CVCT

10th ANNIVERSARY

Global CardioVascular Clinical Trialists Forum

PARIS CVCT 2013

Course Directors: Faiez ZANNAD, Nancy - FRA, Bertram PITT, Ann Arbor - USA

www.globalcvctforum.com

FRIDAY 6 AND SATURDAY 7 DECEMBER 2013

PARIS FRANCE

PULLMAN MONTPARNASSE

FINAL PROGRAM

FACULTY

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Aldo Maggioni (Florence, ITA)
Michel Marre (Paris, FRA)
Alexandre Mebazaa (Paris, FRA)
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William White (Farmington, USA)
Stephan Windecker (Bern, CHE)
Janet Wittes (Washington, USA)
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INDUSTRY

Lance Berman (Relypsa, USA)
Jason A Campagna (Medco, USA)
Rob Cody (J&J, USA)
Blai Coll (Abbvie, USA)
Nancy Cooks Bruns (Bayer, GER)
James Costin (Perosphere, USA)
Wesley Day (Vivus, USA)
Peter DiBattiste (J&J, USA)
Mads David Engelmann (Novo Nordisk, DEN)
Neal Eigler (St. Jude Medical, USA)
Frank Eitner (Bayer, GER)
Christophe Gaudin (Sanofi, FRA)
Peter Held (Astrazeneca, SWE)
Philip Janiak (Sanofi, FRA)
David Kallend (MedCo, USA)
Torsten Kayser (Boston Scientific, BEL)
Jae Kim (Amgen, USA)
Christoph Koenen (BMS, FRA)
Joerg Koglin (Merck, USA)
Peter Kolkhof (Bayer, GER)
Stuart Kupfer (Takeda, USA)
Tim Laske (Medtronic, USA)
Martin Lefkowitz (Novartis, USA)
Guy Lerebours (Servier, FRA)
Ray Lipicky (North Potomac, USA)
Scott Meyer (Boston Scientific, USA)
Tim Meyer (Boston Scientific, USA)
Michele Mercuri (DSI, USA)
Claudio Mori (Vifor Pharma, CHE)
Gunnar Olsson (previously Astrazeneca, SWE)
Alfonso Perez (Takeda, USA)
Susan Petersen-Stejskal (Biocontrol, USA)
Beth Anne Piper (Pfizer, USA)
Thierry Pochet (Boston Scientific, BEL)
David Radzik (Sanofi, FRA)
Lothar Roessig (Bayer, GER)
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Walter Singleton (ISIS, USA)
Moncef Slaoui (GSK, GBR)
James Snider (Critical Diagnostics, USA)
Christina Stahre (Astrazeneca, SWE)
Solomon Steiner (Perosphere, USA)
Martin van Eickels (Bayer, GER)
Frank van Leeuwen (Medtronic, CHE)
Alphons Vincent (Medtronic, CHE)
Patrick Verta (Sunshine Heart, USA)
Karen Wai (Quintiles, SGP)
Gilbert Wagener (Genzyme, GER)
Scott Wasserman (Amgen, USA)
Holger Woehrle (Resmed, GER)

REGULATORY

Angeles Alonso (EMA, ESP)
Denise Bonds (NHLBI, USA)
Randall Brockman (FDA, USA)
Kristina Dunder (EMA, SWE)
Nancy Geller (NHLBI, USA)
David Gordon (NHLBI, USA)
Andrea Laslop (EMA, AUT)
Kiyoshi Nobori (PMDA, JAP)
Krishna Prasad (MHRA, GBR)
Giuseppe Rosano (EMA, ITA)
Yves Rosenberg (NHLBI, USA)
Kaori Shinagawa (PMDA, JAP)
Ferran Torres (EMA, ESP)
Bart Van der Schueren (EMA. BEL)

GENERAL PRESENTATION

Welcome into the cardiovascular clinical trials community.

We are delighted to welcome you to Paris for our 10th Anniversary edition of the Global CardioVascular Clinical Trialists Forum.

How should we intrepret the results of the major recent trials? How would these change clinical practice?
How can we design and conduct better and cheaper trials that address true unmet needs?
How can we improve operating procedures and streamline trial execution?
How to operate within the regulatory environment? Foster cross talk with regulatry agencies?
And more generally, how to create better and safer methods for treating cardiovascular disease?

The Global CardioVascular Clinical Trialists Forum (CVCT) is dedicated to the discussion of clinical trials in cardiovascular disease and aims to provide answers to these questions.

CVCT is a true Forum where scientific productivity and peer-to-peer exchange are at their best.

CVCT meetings are unique, bringing together a carefully selected faculty of opinion leaders, clinical trialists, investigators, regulators, statisticians, industry R&D experts, decision makers and practitioners. Over the years CVCT has attracted audience from over 30 different countries, with participants coming from Western and Eastern Europe, the USA, South America, Asia and Middle East.

The meeting encourages knowledge-sharing between participants as CVCT aims to familiarize practitioners and investigators with the science of clinical trials from protocol design to result interpretation. Further, CVCT Forum puts attendees into direct contact with primary investigators, senior trial scientists as well as research and development experts from pharmaceutical companies and experts from regulatory agencies.

We encourage you to make the most of the next two days. We hope you will agree that CVCT is an ideal meeting place for anyone eager to communicate with physicians and the people who are committed to creating and analyzing major trials and to raising awareness and bringing about change within the sector.

Finally, we extend a special welcome this year to our large group of young investigators, who are preparing to take on the challenges of running tomorrow's clinical trials.

We look forward to meeting and sharing ideas with you.

Pr. Faiez ZANNAD *Dr. Bertram PITT*

BOARD of COURSE DIRECTORS:

- **Arrhythmia and electrophysiology trials** Christophe Leclercq (Nantes) and Cecilia Linde (Stockholm)
- **Atherosclerosis trials** Wolfgang Koenig (Ulm)
- **Biomarker and personalized medicine trials** James Januzzi (Boston)
- **Cardiorenal trials** Georges Bakris (Chicago) and Patrick Rossignol (Nancy)
- **Device and telemonitoring trials** William Abraham (Columbus) and Ileana Piña (New York)
- **Diabetes trials** Michel Marre (Paris), William White (Farmington)
- **Heart failure trials** Faiez Zannad (Nancy) and Christopher O'Connor (Durham)
- **Imaging in CV trials** Ahmad Tawakol (Boston)
- **Interventional cardiology trials** Roxana Mehran (New York) and Patrick Serruys (Rotterdam)
- **Methodology and statistics** Stuart Pocock (London)
- **Thrombosis trials** Freek Verheugt (Amsterdam)
- **US National Heart Blood and Lung Institute trials** David Gordon and Michael Lauer (Bethesda)
- **International academic research organizations** Carolyn Lam (Singapore) and Naoki Sato (Tokyo)
- **Learned societies partners** Keld Kjeldsen (ESC working group on Pharmacology and Drug Therapy); Juan-Carlos Kaski, Gheorghe-Andrei Dan, Felipe Martinez (International Society of Cardiovascular Pharmacotherapy); Gonzalo Calvo and Tabassome Simon (European Association for Clinical Pharmacology and Therapeutics)

SUMMARY

FRIDAY 6 DECEMBER 2013

PARIS / CET	8:00 am - 10:00 am	COFFEE BREAK	10:20 am - 12:25 pm	LUNCHBOXES SERVED	12:35 pm - 3:15 pm	COFFEE BREAK	3:30 pm - 5:30 pm	COFFEE BREAK	5:45 pm - 7:30 pm
MODIGLIANI CONFERENCE ROOM	THROMBOSIS TRIALISTS WORKSHOP: COMPETING NEW THERAPIES IN ATRIAL FIBRILLATION AND HEART FAILURE		THROMBOSIS TRIALISTS WORKSHOP: COMPETING NEW THERAPIES IN ATRIAL FIBRILLATION AND HEART FAILURE		MANAGEMENT OF CO-MORBIDITIES IN HEART FAILURE		THE ATHEROSCLEROSIS TRIALISTS FORUM: NEW LIPID ASSOCIATED TARGETS AND IMPROVED PATHWAY TO SUCCESSFUL CLINICAL TRIALS		THE ATHEROSCLEROSIS TRIALISTS FORUM: NEW LIPID ASSOCIATED TARGETS AND IMPROVED PATHWAY TO SUCCESSFUL CLINICAL TRIALS
SOUTINE / UTRILLO CONFERENCE ROOM	DEVICES AND BIOMARKERS TO GUIDE CARE IN HEART FAILURE: TRIAL METHODOLOGY AND REGULATORY ISSUES		DEVICES AND BIOMARKERS TO GUIDE CARE IN HEART FAILURE: TRIAL METHODOLOGY AND REGULATORY ISSUES		VASODILATORS IN ACUTE HEART FAILURE: HOW TO DESIGN SUCCESSFUL TRIALS?		CORONARY ARTERIAL DISEASE TRIALS: CHANGE IN PRACTICE AND CHANGE IN PATHOPHYSIOLOGICAL UNDERSTANDING		REFINING CARDIAC RESYNCHRONIZATION AND IMPLANTABLE DEFIBRILLATOR THERAPY

SATURDAY 7 DECEMBER 2013

PARIS / CET	8:00 am - 10:00 am	COFFEE BREAK	10:20 am - 12:25 pm	LUNCHBOXES SERVED	12:35 pm - 3:00 pm	COFFEE BREAK	3:20 pm - 6:20 pm
MODIGLIANI CONFERENCE ROOM	ACUTE HEART FAILURE AND HEART FAILURE WITH PRESERVED EJECTION FRACTION: THE NEXT FRONTIER		ACUTE HEART FAILURE AND HEART FAILURE WITH PRESERVED EJECTION FRACTION: THE NEXT FRONTIER		MINERALOCORTICOID RECEPTOR ANTAGONISTS: THE KIDNEY, THE HEART AND BEYOND		LESSONS FROM FIRST POST FDA GUIDANCE CASE STUDIES OF DIABETES CV OUTCOMES TRIALS*
SOUTINE / UTRILLO CONFERENCE ROOM	INTERVENTIONAL CARDIOLOGY TRIALISTS WORKSHOP: DES AND DAPT TRIAL AND IMPLEMENTATION ISSUES		INTERVENTIONAL CARDIOLOGY TRIALISTS WORKSHOP: DES AND DAPT TRIAL AND IMPLEMENTATION ISSUES		NEURAL MODULATION TRIALS: TIME TO MOVE FROM PROOF OF CONCEPT TO OUTCOME TRIALS?		CARDIOVASCULAR MEDICAL DEVICE INNOVATION: BARRIERS AND SOLUTIONS (FINISH 5.30 pm) *

* With live participation of FDA regulatory experts via teleconference

FRIDAY 6 DECEMBER 2013

8.00 am-12.25 pm MODIGLIANI CONFERENCE ROOM

THROMBOSIS TRIALISTS WORKSHOP: COMPETING NEW THERAPIES IN ATRIAL FIBRILLATION AND HEART FAILURE

Moderators: Paulus Kirchhof (Birmingham, GBR); Dan Atar (Oslo, NOR)

- A number of new anti-thrombotic agents and a number of new trials have dramatically changed the management of acute coronary syndromes, atrial fibrillation, and venous thrombo-embolism. New oral anticoagulants (NOACS) have shaken the supremacy of warfarin.
- Warfarin in atrial fibrillation is still the reference oral anticoagulant, but it is now challenged by many new anti-thrombosis strategies.
- Results of the NIH-led trial will answer the question whether the use of genotype-guided warfarin therapy leads to an improvement in anticoagulation control above and beyond the use of only clinical information.
- The results of ENGAGE AF-TIMI48 were presented at AHA 2013 shortly before this CVCT 2013 meeting. The results add to the level of evidence and should be discussed within the context of the previous RE-LY, ROCKET AF and ARISTOTLE trials.
- Stroke risk after AF ablation appears to be favorably influenced; however, it is largely unknown if the benefit extends to all stroke CHADS2 risk profiles of AF patients and to patients with heart failure.
- Evidence from clinical trials and registry data is accumulating with left atrial (LAA) appendage closure, now available for use in Europe. Experts will debate on what further evidence is needed for establishing the value of LAA closure in the various AFib clinical situations.
- The combination of AF after ACS, or the other way around, is very common and is associated with severe bleeding. Do the NOACS with their better safety profile have a role here? Or should we drop aspirin in this specific indication?
- Many complications related to heart failure can be related to thrombosis. Epidemiological and pathophysiological data also link HF to an increased risk of thrombosis, leading to the clinical consequences of sudden death, stroke, systemic thromboembolism and/or venous thromboembolism. In HF patients with reduced LV ejection fraction who are in sinus rhythm there is no evidence of an overall benefit of warfarin on mortality, with risk of major bleeding. New oral anticoagulants that offer a different risk-benefit profile compared with warfarin may appear as attractive therapeutic option, but this would need to be confirmed in clinical trials.

