathophysiology [1,52–55].

The search for biomarkers detectable in human serum or plasma that could help to identify patients with AAAs, monitor the growth of existing AAAs, or predict the rupture of AAAs is of critical importance [56–61]. Some of the recently identified promising AAA biomarkers are catalase (CAT, an enzyme that converts the reactive oxygen species hydrogen peroxide to water and oxygen, thereby mitigating the toxic effects of hydrogen peroxide) [58], peroxiredoxin 1 (PRDX1, also known as the natural killer cell–enhancing factor A) [57], and lipocalin 2 (LCN2, also known as neutrophil gelatinase–associated lipocalin, NGAL, a marker of neutrophil activation) [59].

In a small study of 63 AAA patients, statin treatment reduced aortic wall inflammation by decreasing the levels of nuclear factor-κB, interleukin 6 (IL6), and chemokine (C-C motif) ligand 2 (CCL2, also known as the monocyte chemoattractant protein 1, MCP1), as well as proteases cathepsin K and S [62]. These effects appeared to be independent of lipid-lowering effects of statins. In contrast, no effect was seen on AAA growth in a separate study of 142 AAA patients [62].

Studies on aortic aneurysms in animal models are also crucial in identifying the early molecular mechanisms that lead to AAA development and growth and in testing ways to prevent or delay the growth of AAAs [63–65]. In one study performed with an AAA mouse model, lysyl oxidase, an enzyme needed for crosslinking of elastin and collagen molecules, was shown to reduce CCL2 and prevent macrophage infiltration and AAA progression [63]. In another mouse study discussed at IMAD3, increasing plasma high-density lipoproteins (HDLs) inhibited aortic aneurysm formation via reduced ERK1/2 activation [65]. In a third mouse study, administration of rosiglitazone, an agonist of the nuclear peroxisome proliferator–activated receptors, to mice induced to have aortic aneurysms led to a marked reduction of both aneurysm rupture and development. Rosiglitazone appeared to modulate inflammatory processes by blocking TLR4/JNK (toll-like receptor/c-Jun N-terminal kinase) signaling [64].

Different regions of the human aorta differ in their embryological origins, structure of the aortic wall, and disease susceptibility. Gene expression studies have also shown differences between the thoracic and abdominal aorta. For example, the expression of many homeodomain-containing genes, the so-called HOX genes, demonstrates spatial expression patterns along the length of the aorta, and these genes have decreased expression in human AAA compared with nonaneurysmal aorta [66].

Differences in expression levels of a large number of different genes have been identified between human AAA and nonaneurysmal control aortic samples [1]. The next step is to understand how the expression of these genes is regulated and how it could be modified medically to slow the growth rate of AAAs. These studies have led to the discovery of transcription factors and microRNAs that control the expression of genes in the human aorta [67,68].

Update on Treatment Options for AAA

Patients with small AAAs are being followed up based on the diameter of the AAA and may be treated medically, including by risk factor modification, such as antihypertensive and lipid-lowering drugs, as well as antibiotics and β-blockers. A recent meta-analysis of 4647 patients showed a significant reduction in AAA growth rates in patients taking statins compared with those who did not [69], but other meta-analyses failed to show a growth rate reduction [70,71].

Another meta-analysis on the effects of antibiotics and β-blockers on AAA growth showed that roxithromycin provided a small but significant protective effect and β-blockers showed a very small protective effect on AAA expansion [72]. ACE inhibitors suppress the development of elastase-induced AAA in mice.

Patients taking ACE inhibitors before hospital admission were less likely to present with a ruptured aneurysm than those who did not [73]. Anti-inflammatory agents, inhibitors of mast cell degranulation to reduce aortic wall expansion, and JNK inhibitors are some other potential pharmacological agents that have so far been used only in animal models [74].