Pharmacogenetics and pharmacoproteomics guided anticoagulation: results of the COAG trial and future perspectives
Speaker: Yves Rosenberg (NHLBI, USA)
Discussants: Nancy Geller (NHLBI, USA); Mark Chan (Singapore, SGP)

New oral anticoagulants in Atrial fibrillation
Paulus Kirchhof (Birmingham, GBR)

The latest trial results: ENGAGE-AF
Christian Ruff (Boston, USA)

Reversing the anticoagulant effects of the NOACS
Discussant: James Costin (Perosphere, USA)

What is the role of catheter ablation and LAA closure? Registries, and ongoing trials (CABANA and RAFT AF, PREDICT, PREVAIL)
Cecilia Linde (Stockholm, SWE)

Combination of AF and ACS: the potential role of NOACS
Freek Verheugt (Amsterdam, NED)

NOACS for heart failure with sinus rhythm: rationale and design of the COMMANDER-HF trial
Faiez Zannad (Nancy, FRA)

Industry perspective: Peter DiBattiste (J&J, USA); Joerg Koglin (Merck, USA); Michele Mercuri (DSI, USA); Martin van Eickels (Bayer, GER)

Regulatory perspective: Angeles Alonso (EMA, ESP); Krishna Prasad (MHRA, GBR); Kaori Shinagawa (PMDA, JAP)

Moderated Discussion with Audience Participation
Which therapy for which patient?
Shouldn't stroke prevention in AFib be personalized medicine?

Panellists: Angeles Alonso (EMA, ESP); Dan Atar (Oslo, NOR); Mark Chan (Singapore, SG); Rob Cody (J&J, USA); James Costin (Perosphere, USA); Peter DiBattiste (J&J, USA); Neal Eigler (St. Jude Medical, USA); Christophe Gaudin (Sanofi, FRA); Nancy Geller (NHLBI, USA); Young-Hoon Jeong (Jinju, KOR); Paulus Kirchhof (Birmingham, GBR); Joerg Koglin (Merck, USA); Tim Laske (Medtronic, USA); Andrea Laslop (EMA, Innsbruck, AUT); Basil Lewis (Haïfa, ISR); Cecilia Linde (Stockholm, SWE); Matthias Lorenz (Frankfurt, GER); Felippe Martinez (Cordoba, ARG); Michele Mercuri (DSI, USA); Gilles Montalescot (Paris, FRA); Kiyoshi Nobori (PMDA, JAP); Krishna Prasad (MHRA, GBR); David Radzik (Sanofi, FRA); Yves Rosenberg (NHLBI, USA); Christian Ruff (Boston, USA); Kaori Shinagawa (PMDA, JAP); Tabassome Simon (Paris, FRA); Solomon Steiner (Perosphere, USA); Juan Tamargo (Madrid, ESP); Ferran Torres (EMA, ESP); Martin van Eickels (Bayer, GER); Freek Verheugt (Amsterdam, NED); Sven Wassmann (Munich, GER); Faiez Zannad (Nancy, FRA)

FRIDAY 6 DECEMBER 2013

8.00 am-12.25 pm SOUTINE / UTRILLO CONFERENCE ROOM

DEVICES AND BIOMARKERS TO GUIDE CARE IN HEART FAILURE: TRIAL METHODOLOGY AND REGULATORY ISSUES

Moderators: William Abraham (Columbus, USA); James Januzzi (Boston, USA)

- Technologies and biomarkers can detect pathophysiologic deteriorations in HF patients weeks before symptom onset.
- Many devices are currently under investigation for heart failure, including cardiac contractility modulation, ventricular partitioning devices, intra-atrial shunts, percutaneous valve repair/replacement, transvenous phrenic nerve stimulation, implantable counter-pulsation devices, autonomic nervous system modulation, implantable hemodynamic monitors, and more.
- Progress in the understanding of heart failure biomarker science has led to considerable advances toward application of natriuretic peptides and other biomarkers with a goal to better manage patients and there are increasing numbers of potential candidate biomarkers to chose from for the management of patients with heart failure.
- Some view devices and biomarkers as a way to achieve target drug doses, while others view device/biomarker guided heart failure care as a way to supplement standard management by using an objective tool that reflects heart failure biology. Therefore, device/biomarker guided therapy includes selecting the appropriate therapy to suit individual patient phenotype, as to maximize response rate and minimize adverse events. However, more research has been devoted to the use of device/biomarkers to help optimize dosage.
- HF detection algorithms using multiple physiologic variables, each with its independent prognostic value, may result in a combined prognostic index of superior predictive and personalized value to an algorithm based on a single variable.
- The sponsor role may be central in investigator education, protocol adherence, ongoing data review and feedback to centres, automated versus nurse-directed alerts.
- Challenges and fundamentals of guided therapy trials from the regulatory perspective, including target population, trial design (e.g., observational versus RCT), control groups, monitoring and therapeutic algorithms, endpoints, and more generally what are regulatory agencies looking for need to be aligned with the clinically unmet needs and also met with the appropriate methodologies.
- Finally approvability, regulatory, implementation, economic model and reimbursement issues with large geographical variances and across various heath care systems are other challenges to be addressed.
- Consistency between the US, EU, and other regulatory bodies is a desirable goal.

The goal of this session is to stimulate collaborative practical discussions and generate consensus around appropriate design and execution of device/biomarker guided heart failure trials and the aspects surrounding their evaluation by regulatory agencies.

Implantable hemodynamic monitors
Speaker: William Abraham (Columbus, USA)

Multisense technologies and integrated algorithms
Speaker: Martin Cowie (London, GBR)
Discussant: Torsten Kayser (Boston Scientific, BEL)

Biomarker aspects: which biomarker? How to judge best approach for application?
Speaker: James Januzzi (Boston, USA)
Discussants: Jae Kim (Amgen, USA); James Snider (Critical Diagnostics, USA)

What have we learned so far? An update of the strength and limitations of the recent guided therapy trials
Devices: William Abraham (Columbus, USA)
Biomarkers: Arthur Mark Richards (Singapore, SGP)

Defining device/biomarker guided therapy: what is the target? Drug doses or the biology of heart failure?
Speaker: Javed Butler (Atlanta, USA)
Discussant: Kirkwood Adams (Chapell Hill, USA)

What is the best primary outcome measure? Hans-Peter Brunner-La Rocca (Maastricht, NED)

Biomarkers for mechanistic phenotyping and responder targeted therapy
- **The BIOSTAT approach** Marco Metra (Brescia, ITA)
- **The HOMAGE approach** Faiez Zannad (Nancy, FRA)

Statistical cautions regarding the allure of personalized medicine
Speaker: Stuart Pocock (London, GBR)

Moderated Discussion with Audience Participation
The pathway to regulatory approval -
what do the regulatory agencies think of devices and biomarkers to guide heart failure care?

Panellists: William Abraham (Columbus, USA); Kirkwood Adams (Chapel Hill, USA); Hans-Peter Brunner-La Rocca (Maastricht, NED); Javed Butler (Atlanta, USA); Blai Coll (Abbvie, USA); Martin Cowie (London, GBR); Gaetano DeFerrari (Pavia, ITA); Neal Eigler (St. Jude Medical, USA); Mona Fiuzat (Durham, USA); Philip Janiak (Sanofi, FRA); James Januzzi (Boston, USA); Torsten Kayser (Boston Scientific, BEL); Jae Kim (Amgen, USA); Damien Logeart (Paris, FRA); Alexandre Mebazaa (Paris, FRA); Marco Metra (Brescia, ITA); Tim Meyer (Boston Scientific, USA); Atul Pathak (Toulouse, FRA); Ileana Piña (New York, USA); Thierry Pochet (Boston Scientific, BEL); Stuart Pocock (London, GBR); Arthur Mark Richards (Singapore, SGP); Giuseppe Rosano (EMA, ITA); Veronique Semjonow (Philips, NED); James Snider (Critical Diagnostics, USA); Scott Solomon (Boston, USA); Frank van Leeuwen (Medtronic, CHE); Patrick Verta (Sunshine Heart, USA); Alphons Vincent (Medtronic, CHE); Hans Wedel (Gothenburg, SWE); Holger Woehrle (Resmed, GER); Faiez Zannad (Nancy, FRA)

FRIDAY 6 DECEMBER 2013

12.35 pm-3.15 pm MODIGLIANI CONFERENCE ROOM

MANAGEMENT OF CO-MORBIDITIES IN HEART FAILURE

Moderators: Ewa Jankowska (Wroclaw, POL); Christopher O'Connor (Durham, USA)

- Anemia and iron deficiency are common in patients with heart failure, and are associated with worse symptoms and adverse outcomes in this population. Although the two can occur together, anemia in HF is often not caused by iron deficiency, and iron deficiency can be present without causing anemia. New data on the importance of iron deficiency in HF have become available, and a number of studies with intravenous iron have shown promising results (FAIR-HF). Therefore, this treatment approach is likely to become an attractive option for patients with HF and iron deficiency.
- Sleep disordered breathing (SDB) is very common in patients with HF, with reported prevalence rates of 50-75%. The presence of SDB is associated with decreased survival in HF patients. The only randomized controlled trial investigating mortality in patients with HF treated with CPAP was the CANPAP study. The trial was stopped prematurely after enrolment of 258 of the planned 408 patients, and data analysis did not show a beneficial effect of CPAP treatment. However, a post-hoc analysis suggested that outcomes might be improved if SDB was well controlled. Studies to date have not been of adequate size or duration to determine whether therapy with CPAP is associated with significant reductions in morbidity and mortality in patients with HF and SDB. The SERVE-HF study was designed to address these issues and has recently completed enrolment.
- In the cardiorenal syndrome, the disappointing findings of the CARRESS-HF trial, coupled with previous similar studies, imply that although early aquapheresis could be advantageous for management of patients with acute heart failure, it might not be the ideal option for salvage therapy after development of diuretic resistance. However, UNLOAD and CARRESS-HF have excluded patients with more severe renal dysfunction. In the UNLOAD study, the 90-day HF re-hospitalization was a pre-specified secondary end-point and was positively influenced by aquapheresis.
- The aim of the AVOID-HF study is to confirm and expand the findings of UNLOAD that fluid removal by aquapheresis reduces HF rehospitalizations at 90 days as well as the length of these HF rehospitalizations. The AVOID-HF study is going beyond studying only the amount of fluid removal and will explore whether the modality of fluid removal influences HF outcomes.

Is anemia still a valid therapeutic target? Critical appraisal of TREAT and RED-HF
Aldo Maggioni (Florence, ITA)

Iron deficiency: what can we expect from ongoing trials of iron therapy ferric carboxymaltose (EFFECT-HF, CONFIRM-HF)?
Speaker: Ewa Jankowska (Wroclaw, POL)
Discussant: Claudio Mori (Vifor Pharma, CHE)

Sleep disordered breathing: insight from registry data and update on SERVE-HF morbidity-mortality trial
Speakers: Martin Cowie (London, GBR)
Discussant: Holger Woehrle (Resmed, GER)

Cardiorenal syndrome: critical appraisal of aquapheresis trials and opportunities with the ongoing AVOID-HF trial
Speaker: Javed Butler (Atlanta, USA)
Discussant: Christopher O'Connor (Durham, USA)

Moderated Discussion with Audience Participation

Panellists: Kirkwood Adams (Chapel Hill, USA); Javed Butler (Atlanta, USA); Jason A Campagna (Medco, USA); Blai Coll (Abbvie, USA); Martin Cowie (London, GBR); Ewa Jankowska (Wroclaw, POL); Keld Kjeldsen (Copenhagen, DEN); Carolyn Lam (Singapore, SGP); Aldo Maggioni (Florence, ITA); Claudio Mori (Vifor Pharma, CHE); Bertram Pitt (Ann Arbor, USA); Stuart Pocock (London, GBR); Gianpaolo Rossi (Padua, ITA); Patrick Rossignol (Nancy, FRA); Luis Ruilope (Madrid, ESP); Lars Christian Rump (Dusseldorf, GER); Adriaan Voors (Groningen, NED); Karen Wai (Quintiles, SGP); Holger Woehrle (Resmed, GER); Faiez Zannad (Nancy, FRA)

12.35 pm-3.15 pm SOUTINE / UTRILLO CONFERENCE ROOM

VASODILATORS IN ACUTE HEART FAILURE: HOW TO DESIGN SUCCESSFUL TRIALS?

Moderators: Alexandre Mebazaa (Paris, FRA); Naoki Sato (Tokyo, JAP)

- Many trials in acute heart failure failed. Despite disappointing results, a large number of trials are ongoing, mostly testing new vasodilators in acute heart failure. RELAX-HF was successful and confirms that vasodilators can improve short and long-term outcomes in acute heart failure.
- However, one of the major side effects of vasodilators is hypotension that may occur any time during the course of administration. Hypotension, in the context of old patients with many comorbidities might be very harmful. Are all the vasodilators equal to induce hypotension? Can we adjust inclusion and exclusion criteria to avoid side-effects of vasodilators?
- In order to avoid hypotension, many studies have recently increased the threshold of inclusion blood pressure. This might prevent hypotension. However, this will also select patients who are not those seen in our daily practice.

How can vasodilators save lives in acute heart failure?
Speaker: Dan Longrois (Paris, FRA)
Discussants: Marco Metra (Brescia, ITA); Johannes Holzmeister (Zurich, CHE)

Which data support beneficial effects of vasodilators?
Speaker: Alexandre Mebazaa (Paris, FRA)
Discussant: Lothar Roessig (Bayer, GER)

Hypotension is a major safety issue when assessing drugs with vasodilator properties
Mihai Gheorghiade (Chicago, USA)

How did I design my trial to be successful?
Speaker: Marco Metra (Brescia, ITA)
Discussant: Alexandre Mebazaa (Paris, FRA)

Moderated Discussion with Audience Participation
What is the pathway for a successful acute heart failure trial?

Panellists: Angeles Alonso (EMA, ESP); Rob Cody (J&J, USA); Nancy Cooks Bruns (Bayer, GER); Mihai Gheorghiade (Chicago, USA); Johannes Holzmeister (Zurich, CHE); Jae Kim (Amgen, USA); Dan Longrois (Paris, FRA); Alexandre Mebazaa (Paris, FRA); Marco Metra (Brescia, ITA); Arthur Mark Richards (Singapore, SGP); Lothar Roessig (Bayer, GER); Naoki Sato (Tokyo, JAP); Scott Solomon (Boston, USA); Faiez Zannad (Nancy, FRA)

FRIDAY 6 DECEMBER 2013

3.30 pm-7.30 pm MODIGLIANI CONFERENCE ROOM

THE ATHEROSCLEROSIS TRIALISTS FORUM: NEW LIPID ASSOCIATED TARGETS AND IMPROVED PATHWAY TO SUCCESSFUL CLINICAL TRIALS

Moderators: Wolfgang Koenig (Ulm, GER); Bart Staels (Lille, FRA)

- Despite widespread early intervention in acute coronary syndromes and complete revascularization of stenotic lesions complemented by aggressive polypharmacy, still a high percentage of patients develop a secondary event. This has been shown in various registries and recent data from the GRACE registry have suggested that we grossly underestimate long-term risk in these patients. Thus, despite all our current efforts there is room for improvement.
- A very active research program is delivering an important number of new potential therapeutic targets that may be ready for trial testing. A fairly large number of lipid-associated new targets or targets reflecting other pathways of the complex atherosclerotic process are being evaluated in mechanistic imaging studies but also in large outcome trials.
- Yet, phase III clinical endpoint trials evaluating treatments for atherosclerosis typically require very large sample sizes, cost hundreds of millions of dollars and historically have had very low success rates. As a result, few new therapies that attenuate the progression of atherosclerosis have been identified in over 30 years (since the discovery of statins), and actually many recent large trials were disappointingly “negative”.
- Nearly a decade ago, in recognition of the low success of phase III trials, regulatory agencies called for the adoption of new biomarkers or surrogate endpoints to enhance the rate of clinical development. To that end, several cardiovascular imaging technologies have gone through evolutionary cycles of validation over the past decade and several have demonstrated promise as clinical tools and as clinical trial biomarkers.
- With imaging biomarker tools as gatekeepers, only those treatments with proven efficacy during phase II trials would be promoted to phase III with the expectation of high likelihood of success in the clinical endpoint trials. By enhancing the success rate of phase III clinical trials, use of these imaging tools have the potential to accelerate the discovery of treatments for atherosclerosis.

Overview on potential new targets
Bart Staels (Lille, FRA)

Monoclonal antibody: for lipid lowering or for CV prevention?
Speaker: Evan Stein (Cincinnatti, USA)
Discussant: Scott Wasserman (Amgen, USA)

New targets based on antisense technology: ApoB, Lp(a), APO CIII, CRP
Walter Singleton (ISIS, USA)

What have we learned from recent “failed” trials?
Wolfgang Koenig (Ulm, GER)

Why are imaging endpoints needed in atherosclerosis clinical trials
Hector Garcia (Rotterdam, NED)

Established measures of atherosclerosis: IMT as a surrogate of vascular event risk?
Matthias Lorenz (Francfort, GER)

Tomographic measures of atherosclerosis: CTA and MRI
Udo Hoffmann (Boston, USA)

New multi-modality measures of atherosclerosis: PET-CT and PET-MRI
Ahmed Tawakol (Boston, USA)

Industry perspective: David Kallend (MedCo, USA); Walter Singleton (ISIS, USA); Scott Wasserman (Amgen, USA)

Regulatory perspective: What kind of data may be needed for a go or no go decision in drug development?
Kiyoshi Nobori (PMDA, JAP); Ferran Torres (EMA, ESP)

Moderated Discussion with Audience Participation
Is there a safer trial pathway for a more successful delivery of new atherosclerosis therapies?

- Where do we go from here? Do we need new trial designs? The end of one size fits all?
- Personalized/individualized approach using adequate markers to identify suitable patients for specific treatments: e.g. CRP (CANTOS), Lp-PLA2 activity (STABILITY, SOLID)
- Can Omics technologies help to generate such markers?
- Need for prospective validation of surrogate biomarkers (Some data for IVUS, controversial data on IMT, no data for PET/MRI)
- What methods can be successfully combined on the way to Phase III trials? (Imaging, biomarkers, mendelian randomization results?)

Panellists: Stefan Agewall (Oslo, NOR); Henry Black (New York, USA); Denise Bonds (NHLBI, USA); Gonzalo Calvo (Barcelona, ESP); Edoardo Camenzind (Geneva, CHE); Gheorghe-Andrei Dan (Bucharest, ROM); Kristina Dunder (EMA, SWE); Hector Garcia (Rotterdam, NED); David Gordon (NHLBI, USA); Udo Hoffmann (Boston, USA); David Kallend (MedCo, USA); Jae Kim (Amgen, USA); Wolfgang Koenig (Ulm, GER); Basil Lewis (Haïfa, ISR); Matthias Lorenz (Frankfurt, GER); Kiyoshi Nobori (PMDA, JAP); Yves Rosenberg (NHLBI, USA); André Scheen (Liège, BEL); Harald Schmidt (Maastricht, NED); Kaori Shinagawa (PMDA, JAP); Tabassome Simon (Paris, FRA); Walter Singleton (ISIS, USA); Moncef Slaoui (GSK, GBR); Bart Staels (Lille, FRA); Evan Stein (Cincinnati, USA); Ahmed Tawakol (Boston, USA); Christian Torp-Pedersen (Copenhagen, DEN); Ferran Torres (EMA, ESP); Gilbert Wagener (Genzyme, GER); Scott Wasserman (Amgen, USA); Hans Wedel (Gothenburg, SWE)

FRIDAY 6 DECEMBER 2013

3.30 pm-5.30 pm SOUTINE / UTRILLO CONFERENCE ROOM

International Society of Cardiovascular Pharmacology (ISCP-CVCT) joint session

CORONARY ARTERIAL DISEASE TRIALS:

CHANGE IN PRACTICE AND CHANGE IN PATHOPHYSIOLOGICAL UNDERSTANDING

Moderators: Gheorghe-Andrei Dan (Bucharest, ROM); Felipe Martinez (Cordoba, ARG)

- The results of COURAGE and of other trials suggest that stent therapy will improve symptoms and reduce the likelihood of needing a subsequent interventional procedure, but we still do not know whether this therapy improves survival and the risk of MI. The NIH funded ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) is still to deliver an answer to this question.
- The evidence base to support the recommendation for the use of beta-blockers after MI dates back to the mid-1980s. In the past 25 years, the introduction of coronary reperfusion and of effective non-reperfusion therapies has changed the natural history of MI and there have been substantial changes in the definition of MI. Recent analyses have questioned the widespread use of beta-blockers as first-line therapy in patients with stable coronary heart disease and no LV dysfunction.
- New anti-anginal, heart rate slowing non beta-blocker drugs.