The advantages of endovascular aneurysm repair (EVAR) over open surgical repair (OSR) include significantly lower periprocedural stress for the patient, which results in early mobilization, a limited need for a stay in the intensive care unit, a shorter overall hospital stay, and significantly lower early complication and mortality rates [75]. These early benefits disappear over time. Approximately 20% of all EVAR patients will require reintervention during follow-up, and 1% will experience aneurysm rupture after EVAR. Reports on more recent patient cohorts indicate a gradual improvement in these figures, mainly attributed to better preoperative planning and device design [76]. Endoleaks, aortic and endograft remodeling, and the potential for aneurysm rupture after elective repair make long-term surveillance necessary. Elective EVAR in patients aged $\geq$80 years yields significantly lower immediate postoperative mortality and morbidity than OSR and should be considered the treatment of choice in these patients. Long-term survival is certainly lower, which reflects the more extensive comorbidities in this patient subgroup [77]. Anatomic constraints, specifically adequate access vessels, sufficient proximal and distal landing zones, and angulation, along with the need for long-term surveillance, are the main EVAR limitations. As endografts continue to be modified, many of the initial difficulties may be overcome, leading to a more widespread adoption of this treatment modality.

Reports from centers performing large numbers of OSRs demonstrated low perioperative morbidity and mortality, but population-based studies showed higher mortality of up to 8% [78]. Patients with an acceptable risk profile, despite an increased early mortality and a longer recovery period than with EVAR, have similar mid- and long-term outcomes and perhaps better long-term quality of life. Currently, anatomic unsuitability for EVAR is one of the main indications for OSR, and therefore, OSR is more common in female patients. Perioperative complications include cardiac ischemic events, arrhythmias, hemorrhage, renal and respiratory failure, colonic ischemia, and distal embolization. Long-term complications are uncommon and include graft infection, erosion to nearby structures, abdominal wall hernias, and anastomotic disruption.

Valvular Diseases

Bicuspid aortic valve (BAV) is the most prevalent inherited cardiac malformation [79] and accounts for 30%–50% of all adult aortic valve pathologies that undergo operation in Western countries [80]. The association between BAV and diseases of the ascending aorta was emphasized during IMAD3, although the nature and the extent of the relationship remain unclear [81]. Over the past 15 years, the hypothesis that the "intrinsic pathology" of the ascending aorta was the main determinant for aneurysm development and aortic complications has prevailed. This intrinsic/genetic pathology hypothesis was supported by the recognition of the role of neural crest cells in the development of both aortic valve and ascending aorta pulmonary trunk [82], as well as by specific features of the dilated aorta with BAV compared with tricuspid valves [83–85].

The alternative hypothesis, supported by recent hemodynamic and flow-imaging studies, emphasizes the role of abnormal mechanical stress on the aortic wall in BAV [86]. The abnormal parietal stress in specific regions of the ascending aorta is related to jet asymmetry, which in itself is conditioned by the opening and therefore the morphology of the BAV (position of the raphe, i.e., area of fusion between the two incompletely developed cusps and corresponding hypoplastic in the leaflet triangle) [87].

The stress-induced aortopathy hypothesis is also supported by many clinical observations reporting the relatively good prognosis of patients with mild to moderate aortic dilatation after isolated aortic valve replacement [88,89]. The pendulum therefore swings from an intrinsic degenerative aortopathy deserving special prophylactic management, such as in Marfan syndrome, toward a more mechanistic, stress-driven disease in which size remains the best predictor of complications. This relative shift of paradigm has influenced the guidelines for the valve and aortic management in BAV. There is a trend toward recommending prophylactic replacement of

the ascending aorta, if >45–50 mm, except if the aneurysm is rapidly progressing or in case of a strong family history of dissection or rupture or with planned pregnancy. Guidelines of the American College of Cardiology, American Heart Association, and the European Society of Cardiology recommend elective repair in symptomatic patients with dysfunctional BAV [90,91]. At IMAD3, the Saint-Luc group from Brussels reported on 475 patients undergoing aortic valve repair for aortic insufficiency or aortic aneurysm with outstanding outcomes for the reimplantation technique with or without leaflet repair, the only obstacle to a conservative surgery being the intrinsic quality of the leaflet [92].

Benefits of medical therapy on aortic valve disease are limited. According to European Society of Cardiology guidelines, vasodilatators and inotropic agents can be used to improve the condition of severe heart failure patients before proceeding with aortic valve surgery. In individuals with chronic severe aortic regurgitation and heart failure, vasodilators (ACE inhibitors and angiotensin-receptor blockers, ARB) are useful in hypertensive patients when surgery is contraindicated or left ventricular dysfunction persists postoperatively. Benefits of these agents or the dihydropyridine calcium channel blockers in asymptomatic patients without hypertension in order to delay surgery are unknown. In patients with Marfan syndrome, β-blockers may slow aortic root dilatation and reduce the risk of aortic complications and should be considered before and after surgery. Preliminary findings suggest that selective ARBs promote preservation of elastin fibers in the aortic wall, but their clinical benefit remains to be proven by ongoing trials [90].

Transcatheter aortic valve implantation was discussed in the presence of severe aortic stenosis. Results from the subclavian approach are encouraging and may (with the 18F CoreValve ReValving System) avoid the need for transapical approach. From the experience in octogenarians reported by Dr. Inez Rodrigus and the discussion of "difficult" clinical cases by Dr. Victor Legrand, a consensus emerged among the participants that the transcatheter aortic valve implantation procedure should be reserved for patients with definite contraindication to surgery or high-risk surgery, provided an improvement in the quality of life can be obtained.

Recent Advances and Future Directions of Aortic Diseases

The last session of the IMAD3 was devoted to presentations discussing recent and future developments related to aortic diseases, such as whether outcomes differ between EVAR and open repair for AAA and whether it is possible to tell which AAA is going to rupture and which one is more stable either by positron emission tomography (PET) imaging studies or by use of predictive modeling of wall stress.

In the OVER trial (Open Versus Endovascular Repair Trial for Abdominal Aortic Aneurysms), a 9-year VA Cooperative study, endovascular and open repair resulted in similar long-term survival [93]. The perioperative survival advantage of endovascular repair was significant for 3 years, but the survival curves were the same from 5 years onward. Six ruptures occurred during 4,576 patient-years of follow-up (1.3/1,000 patient-years), less than one third the rate seen in EVAR-1 (25 ruptures during 5309 patient-years of follow-up; 4.7/1,000 patient-years), but as in EVAR-1, all were in the endovascular group, which remains a cause for concern. Endovascular repair resulted in better long-term survival in patients younger than 70 years but tended to be worse in older patients, for whom it had been most hoped a benefit could be shown [93].

Conventional imaging tools give anatomic and morphological information about aneurysms, but the key question is how to identify aneurysms with the highest activity of inflammation and oxidative stress. Recently developed imaging techniques such as PET provide molecular and cellular evaluation of atherothrombosis in the arterial wall [54,94–96]. PET studies are performed with fluorodeoxyglucose (FDG) F 18, a glucose analog, which reflects glucose uptake and metabolism in the cell. Once inside the cells, FDG is phosphorylated to FDG-6-phosphate, which is not a substrate for the enzymes of the glycolytic chain. Several PET studies have investigated its usefulness to monitor the development and rupture risk of AAAs. An association between ^{18}F-FDG uptake by the aneurysm wall and rapid expansion of the aneurysm was found in some cases [95–99]. A correlation between the increased FDG uptake and high macrophage activity in symptomatic AAAs has also been reported [97], but no correlation between maximum standard uptake value and maximum cross-sectional infrarenal AAA

diameter was found [98]. In their recent study of >270 patients (unpublished data presented during IMAD3), Sakalihasan et al confirmed an association between ^{18}F-FDG uptake by the aneurysm wall and rupture of the aneurysm in seven cases, four of which were <55 mm in diameter. None of the patients without ^{18}F-FDG uptake developed any of the clinical signs or symptoms of the PET-positive patients.

Although previous biomechanics studies using finite element analysis demonstrated a strong correlation between high wall stress and rupture, the influence of local variation, such as presence of thrombus and asymmetry of AAA, needs to be better understood [100–102]. The initial change in an aneurysm is structural and results from a degenerative process in the vascular wall. As the morphology changes, the blood flow pattern changes, with consequential modification of fluid stresses and their interaction with the mechanical stresses within the arterial wall [96]. At IMAD3, the possible correlation between the growth rate of an AAA and biomechanical rupture risk factor indices such as peak wall stress and peak wall rupture risk were also discussed. The biomechanical AAA rupture risk assessment integrates information on size, shape, sex, wall weakening associated with the intraluminal thrombus, family history, and elevated blood pressure. The rupture risk equivalent diameter expresses this information through the diameter of the "average" AAA with the same risk of rupture, i.e., having the same peak wall rupture risk. Consequently, the rupture risk equivalent diameter reflects an individualized biomechanical assessment of the diameter-based information collected from clinical studies. A study using three-dimensional aneurysm models based on computerized tomographic angiography concluded that multiple centerline-based diameter measurements could help clinicians decide when to operate on AAAs [103].