Clinical utility of coronary investigations in stable CAD patients
Gilles Montalescot (Paris, FRA)

Is there still a need to treat angina? Trial population vs. real-life population: lessons from CLARIFY
Nicolas Danchin (Paris, FRA)

Antianginal vs. anti-ischemic vs. disease modifier drugs: evidence-based drug therapy in stable CAD patients
Marco Metra (Brescia, ITA)

Evidence for beta-blocker in post MI patients without LVD, still valid?
Giuseppe Rosano (EMA, ITA)

Moderated Discussion with Audience Participation
Where does drug therapy fit in the management of coronary artery disease in the age of PCI?

Panellists: Angeles Alonso (EMA, ESP); Farzin Beygui (Caen, FRA); Edoardo Camenzind (Geneva, CHE); Gheorghe-Andrei Dan (Bucharest, ROM); Nicolas Danchin (Paris, FRA); Dayi Hu (Beijing, CHN); Guy Lerebours (Servier, FRA); Felipe Martinez (Cordoba, ARG); Marco Metra (Brescia, ITA); Gilles Montalescot (Paris, FRA); Giuseppe Rosano (EMA, ITA); Juan Tamargo (Madrid, ESP); Stephan Windecker (Bern, CHE)

5.45 pm-7.30 pm SOUTINE / UTRILLO CONFERENCE ROOM

REFINING CARDIAC RESYNCHRONIZATION AND IMPLANTABLE DEFIBRILLATOR THERAPY

Moderators: Gaetano DeFerrari (Pavia, ITA); Cecilia Linde (Stockholm, SWE)

- Inappropriate shock with CRT-D and ICD devices may be a barrier to therapy. Better programming or new algorithms can solve this. MADIT-RIT and ADVANCE III studies have enrolled different kind of patients, which is important to realize and discuss to give it the right interpretation.
- The BLOCK HF study was recently published in the NEJM (CRT-P in AV block with EF below 50%) and the results were incorporated in the new ESC guidelines for Cardiac Pacing and Cardiac Resynchronization Therapy. How important are these data to move from CRT as a therapy for heart failure to CRT to prevent heart failure is a matter for debate.
- The EchoCRT trial was recently halted due to futility. (Although patients and investigators have been informed of the early stopping, no public announcement by the company or the sponsor has been made to date.) The trial had been designed to evaluate the effect of CRT on morbidity and mortality in heart failure patients with a narrow QRS (< 130 ms) and with echo evidence of dyssynchrony. Results of the trial are expected to be presented at a medical meeting in the near future. However, it appears unlikely that they will support an expanded FDA indication for CRT or that another large trial will be performed in this population
- Other trials include the recently initiated MIRACLE EF trial, which is looking at CRT as a primary treatment in heart failure patients with LBBB and mild LV dysfunction, and the ongoing PROMPT trial, which is evaluating LV or biventricular pacing as a treatment to prevent adverse myocardial remodeling early after myocardial infarction.

Evidence based progress in ICD therapy: new algorithms, better programming, subcutaneous ICDs
Maurizio Gasparini (Rozzano, ITA)

CRT solutions for slowing the progression of LV dysfunction: insight from BLOCK-HF, and expectations from MIRACLE EF and PROMPT trials
Speaker: Cecilia Linde (Stockholm, SWE)
Discussant: Claude Daubert (Rennes, FRA)

LBBB, QRS cut offs and echo dyssynchrony any reason to revise the CRT guidelines?
Speaker: Johannes Holzmeister (Zurich, CHE)
Discussant: Gaetano DeFerrari (Pavia, ITA)

Industry perspective: Thierry Pochet (Boston Scientific, BEL); Alphons Vincent (Medtronic, CHE)

Moderated Discussion with Audience Participation
Putting evidence into clinical practice

Panellists: Claude Daubert (Rennes, FRA); Gaetano DeFerrari (Pavia, ITA); Maurizio Gasparini (Rozzano, ITA); Edoardo Gronda (Milan, ITA); Johannes Holzmeister (Zurich, CHE); Torsten Kayser (Boston Scientific, BEL); Cecilia Linde (Stockholm, SWE); Tim Meyer (Boston Scientific, USA); Thierry Pochet (Boston Scientific, BEL); Alphons Vincent (Medtronic, CHE)

SATURDAY 7 DECEMBER 2013

8.00 am-12.25 pm MODIGLIANI CONFERENCE ROOM

ACUTE HEART FAILURE AND HEART FAILURE WITH PRESERVED EJECTION FRACTION: THE NEXT FRONTIER

Moderators: Mihai Gheorghiade (Chicago, USA); Burkert Pieske (Graz, AUT)

Despite the disappointing results of aliskiren in the acute heart failure trial ASTRONAUT, and the intriguing finding of benefit possibly only in the non-diabetes patients, ATMOSPHERE is still ongoing in CHF patients with low EF.

So many acute heart failure trials failed. Most recently, RELAX-HF was the very first trial to show that a short term IV administration of a drug could have long-term clinical benefit, in addition to short-term relief of dyspnea.

- The hypothesis that acute drug administration might protect against the long-term consequences of acute heart injury is supported by a wealth of biomarker data.
- However, a second confirmatory trial might be needed in order to understand the long-term mortality benefit with no significant effect on the rate of HF readmission.
- Other original findings are the equal effect in HFREF and HFPEF.
- Other opportunities are exploring the efficacy of super early administration.

The very first HFPEF trials were complex to perform, took very long to enroll patients or had neutral results. More recent trials adopted different strategies attempting to better define patient populations enrolled in the trials.

- Is it possible to homogenize the heterogeneous HF-PEF population?
- What approaches are most promising? (e.g. biomarkers, hemodynamics, echo parameters, omics, other?)
- How to better target a primary pathophysiology?
- How soon after heart failure admission should patients be ideally enrolled?
- How to deal with the confounding role of concomitant comorbidity?
- What are the implications for industry?

Insight from epidemiology
Carolyn Lam (Singapore, SGP)

Mechanisms and clinical relevance of insufficient sGC/cGMP signaling and oral sGC stimulators compared with other pathways to treat cGMP deficiency in HF
Speaker: Dirk L. Brutsaert (Antwerp, BEL)
Discussant: Javed Butler (Atlanta, USA)

sGC stimulator SOCRATES programme and future trials
Mihai Gheorghiade (Chicago, USA)

TOPCAT, lessons learned and implications for clinical practice and for the design and conduct of future trials
Speaker: Bertram Pitt (Ann Arbor, USA)
Discussant: Faiez Zannad (Nancy, FRA)

Serelaxin in acute heart failure. Equally effective in HFREF and HFPEF?
Adriaan Voors (Groningen, NED)

LCZ696D: from PARAMOUNT to PARAGON, the ultimate design?
Speaker: Scott Solomon (Boston, USA)
Discussant: Martin Lefkowitz (Novartis, USA)

Drugs and trials on the horizon: Soluble Guanylate Cyclase stimulator, and PDE inhibitors
Speaker: Alexandre Mebazaa (Paris, FRA)
Discussants: Burkert Pieske (Graz, AUT); Lothar Roessig (Bayer, GER)

Moderated Discussion with Audience Participation

Panellists: Kirkwood Adams (Chapel Hill, USA); Angeles Alonso (EMA, ESP); Dirk L. Brutsaert (Antwerp, BEL); Javed Butler (Atlanta, USA); Jason A Campagna (Medco, USA); Blai Coll (Abbvie, USA); Alan Fraser (Cardiff, GBR); Mihai Gheorghiade (Chicago, USA); Jae Kim (Amgen, USA); Carolyn Lam (Singapore, SGP); Martin Lefkowitz (Novartis, USA); Aldo Maggioni (Florence, ITA); Alexandre Mebazaa (Paris, FRA); Burkert Pieske (Graz, AUT); Bertram Pitt (Ann Arbor, USA); Stuart Pocock (London, GBR); Arthur Mark Richards (Singapore, SGP); Lothar Roessig (Bayer, GER); Naoki Sato (Tokyo, JAP); Scott Solomon (Boston, USA); Adriaan Voors (Groningen, NED); Karen Wai (Quintiles, SGP); Faiez Zannad (Nancy, FRA)

SATURDAY 7 DECEMBER 2013

8.00 am-12.25 pm SOUTINE / UTRILLO CONFERENCE ROOM

INTERVENTIONAL CARDIOLOGY TRIALISTS WORKSHOP: DES AND DAPT TRIAL AND IMPLEMENTATION ISSUES

Moderators: Ileana Piña (New York, USA); Patrick Serruys (Rotterdam, NED)

- Among the statutory obligations of the US Food and Drug Administration to regulate the marketing of cardiovascular devices based on valid scientific evidence, the use of Objective Performance Criteria and Goals (OPC and OPG) for the evaluation of cardiovascular devices has become established as an alternative to randomized, controlled trials (RCTs). These single-armed comparisons may facilitate rapid entry of novel devices to the market. Unlike RCTs, they do not establish superiority or non-inferiority of the examined therapy, and study populations must be carefully inspected to ensure validity of comparisons to historical controls. The OPC model allows rapid entry of innovative devices to the market. How to secure that innovations reaching the market translate into safe and effective therapies based on clinical and cost effectiveness endpoints is a matter of debate.
- Durable polymer coatings on drug-eluting stents have been associated with chronic inflammation and impaired healing. Bioabsorbable polymer-coated drug-delivery systems may reduce the risk of late adverse events, including stent thrombosis, and thus the need for prolonged dual-antiplatelet therapy. Optimal duration of dual-antiplatelet after drug-eluting stents has become a matter of debate with some defending prolonged duration and others – based on recent studies and analysis – short-term use.
- Results from the PROTECT trial suggest that information about stent thrombosis rate with a given drug-eluting device has to be assessed with caution and always in perspective of the concomitant dual antiplatelet therapy treatment and duration of follow-up.
- Although prasugrel is an effective and relatively safe agent in the invasive management of ACS, will comparative effectiveness and/or registry data better inform on whether we should refrain from giving it upfront before the cathlab, or from giving it late in patients on clopidogrel? Or is ticagrelor the better choice for all options in ACS?
- There are several limitations of available oral antiplatelet drugs when they are used for urgent or periprocedural treatment of patients with cardiovascular disease who may undergo PCI, including a delayed onset of action. Intravenous glycoprotein IIb/IIIa inhibitors, like abciximab can be effective in reducing the incidence of ischemic events, but their effects last long and cannot be quickly reversed. Whether cangrelor, a potent, intravenous, fast acting, and reversible antiplatelet agent could address this unmet clinical need has been addressed by the recently published CHAMPION PHOENIX trial. Where this new therapy may fit within the current antiplatelet armamentarium is a new matter of debate.

Justifying an objective performance criteria (OPC) model for drug-eluting stents approval: general principles

Clinical perspectives:
EU: Patrick Serruys (Rotterdam, NED)
USA: Ileana Piña (New York, USA)

Bioabsorbable Polymer Delivery and Bioabsorbable Scaffolds: from OPC to clinical benefit
Speakers: Robert Byrne (Munich, GER); Adnan Kastrati (Munich, GER)

Current long-term DAPT studies: does it really matter?
Gregg Stone (New York, USA)

Targeting DAPT to time dependent risk
Edoardo Camenzind (Geneva, CHE)

More potent DAPT for more complex PCI: label expansion from ACS to stable disease?
Stephan Windecker (Bern, CHE)

What does Cilostazol have to offer?
Young-Hoon Jeong (Jinju, KOR)

Regulatory perspectives: Andrea Laslop (EMA, AUT); Krishna Prasad (MHRA, GBR)

Industry perspectives: Gunnar Olsson (previously Astrazeneca, SWE); David Rutledge (Abbott Vascular, USA)

Moderated Discussion with Audience Participation
How to improve OPCs for DES? Dual Antiplatelet therapy after DES

Panellists: Robert Byrne (Munich, GER); Edoardo Camenzind (Geneva, CHE); Mark Chan (Singapore, SGP); Young-Hoon Jeong (Jinju, KOR); Adnan Kastrati (Munich, GER); Torsten Kayser (Boston Scientific, BEL); Wolfgang Koenig (Ulm, GER); Tim Laske (Medtronic, USA); Andrea Laslop (EMA, AUT); Gunnar Olsson (previously Astrazeneca, SWE); Ileana Piña (New York, USA); Krishna Prasad (MHRA, GBR); David Rutledge (Abbott Vascular, USA); Patrick Serruys (Rotterdam, NED); Kaori Shinagawa (PMDA, JAP); Gregg Stone (New York, USA); Frank van Leeuwen (Medtronic, CHE); Stephan Windecker (Bern, CHE)

SATURDAY 7 DECEMBER 2013

12.35 pm-3.00 pm MODIGLIANI CONFERENCE ROOM

MINERALOCORTICOID RECEPTOR ANTAGONISTS: THE KIDNEY, THE HEART AND BEYOND

Moderators: John Funder (Melbourne, AUS); Bertram Pitt (Ann Arbor, USA)

- Despite their proven benefits in large-scale, prospective, double-blind, randomized trials and recommendations for their use included in international guidelines, adoption of optimal therapy including Mineralocorticoid receptor antagonists (MRAs) is slow and mainly hindered by concerns over the risk of hyperkalemia, especially in the elderly and in patients with concomitant CKD and diabetes
- Hyperkalemia may result from the use of multiple renin-angiotensin-aldosterone inhibitors or blockers, particularly in patients with heart failure and concomitant chronic kidney disease. Interventions to reliably control serum potassium during renin-angiotensin-aldosterone inhibition have not been available to date, and would be of particular value with the use of mineralocorticoid receptor antagonists that have been shown to reduce mortality in patients with heart failure and a reduced left ventricular ejection fraction.
- Whether potassium-binding polymers may lower the incidence of hyperkalemia and allow a higher proportion of heart failure patients to receive life saving multiple renin-angiotensin-aldosterone inhibitors is an attractive solution being currently tested in several clinical trials.
- Prevention of heart failure is high on the agenda. Although there is no low hanging fruits, metabolic syndrome, diabetes, CKD, resistant hypertension and a whole host of potential indications offer important opportunities for novel agents action on the aldosterone pathways.

Beyond spironolactone and eplerenone, there is a need for more selective, better-tolerated MRAs. The next generation of MRAs has entered the clinical trial development phase (ARTS trials with FINERENONE, Mitsubishi agent). How to position them vis-a-vis the available MRAs in heart failure needs creativity in designing novel trials with more focused patient populations.

Sudden cardiac death and other risks related to hypo- and hyperkalemia as triggers. What is the evidence?
Keld Kjeldsen (Copenhagen, DEN)

Interpreting renal function changes and hyperkalemia under multiple RAAS blockade in heart failure: trial and registry data
Speaker: Patrick Rossignol (Nancy, FRA)
Discussant: Scott Solomon (Boston, USA)

How to predict, prevent, and manage hyperkalemia with RAAS inhibitor and MRA therapy: need for and approvability of potassium binding polymers
Bertram Pitt (Ann Arbor, USA)

Can mineralocorticoid receptor antagonist be kidney friendly? Insight from ARTS trials, and opportunities for expanding MRA therapy
Speaker: Faiez Zannad (Nancy, FRA)
Discussant: Frank Eitner (Bayer, GER)

What is in the pipeline? Next generation MRAs and aldosterone synthase inhibitors
Speaker: John Funder (Melbourne, AUS)
Discussants: Michel Azizi (Paris, FRA); Peter Kolkhof (Bayer, GER)

Moderated Discussion with Audience Participation
The future of MRA therapy

Panellists: Kirkwood Adams (Chapel Hill, USA); Angeles Alonso (EMA, ESP); Michel Azizi (Paris, FRA); Lance Berman (Relypsa, USA); Javed Butler (Atlanta, USA); Frank Eitner (Bayer, GER); John Funder (Melbourne, AUS); Qifang Huang (Shanghai, CHN); Keld Kjeldsen (Copenhagen, DEN); Peter Kolkhof (Bayer, GER); Stuart Kupfer (Takeda, USA); Felippe Martinez (Cordoba, ARG); Christopher O'Connor (Durham, USA); Bertram Pitt (Ann Arbor, USA); Arthur Mark Richards (Singapore, SGP); Giuseppe Rosano (EMA, ITA); Gianpaolo Rossi (Padua, ITA); Patrick Rossignol (Nancy, FRA); Danni Shi (Novartis, CHN); Scott Solomon (Boston, USA); Faiez Zannad (Nancy, FRA)

12.35 pm-3.00 pm SOUTINE / UTRILLO CONFERENCE ROOM

NEURAL MODULATION TRIALS: TIME TO MOVE FROM PROOF OF CONCEPT TO OUTCOME TRIALS?

Moderators: Paul Hauptman (Saint Louis, USA); John Bisognano (Rochester, USA)

Trials: SYMPLICITY-HTN, SYMPLICITYHF; NNEOS, DENER-HTN, NECTAR-HF, INSPiRED, DERENEDIAB; PRAGUE-15, DREAMS; ACHIEVE; RENSYMPIS; EnligHTN II; REACH; SAVE; H-FIB; RSDforAF; RESCUE-VT; ANTHEM-HF; INOVATE-HF; STARTSTIM; Defeat-HF, HOPE4HF.

Resistant hypertension: is lowering BP also a valuable surrogate in device trials?

- **Renal denervation**
  Georges Bakris (Chicago, USA)
- **Barostimulation**
  Speaker: John Bisognano (Rochester, USA)
  Discussant: Rolf Wachter (Göttingen, GER)

Heart failure: what is being learnt from POC trials?

- **Renal denervation**
  Atul Pathak (Toulouse, FRA)
- **Vagal modulation**
  Speaker: Paul Hauptman (Saint Louis, USA)
  Discussant: Gaetano DeFerrari (Pavia, ITA)
- **Barostimulation**
  Speaker: Rolf Wachter (Göttingen, GER)
  Discussant: John Bisognano (Rochester, USA)

Angina, arrhythmias, CKD, metabolic syndrome and other potential indications: would neural modulation become a cure-all therapy?

Speaker: Edoardo Gronda (Milan, ITA)
Discussant: Stephan Windecker (Bern, CHE)

Industry perspective: Scott Meyer (Boston Scientific, USA); Dan Schaber (Medtronic, USA)

Moderated Discussion with Audience Participation
What level of evidence? Effectiveness and Cost-effectiveness issues

Panellists: William Abraham (Columbus, USA); Georges Bakris (Chicago, USA); John Bisognano (Rochester, USA); Gaetano DeFerrari (Pavia, IT); Neal Eigler (St. Jude Medical, USA); Edoardo Gronda (Milan, ITA); Paul Hauptman (Saint Louis, USA); Torsten Kayser (Boston Scientific, BEL); Scott Meyer (Boston Scientific, USA); Atul Pathak (Toulouse, FRA); Ileana Piña (New York, USA); Dan Schaber (Medtronic, USA); Frank van Leeuwen (Medtronic, CHE); Rolf Wachter (Göttingen, GER); Stephan Windecker (Bern, CHE)

SATURDAY 7 DECEMBER 2013

3.20 pm-6.20 pm MODIGLIANI CONFERENCE ROOM

LESSONS FROM FIRST POST FDA GUIDANCE CASE STUDIES OF DIABETES CV OUTCOMES TRIALS

Moderators: Michel Marre (Paris, FRA); William White (Farmington, USA)

- Improved glycemic control has been shown to reduce the risk of many of the microvascular complications of diabetes. However, recent studies have not yet determined a similar impact for glycemic control in reducing macrovascular events in moderate CV risk patients. Rather, there has been concern regarding the association of anti-diabetic agents with negative CV outcomes.
- Consequently, the FDA released a guidance that outlines a new approach to CV safety requirements, designed to gather sufficient data during a development program to show that new anti-diabetic therapies are not associated with an unacceptable increase in CV risk. A large number of trials have since been initiated, adhering to the new guidance.
- As mandated by the FDA, trials should attempt to rule out a pre-approval level of risk (inferiority margin 1.8) following approximately 1 year of treatment in a portion of the study population but then continuing the study for up to 3 to 4 additional years to continue to collect CV safety data (inferiority margin 1.3). However in a number of trials, while the intent is to first rule out harm of the study drug, there is also the possibility that some new agents may reduce CV harm and, in many trials, testing for superiority of the agent over that of placebo is part of the analysis plan if non-inferiority is proven.
- Fundamental to this study design was the capacity to prevent the release of interim data defining the effects of the compound on cardiovascular outcomes in the review process of the data by the regulators when the 1.8 non inferiority margin is achieved, until the 1.3 margin is achieved next, or until study completion if the trial is planned for superiority. The steering committees must struggle with creative ways to prevent significant breach in the integrity of the trial.
- The EXAMINE and SAVOR-TIMI 53 trials represent the first studies completed in adherence with the post-FDA new guidance, reporting the results of DPP-4 inhibitors (Alogliptin, Saxagliptin) in diabetic patients with CV risk. The trials are quite different, while EXAMINE aimed at non inferiority, SAVOR also aimed at superiority, and finally both met the non inferiority objective with MACE as the primary endpoint. Debate is to be expected regarding secondary outcomes.
- In the CANVAS trial, yet with another class of drug, the SGLT2 inhibitor Canagliflozin, a strategy that would ensure concealment of the hazard ratio for the primary outcome was not implemented, and the sponsor elected to un-blind the data to obtain better insight into the effects of the compound while preparing materials for submission to the regulators. Accordingly, recruitment to the second phase of the study was stopped and a separate large outcome trial is being considered.
- Following another strategy, Sanofi recently announced its decision to withdraw the lixisenatide NDA in the US, which included early interim results from the ongoing ELIXA cardiovascular outcomes study. The company plans to resubmit the NDA after completion of the trial. The decision to withdraw the lixisenatide application follows discussions with the FDA regarding its proposed process for the review of interim data. Sanofi believes that potential public disclosure of early interim data could potentially compromise the integrity of the ongoing study.
- Finally, Novo Nordisk recently announced that it received a Complete Response Letter from the FDA regarding the New Drug Applications for insulin degludec and insulin degludec/insulin aspart requesting post-approval cardiovascular outcomes trial commitment.
- From the kidney protection side, patients with diabetic nephropathy represent a high unmet medical need. Glycemic control in type 2 diabetes is not automatically translated into improved kidney outcomes.. Endothelin receptor antagonists are a promising class of drugs, although the risk of fluid retention and congestive heart failure has driven some programs to be prematurely stopped. The program with atrasentan (two completed phase 2b studies and an ongoing phase 3 registration trial is specifically addressing this risk.