Concluding Remarks

In this report, we have summarized recent discoveries concerning epidemiology, genetics, pathophysiology, and treatments of diseases that affect the thoracic and abdominal aorta, as well as the aortic valve. Considerable progress has been made recently, but there is clearly much work to be undertaken, for example, in identifying novel biomarkers and understanding the biological mechanisms of the genetic associations. It is encouraging that highly collaborative multinational approaches have been adopted that are likely to yield further substantial advances in the near future.

The codirectors of this meeting witnessed with delight the diversity of the meeting participants, who came from 28 different countries, and were particularly pleased to see the large number of junior investigators presenting. Four highly competitive travel awards in honor of the late professor Raymond Limet and Camillo Di Croce (Table 1) were given to junior investigators. The tradition of Liège meetings will continue, and planning for the fourth *International Meeting on Aortic Diseases* (IMAD4) is already in progress. It will take place in Liège, Belgium, in 2014 (for details, please visit the conference website at http://www.chuliege-imaa.be/).

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EDITOR'S COMMENTS

Dr. Roberto Chiesa, Professor, University di Bologna, Italy

The IMAD 3 (3rd International Meeting on Aortic Disease) contributions on current research and treatment of aortic disease are discussed in this paper. The authors analyzed recent discoveries on epidemiology, genetics, pathophysiology and medical and surgical treatment of aortic disease and valve pathology.

Connective tissue disorders resulting in thoracic aortic involvement currently represent one of the most complex research issues in medicine, due to multimodal manifestations related to phenotypic and genotypic heterogeneity. The IMAD reports conclude that multigenic mutations, particularly on TGFB genes, need to be analyzed in patients as well as with correlations to experimental animal models.

Open repair of arch and thoracoabdominal aortic aneurysms is currently the best therapeutic option, using contemporary adjuncts addressing brain, spinal cord, and visceral protection. Deep hypothermic circulatory arrest, with or without antegrade selective cerebral perfusion, can be useful for brain protection during aortic arch surgery. During thoracoabdominal aortic repair, the use of left heart bypass seems to be mandatory, along with cerebro-spinal fluid drainage and reimplantation of key intercostal arteries, with or without evoked potential monitoring and mild hypothermia.

Regarding abdominal aortic aneurysm (AAA), the paper reported a significant overall mortality reduction achieved using a combination of elective repair, supplemented with statin and antihypertensive drug administration. The future will provide further results regarding the impact of genetic mutations, inflammation responses, and oxidative stress on the aortic wall in patients with AAA. Detectable serum or plasma biomarkers will help identify patients with AAA, monitor growth, and predict rupture. The protective role of statins on the aortic wall is currently discussed. Recent improvements in vascular disease imaging can offer optimal anatomical and morphological information, and the latest research focused on PET imaging will provide data about inflammation and oxidative stress.

Comparison between EVAR and Open Repair is discussed, concluding that early benefits of EVAR sig-

nificantly disappear over time due to the 20% rate of secondary intervention and the 1% rate of index aneurysm rupture during follow up. Elective EVAR remains the procedure of choice in elderly patients or those with severe comorbidities.

The correlation between bicuspid aortic valve and ascending aortic pathology is emphasized, and two hypotheses are described: (1) The "intrinsic genetic" aneurysm predisposition secondary to specific aortic and valve features related to neural crest cell changes, and (2) The "stress induced aortopathy" secondary to abnormal flow patterns and parietal stress in specific aortic segments. While the benefits of medical therapy in aortic valve disease are limited, surgical repair continues to offer good results. TAVI seems to be indicated in high-risk patients.

This article provides a wide range of interesting topics related to aortic and valve disease and represents an appreciable informational update, based on interchange and debate between the distinguished clinicians and scientists participating in the IMAD 3 symposium.