The goal of this session is to use the recently available data as first real case-studies discussing the appropriateness and challenges of FDA Guidance trials to establish the CV safety of diabetes agents, and discuss the likely important consequences on ongoing trials in the area, as well as the area of CV safety of weight loss drug.

Where are the unmet needs? The challenge of CV prevention: blood glucose, blood pressure and blood lipids
Dayi Hu (Beijing, CHN)

Results of and lessons from the first CV safety trials of oral diabetes drugs, in the new FDA regulation environment

- **The EXAMINE trial** William White (Farmington, USA)
- **The SAVOR TIMI 53 trial** Ofri Mosenzon (Jerusalem, ISR)
- **Other ongoing diabetes CV safety trials: the various scenarii of interim or no interim results for approval**
  Harald Sourij (Oxford, GBR)

Clinical perspective: The cardiologist view: Faiez Zannad (Nancy, FRA)
The diabetologist view: Michel Marre (Paris, FRA)

Operational challenges in conducting FDA guidance diabetes CV safety trial

- **Industry perspective:** Christoph Koenen (BMS, FRA), Stuart Kupfer (Takeda, USA); Christina Stahre (Astrazeneca, SWE)
- **Regulatory perspective:** Angeles Alonso (EMA, ESP); Kristina Dunder (EMA, SWE)

Atrasentan for the treatment of diabetic nephropathy: how to control the risk of heart failure?

Speaker: Peter McCullough (Novi, USA)
Discussant: Blai Coll (Abbvie, USA)

Why and how to think about Rule Out trials: Ray Lipicky (North Potomac, USA)

Moderated Discussion with Audience Participation
Updating the guidelines and changing practice

Panellists: Angeles Alonso (EMA, ESP); George Bakris (Chicago, USA); Henry Black (New York, USA); Jeffrey Borer (New York, USA); Gonzalo Calvo (Barcelona, ESP); Blai Coll (Abbvie, USA); Wesley Day (Vivus, USA); Kristina Dunder (EMA, SWE); Mads David Engelmann (Novonordisk, DEN); David Gordon (NHLBI, USA); Samy Hadjadj (Poitiers, FRA); Peter Held (Astrazeneca, SWE); Dayi Hu (Beijing, CHN); Christoph Koenen (BMS, FRA); Wolfgang Koenig (Ulm, GER); Stuart Kupfer (Takeda, USA); Ray Lipicky (North Potomac, USA); Michel Marre (Paris, FRA); Peter McCullough (Novi, USA); Ofri Mosenzon (Jerusalem, ISR); Alfonso Perez (Takeda, USA); Beth Anne Piper (Pfizer, USA); André Scheen (Liège, BEL); Harald Schmidt (Maastricht, NED); Harald Sourij (Oxford, GBR); Christina Stahre (Astrazeneca, SWE); Juan Tamargo (Madrid, ESP); Bart Van der Schueren (EMA, BEL); William White (Farmington, USA); Faiez Zannad (Nancy, FRA)

SATURDAY 7 DECEMBER 2013

3.20 pm-5.30 pm SOUTINE / UTRILLO CONFERENCE ROOM

CARDIOVASCULAR MEDICAL DEVICE INNOVATION: BARRIERS AND SOLUTIONS

Moderators: Ileana Piña (New York, USA); Patrick Serruys (Rotterdam, NED)

- A new regulation to govern the evaluation and approval of medical devices in Europe is as an important step towards improving patient safety. The European Society of Cardiology (ESC) have outlined five suggestions that they feel would make the legislation stronger: a requirement to establish the clinical efficacy of certain new high-risk devices, greater transparency, a formalized European system for obtaining expert scientific and medical advice, specialisation of Notified Bodies evaluating high-risk medical devices, the establishment of independent post-market surveillance.
- The FDA Safety and Innovation Act (FDASIA) includes the Medical Device User Fee Amendments of 2012 (MDUFA III) as well as other medical device provisions. MDUFA includes performance goals. These will change the way the FDA approves clinical trials, provide a new de novo pathway for risk-based classification of devices, expand FDA's post-market surveillance capabilities, and change the process for reclassification of devices.
- The FDA has recently published for consultation a guidance document developed to facilitate the initiation of clinical investigations to evaluate medical devices.

The FDA's Safety and Innovation Act: impact of FDASIA on clinical trials
Randall Brockman (FDA, USA)

The European Innovation Strategies
Alan Fraser (Cardiff, GBR)

Challenges from the prospective of a clinician
Patrick Serruys (Rotterdam, NED)

Challenges from the perspective of a statistician/trialist
Stuart Pocock (London, GBR)

A view from industry on global harmonization
David Rutledge (Abbott Vascular, USA)

Moderated Discussion with Audience Participation
Gobal cross talk - a view to the future

Panellists: William Abraham (Columbus, USA); Randall Brockman (FDA, USA); Edoardo Camenzind (Geneva, CHE); Gaetano DeFerrari (Pavia, ITA); Neal Eigler (St. Jude Medical, USA); Alan Fraser (Cardiff, GBR); Torsten Kayser (Boston Scientific, BEL); Tim Laske (Medtronic, USA); Kiyoshi Nobori (PMDA, JAP); Ileana Piña (New York, USA); Stuart Pocock (London, GBR); Luis Rios-Nogales (Gambro, USA); David Rutledge (Abbott Vascular, USA); Patrick Serruys (Rotterdam, NED); Frank van Leeuwen (Medtronic, CHE); Patrick Verta (Sunshine Heart, USA); Alphons Vincent (Medtronic, CHE); Stephan Windecker (Bern, CHE)

CVCT YOUNG TRIALISTS MENTORING

Global CVCT Forum supports **Young Investigators** through a grant scheme enabling them to access and participate to CVCT Forum, an event dedicated to clinical trials in cardiovascular disease, with the aim of making them learn from and network with key decision makers, principal investigators, sponsors, and regulatory experts, and shape their future practice toward CV clinical trial related activities.

The Grant includes one full scientific registration to attend CVCT 2013 in Paris as well as hotel accommodation and a 200 EUR travel grant.

Our scientific committee learns about candidates in the following ways:

1. **Grant applications that may be submitted via the CVCT website - www.globalcvctforum.com**
2. **Nomination by CVCT Faculty members -** CVCT Meetings are supported by unrestricted educational grants with no allocation for speakers' fees. In recognition the valued contribution of faculty members and with a view to attracting **Young Investigators** to the field of cardiovascular clinical trial science, CVCT invites Faculty members to recommend one fellow who could be invited to attend the CVCT Forum.

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We are very pleased to offer a complete record of previous CVCT Forum presentations, including the webcast programs of 2011 and 2012, freely available on our website: **www.globalcvctforum.com**

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The dedicated CVCT writing group produces manuscripts resulting from high-level scientific discussions at the CVCT Forum, working with key faculty and leadership from the sessions.

The composition of the writing group includes the CVCT Course Directors, Drs. Zannad and Pitt; Dr. Christopher O'Connor as the Chair of the publications committee, and Dr. Mona Fiuzat as the Director of the editorial board and writing group; along with junior faculty or fellows who have been identified as members.

The following topics will be highlighted in the publications following CVCT 2013:

- Acute heart failure including preserved EF: a focus on trial methodology
- Acute heart failure and vasodilators
- CRT and device implantation
- Comorbidities in heart failure
- MRA updates – TOPCAT; from HF to kidneys
- Devices and biomarkers to guide care – methodologic issues
- Atherosclerosis – new lipid targets and imaging modalities
- Device innovation (new regulations)

CVCT publications reference list

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CVCT FORUM IS ENDORSED BY

Cardiovascular Pharmacology and Drug Therapy
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10th Global CardioVascular Clinical Trialists Forum

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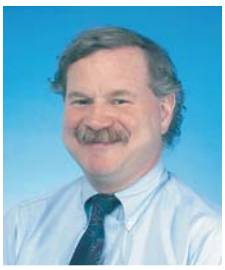
SPEAKER BIOGRAPHIES AND ABSTRACTS

William Abraham (Columbus, USA)

William T. Abraham MD, F.A.C.P., F.A.C.C., F.E.S.C. is Chair of Excellence in Cardiovascular Medicine, Professor of Internal Medicine, Physiology and Cell Biology and Chief of the Division of Cardiovascular Medicine at The Ohio State University College of Medicine. He also serves as Deputy Director of the Dorothy M. Davis Heart and Lung Research Institute. Dr. Abraham earned his medical degree from Harvard Medical School in Boston, Massachusetts, following which he completed his residency in Internal Medicine and fellowships in Cardiovascular Disease and Advanced Heart Failure and Transplant Cardiology at the University of Colorado Health Sciences Center. He previously held faculty appointments at the University of Colorado, the University of Cincinnati, and the University of Kentucky. He is board certified in Internal Medicine, Cardiovascular Diseases, and Advanced Heart Failure and Transplant Cardiology. Dr. Abraham's research interests include hemodynamic and neurohormonal mechanisms in heart failure, sleep disordered breathing in heart failure, and clinical drug and device trials in heart failure and cardiac transplantation. Dr. Abraham has received grants from the National Institutes of Health, American College of Cardiology, and Aetna Quality Care Foundation and has participated as a site Principal Investigator in more than 100 multicenter clinical drug and device trials. He has also served as national or international Principal Investigator and on the Steering Committees of more than 30 multicenter clinical drug and device trials. In addition to authoring more than 600 original papers, abstracts, book chapters, and review articles, Dr. Abraham has co-edited a leading textbook on heart failure entitled Heart Failure: A Practical Approach to Treatment. *Dr. Abraham serves on the editorial boards of several major journals including the* European Heart Journal *(International Associate Editor),* Congestive Heart Failure *(Assistant Editor), and* Journal Watch Cardiology *(Contributing Editor). Dr. Abraham has been recognized as one of the "Best Doctors in America" for ten consecutive years.*



Kirkwood Adams (Chapel Hill, USA)

Kirkwood F. Adams Jr., MD, is Associate Professor of Medicine and Radiology in the Division of Cardiology, University of North Carolina at Chapel Hill, where he founded and for many years directed the UNC Heart Failure Program and served as the first transplant cardiologist for two decades. helping to establish this treatment at UNC. Dr. Adams is currently involved in numerous research activities related to heart failure with particular focus on novel drug development in acute heart failure and translational research concerning the identification and clinical application of cardiovascular biomarkers and pharmacogenomics. Dr. Adams received his medical degree from the University of North Carolina. He did his internship and residency at North Carolina Memorial Hospital, where he also completed a fellowship in cardiology. He is a diplomate of the American Board of Internal Medicine, with subspecialty certification in cardiology. Dr. Adams has been involved in more than 120 completed grant- and industry-funded research projects, and he is currently leading or participating in five drug development trials, several registry and database studies, and has recently been involved in three NHLBI-funded trials: ACTION (investigating outcomes of exercise training in patients with heart failure), DISCOVER (investigating stress and heart failure), and ESCAPE (role of right heart catheterization in the management of advanced heart failure). Dr. Adams is the principal investigator for the national multicenter database group, UNITE-HF, which focuses on registries of patients with heart failure. Through his leadership, this group has published extensively on the prevalence and relationship to quality of life of anemia in heart failure, and the association of various biomarkers with anemia of heart failure. Dr. Adams has served as editorial advisor to American Heart Journal, Journal of Cardiac Failure, and TheHeart.org. *Dr. Adams has also been a reviewer for a number of cardiovascular journals. He has published more than 150 manuscripts in refereed journals, a number of book chapters and monographs, and more than 150 abstracts.*

Angeles Alonso (EMA, ESP)

Honorary Senior Lecturer, Cardiovascular Sciences Research Centre. St. George's, University of London
Senior Medical Assessor. Medicines & Healthcare Products Regulatory Agency,UK (MHRA)
Member of the Scientific Working Party of the European Medicines Agency (EMA)

Member of the EuroObservational Research Program (EORP). European Society of Cardiology.
Member of the Regulatory Affairs Committee. European Society of Cardiology.

Graduated from the School of Medicine at the Universidad Autónoma de Madrid (1979). Ph.D at the Medical School (1991). Staff member of the Department of Cardiology at the Academic Hospital Puerta de Hierro (Madrid), since 1987. Head of the Coronary Care Unit (1987-2000). Senior Consultant as a Clinical Cardiologist (involved in clinical trials on Heart Failure, Ischaemic Heart Disease and Cardiovascular Prevention) 2000-2012. Member of the Committee for Ethics and Clinical Investigation (2000-2009). Coordinator, Chairperson and speaker of several post-degree Ph D Courses at the Academic Hospital Puerta de Hierro de Madrid since 1986. Member of the Heart Failure.

Ischemic Diseases, Women and CV Disease, Pharmacology Working Groups of the Spanish Society of Cardiology, General Vice-Secretary elect of the Spanish Society of Cardiology: 1999-2001, General Secretary of the Spanish Society of Cardiology: 2001-2003 and President of the International Relations Department of the Spanish Society of Cardiology and Member of the Editorial Committee of the Spanish Heart Journal. Fellow of the European Society of Cardiology since 2001, currently involved in several proyects with the European Society of Cardiology (Clinical Guidelines, Cardiovascular Round Table, Congress Programm Committee, Registries and Pharma Working Group).

Dan Atar (Oslo, NOR)

Dan Atar, MD, is Head of Research at Oslo University Hospital Ulleval, Dept. of Mecidine, Oslo, Norway, and holds a full Professorship in Cardiology at the University of Oslo, Norway, along with a Visiting Associate Professorship at the Johns Hopkins Unversity, Baltimore, Maryland, USA. Dan Atar trained in Denmark, Switzerland, and the United States before receiving his board certification in Internal Medicine and Cardiology in 1995. His research focuses on myocardial biomarkers, myocardial function, heart failure and cardiovascular pharmacology. He has written more than 200 articles and book chapters and holds the fellowship-titles FESC, FACC, and inaugural FAHA. Dan Atar is the past-Chairman of the ESC Working Group on Cardiovascular Pharmacology and Drug Therapy, and Associate Editor of the international peer-reviewed journal Cardiology *(Karger). He is currently chairing a EU-FP7 research consortium (Mitocare). Dan Atar was on a number of ESC guideline writing committees, amongst others the* 2010 ESC Guideline on Atrial Fibrillation *as well as the* 2012 ESC Guideline Update on Atrial Fibrilliation. *In 2012, Dan Atar was elected as Councillor and Board member of the ESC.*

Michel Azizi (Paris, FRA)

Michel Azizi is Professor of Vascular Medicine and Head of the Clinical Investigation Center, Responsible for Clinical Research and Teaching in the Common and Rare Arterial Diseases University Department, and Cardiovascular consultant in the Hypertension unit, Georges Pompidou University Hospital, Paris. He received his MD from René Descartes University and his PhD from Pierre et Marie Curie University, Paris, France. He is member of the Clinical Research Commission of the INSERM, in France. His main research interests include the treatment of resistant hypertension and the physiology, genetics and pharmacology of the renin–angiotensin–aldosterone system. He has published more than 150 papers in peer reviewed journals, many of which have focused on the renin-angiotensin-system. He has received the Jean Hamburger prize for Medical Research in 2007, the University Paris-Descartes Scientific Award in 2009, Paris, France, the Peter van Zwieten award of the European Society of Hypertension in 2011, Milan, Italy, the Scientific award of the Italian Society of Hypertension in 2013. He is member of the French Society of Cardiology, the European Society of Hypertension, the European Society of Cardiology and of the RAAS working group of the European Society of Hypertension. He is member of the council of the European Society of Hypertension.

George Bakris (Chicago, USA)

George L. Bakris, MD, F.A.S.H., F.A.S.N., F.A.H.A, completed training in Internal Medicine at the Mayo Graduate School of Medicine where he also completed a research fellowship in Physiology and Biophysics. He completed fellowships in Nephrology and Clinical Pharmacology at the University of Chicago. He served as Director of Renal Research at the Ochsner Clinic (1988-1991) and was an Assistant Professor of Medicine and Physiology at the Tulane University School of Medicine. He was then Director of the Rush University Clinical Trials Unit (1995-2006) in Chicago. He has served as an expert-member on the Cardio-Renal Advisory Board of FDA (1993-2003) and is currently a special consultant. He chaired the first National Kidney Foundation Consensus report on blood pressure and kidney disease progression (2000) and served on many national guideline committees including the JNC VI & 7, the American Diabetes Association, and National Kidney Foundation (K-DOQI) BP and Diabetes Guideline committees. He is the past-President of the Am. College of Clin. Pharmacol. and the Am. Soc. of Hypertension (ASH). He has published over 600 peer-reviewed publications and book chapters. He is the current Editor of Am J Nephrology, *the Hypertension, Section Editor of* Up-to-Date, *and an Assoc. Ed of* Diabetes Care *and* Nephrol, Dialysis & Transplant. *He also serves on 14 editorial boards. Dr. Bakris is currently Professor of Medicine and Director of the ASH Comprehensive Hypertension Center at the University of Chicago Medicine.*

ABSTRACT

Time to Move from Proof of Concept to Outcome Trials for Renal Denervation?

George Bakris, MD

There are more than half a century of data on blood pressure reduction and cardiovascular outcomes, all

demonstrating as clear relationship between decreases in blood pressure translating into significant reduction in cardiovascular events. The data are so consistent that the FDA has issued a statement in 2009 stating that a reduction in blood pressure will translate into a cardiovascular risk reduction. This has also been put into the labels of recently approved antihypertensive medications. The renal denervation procedure has evaluated, thus far, people at highest risk for cardiovascular events who have failed conventional antihypertensive therapy. Initial trials demonstrated a clear reduction in blood pressure following the procedure. The early trials, however, suffered from lack of appropriate placebo or sham controls and strict criteria for enrollment with ambulatory blood pressure monitoring and adherence logs for medications. The current ongoing trial, Symplicity HTN-3, has a sham control arm and requirement for ambulatory blood pressure control for all participants. Additionally, pharmacy records and patient logs of medications have all been documented to ensure adherence with blood pressure lowering medications. The screening failures for Symplicity HTN 3 were very high due the prerequisite of meeting the inclusion criteria to provide a minimum of three maximally tolerated doses of blood pressure lowering medications with complementary mechanisms (thiazide-like diuretic, RAS blocker, and calcium antagonist). Additionally, spironolactone was strongly encouraged as a fourth drug. Given that this trial will show a reduction in blood pressure to levels averaging <160 mmHg systolic all epidemiological studies and prospective clinical trials demonstrate a reduced CV risk especially for stroke. Thus, given the difficulty in recruiting such patients and the fact that most of these people have already failed 5-7 medications, such a trial would be unethical since you already know their event rate is very high and a placebo or sham procedure would offer nothing. Moreover, it would take years to recruit in order to have appropriate power. Lastly, the FDA has gone on record as not wanting an outcome trial if Symplicity HTN-3 is positive.

John Bisognano (Rochester, USA)

John Bisognano MD, PhD, is a professor of medicine and director of outpatient cardiology at the University of Rochester Medical Center in Rochester, New York. He obtained bachelor's degrees in Biology and Political Science from Massachusetts Institute of Technology and went on to obtain a Ph.D. in Physical Chemistry from the State University of New York at Binghamton. He received his medical degree at the State University of New York at Syracuse and did residency at the University of Michigan followed by a fellowship in preventive cardiology. He did a fellowship in cardiology with specialty in heart failure and transplantation at the University of Colorado before accepting a position in the faculty at the University of Michigan. He subsequently joined the faculty at the University of Rochester. He has been involved in many clinical and basic science studies that include approaches to treatment of patients with resistant and refractory hypertension, including clinical trials testing new medical devices. He is also engaged in community-wide efforts at blood pressure reduction as well as NIH funded in investigating novel methods for treatment of patients with Stage I hypertension. He is a frequent lecturer on hypertension guidelines, treatment approaches, and clinical research both locally as well as internationally.

Dr. Bisognano is member of numerous editorial boards and has served as President of the New York State Chapter of the American College of Cardiology, Secretary-Treasurer of the American Society of Hypertension, and Director of the ASH Comprehensive Hypertension Center at the University of Rochester.

ABSTRACT

Barostimulation – Resistant hypertension: is lowering BP also a valuable surrogate in device trials?

John D. Bisognano, MD, PhD

For many decades, the sympathetic nervous system has been a ready target for modulation of blood pressure. Direct electrical stimulation of the carotid sinus received brief attention in the 1960's, but was a technology soon eclipsed by successes in drug development. The original bulky device was difficult to implant, and required electronics that were inconvenient for any patient. In the new millennium, a golden triad of opportunity has emerged. First, the prevalence of resistant hypertension has increased dramatically, and the disastrous results of untreated severe hypertension are better recognized for the toll that they take on patients, their families, and the public health care economics. Secondly, the successes of drug development have reached a plateau. Thirdly, the electronics that previously made development of carotid stimulation devices have greatly miniaturized, and device therapy for numerous diseases has become more commonplace.

In this session, the history of baroreflex stimulation devices will be explored, and the current state of the art discussed. The track record of older devices will be discussed as will the recent development of newer devices that have potential to impact the treatment of severe resistant hypertension in the future.

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ABSTRACT

Heart Failure: what is being learnt from POC trials? Barostimulation

John D. Bisognano, MD, PhD

Despite numerous advances in the treatment of heart failure with both decreased and with preserved ejection fraction, it remains a major cause of death worldwide. The baroreflex provides a new potential target of therapy for this large population that may complement the present drug and device therapy that is available. A brief history of the development of this technology will be discussed and the recent proof of concept data for its efficacy.

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Randall Brockman (FDA, USA)
attending by conference call

Dr. Randall Brockman MD, F.A.C.C joined the FDA in 2003. From 2003 to 2012 he served as a medical reviewer in the Division of Cardiovascular Devices. Currently, he is the Associate Director and Chief Medical Officer for the Office of Device Evaluation in the Center for Devices and Radiological Health. Prior to joining the FDA, he was in private practice. His clinical training included fellowships in cardiac electrophysiology and cardiology at the University of Maryland, and a residency in Internal Medicine at the University of North Carolina, Chapel Hill. He received both his MD and undergraduate degrees from the University of Virginia.

Hans Pieter Brunner La Rocca (Maastricht, NED)

Hans-Peter Brunner-La Rocca has long-term experience as heart failure specialist, both in clinical practice and in clinical research. Currently, he is the director of the heart failure clinic at the Maastricht University Medical Centre (MUMC) in the Netherlands and is vice chairman of the Department of Cardiology at MUMC. He is professor of Cardiology at the University of Maastricht.

He has a special interest in biomarker research in heart failure. Among other, he has led the TIME-CHF study which is still the so far largest study on NT-proBNP guided therapy in heart failure. He is active in clinical research on biomarker related personalized medicine, telemedicine and co-morbidities in heart failure. He is actively involved in many trials on these topics. He has authored more than 170 articles.

ABSTRACT

Devices and biomarkers to guide care in heart failure: Trial methodology and regulatory issues
What is the best primary outcome measure?

Hans-Peter Brunner-La Rocca, Maastricht

Biomarker and/or device guided therapies in heart failure have been tested in different populations, settings and using different therapies to achieve the goal of superior and/or more cost-effective care. Still until now, none of the approaches have been implemented into clinical routine despite some very promising results. The question is why. On the one hand, this is related to the difficulty to compare the different approaches as even using the same measure to guide therapy (e.g. NT-proBNP), the trials varied significantly. Thus, targets of NT-proBNP differed, intervals of measuring biomarkers differed, therapeutic actions as response to knowing NT-proBNP levels differed, making the direct comparison between the trials difficult.

On the other hand, primary outcome measure differed significantly between the trials. Basically all trials in this regard used combined endpoints, varying from disease specific endpoints – i.e. combined endpoint of heart failure hospitalisation and heart failure related mortality or cardiovascular mortality, some even including other clinical endpoints such as need of iv treatment or NYHA class – to unspecific endpoints, i.e. all-cause hospitalisation and all-cause mortality. Importantly, all these trials were of small to medium size because these trials were usually investigator initiated (most biomarker trials), had limited resources despite industry sponsoring or were invasive in nature (device studies). Taken together, the trials done so far were not sufficiently uniform and this lack of uniformity also included the choice of the primary outcome measure.

Interestingly enough, the metanalysis of the NT-proBNP or BNP-guided therapy trials conducted so far showed a very strong signal of benefit in reduction of mortality. Combined endpoints including the disease specific endpoint of heart failure hospitalisation free survival were less convincingly reduced. To some extent, this is not surprising since

knowing some signals of potential deterioration might trigger hospitalisation. Thus, increase in NT-proBNP and BNP, respectively, or indication of increasing fluid overload by e.g. pulmonary pressure or thoracic impedance might not only result in intensified outpatient therapy, but also trigger hospitalisation.

In addition, depending on the population included, co-morbidities may result in hospitalisation independent of the cardiac disease, whereas mortality is to a large extent cardiac related. Finally, there is not only interest but also much suspiciousness regarding biomarker or device guided therapy in heart failure, particularly in Europe. And, biomarkers are often used as surrogate endpoints and using these surrogate endpoints to influence other surrogate endpoints is generally not seen as sufficient to implement the concept of biomarker guided therapy approach into clinical practice.

Taking all these aspects together, such trials must have a hard primary outcome that is generally accepted from large drug or device (ICD, CRT) trials. As an absolute minimum, this is cardiovascular hospitalisation free survival. However, I think that the chance to positively influence mortality is at least as large and nobody would argue about the importance of this endpoint. Then, secondary endpoints including quality of life and cost-effectiveness can be included.

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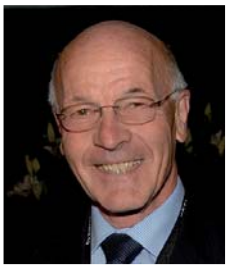

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Dirk L. Brutsaert, MD, PhD, EFESC, EFACC, is Professor-Emeritus at the University of Antwerp in Belgium. He is also Chairman, European Heart Health Institute, European Heart Agency of ESC, in Belgium. He held the position of Professor of Physiology and Medicine with joint appointment in Department of Medicine, University of Antwerp, Belgium (1966-2002) and Co-chairman, Department of Cardiology, University Hospital Antwerp (UZA) (1981-2002). He was Honorary Consultant, Department of Cardiology, Middelheim Hospital, University of Antwerp, Antwerp (2002–2007). Pr Brutsaert was a Founding President of the Heart Failure Association (HFA) of the European Society of Cardiology (2004-2006) and President of the Royal Academy of Medicine of Belgium (2004-2006). Major research interest: Myocardial and ventricular function (contraction, relaxation and filling, non-uniformity) in health and disease, in particular in heart failure, including the role of cardiac endothelium in endothelial-cardiomyocyte cell communication and therapeutic implications.

Javed Butler (Atlanta, USA)

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He is currently Professor of Medicine at the Emory University. Before moving to Emory, he was the director for the Heart and Heart-Lung Transplant programs at Vanderbilt University. He currently also serves as the Deputy Chief Science Officer for the American Heart Association. He is the Principal Investigator for the NIH Emory University Heart Failure Clinical Research Network. He is on the Editorial Board for the Journal of the American College of Cardiology, Journal of Cardiac Failure, American Heart Journal, Circulation Cardiovascular Quality and Outcomes, JACC Heart Failure, and Heart Failure Clinics.

Dr. Butler's research focuses primarily on development of novel therapies for patients with acute heart failure. He has published over 200 peer-reviewed papers and additionally

many more book chapters, review articles, and editorials. He serves on the national board, events committee, data safety and monitoring board, and steering committees of several multicenter clinical trials. He current research portfolio includes funding from the NIH, Food and Drug Administration, and several pharmaceutical industries.

Dr. Butler is involved in the evaluation and management of all aspects of patients with heart failure including cardiac transplantation and left ventricular assist devices.

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ABSTRACT

Drug eluting stents (DES) and dual antiplatelet therapy (DAPT) trials and implementation issues:

Targeting dual antiplatelet therapy (DAPT) to time dependent risk

Edoardo Camenzind / University of Geneva

Duration of DAPT after DES deployment is not known. (1) However that DAPT is important after DES deployment to prevent thrombotic complications is well-known. (2,3)

Further some studies have identified DAPT interruption after DES as a major predictor of stent thrombosis. (4) Recently a prospective registry has also evaluated the influence of the type of interruption (discontinuation, interruption and disruption) on the incidence of thrombotic events (5).

In the search of an optimal DAPT duration after DES, a few randomized trials have evaluated (6-8) or are on-going to evaluate (9) this unsolved issue using a factorial design. Thus these trials are randomizing different DES-types and different DAPT-duration aiming to detect an optimal DAPT duration. Interestingly the initial analysis of the trials did not take into consideration potential biological differences among DES and analyzed DES effect as uniform in a pooled manner (7,8). Conversely when the different DES types were considered and analyzed separately - allowing a potential distinction between DES types - the different DAPT-durations were pooled (6).This way of proceeding assumes that all DES have the same biological effect and that DAPT use has not to be cut-tailored to the type of device, despite of documented DES specific vascular reactions in-human specimens (10).

Recently PRODIGY was further analyzed taking into account both deployed DES-types(four stent types) and different DAPT-durations(6 and 12 months) and a significant interaction could be observed, mainly driven by an improved primary endpoint (composite of death, myocardial infarction or cerebrovascular accident) as well as lower incidence of stent thrombosis after short term DAPT in a zotarolimus-eluting stent and a higher incidence of stent thrombosis after short-term DAPT in a paclitaxel-eluting stent (11). The authors concluded that optimal duration of DAPT may be stent specific. However, no satisfactory answer to the patho-physiological mechanisms underlying this observation could be given.

PROTECT (12) the largest superiority trial comparing two DES type with very different healing characteristics, using a physician-guided duration of DAPT and 90% powered for the primary endpoint (definite or probable ST at 3 years) suggests that adherence to DAPT modifies outcome of stent thrombosis to a greater extent after deployment of a DES with a less predictable healing response than with a predictable healing response. These findings advocate that duration of DAPT may be stent-specific due to the biological properties of the deployed stent. Further other patient related characteristics may determine time dependent risk.

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Blai Coll (Abbvie, USA)

Blai Coll is currently Medical Director, Renal Development at Abbvie, where he provides medical guidance and leadership and supervises the development of renal clinical investigational plans from phase I to phase III studies. He is a physician and clinical researcher with experience in patient care, cardiovascular and metabolism medicine, and clinical research.

ABSTRACT

Atrasentan for the treatment of diabetic nephropathy: how to control the risk of heart failure?

Dr. Blai Coll

Diabetic Nephropathy is the leading cause of End Stage Renal Disease (ESRD) in the world and there is a huge unmet medical need. Renin angiotensin inhibitors are the approved drugs, but half of the patients still present with residual albuminuria, and therefore have a significant higher risk to progress to ESRD.

Atrasentan is a selective endothelin A receptor antagonist, in development for subjects with diabetic nephropathy and macroalbuminuria (>300 mg/g). Phase 2 b studies will be discussed and the design of the ongoing phase 3 will be reviewed (SONAR). Special emphasis will be made to the design of the study (enrichment design) and to the strategies to mitigate the risk of congestive heart failure (BNP, enrichment design, etc).

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James Costin is Vice President of Clinical and Medical Affairs a Perosphere, Inc. in Danbury, CT, USA. He obtained his MD degree from Emory University School of Medicine and competed his cardiology training at Yale University School of Medicine where he was on the full time faculty before joining the pharmaceutical industry. Prior to Perosphere, he was Corporate Vice President of Scientific Affairs at Carter-Wallace and was also at ICI Americas prior to that. He has worked on the research and development of numerous drugs including Tenormin (atenolol) and Felbatol (felbamate).

ABSTRACT

Aripazine (PER977) reverses Heparins, Fondaparinux, and new oral anticoagulants

Sasha Bakhru, James Costin, Bryan Laulicht, Solomon Steiner
Perosphere, Inc.

Aripazine (PER977) is a small molecule designed and synthesized to non-covalently bind to unfractionated and low molecular weight heparins (UFH, LMWH) and fondaparinux as well as the new oral anticoagulants (NOACs) including edoxaban, apixaban, rivaroxaban, and dabigatran. By binding to these other drugs, aripazine prevents the binding of the anticoagulant to their endogenous targets and thereby reverses the anticoagulation induced by these drugs. A Phase I, 7-cohort, ascending dose trial using both aripazine alone and in combination with 60 mg of oral edoxaban has been completed and shows reversal of edoxaban beginning at 50 mg of aripazine with no serious adverse events and minor, non-dose limiting, transient adverse events (flushing, cool sensations). No pro-coagulation signals (d-dimer, F_{1+2}, or TFPI) have been observed with aripazine in either preclinical or clinical testing. Aripazine reverses the biomarker used with each anticoagulant and more importantly reverses the bleeding in mucosal bleed models while re-establishing the integrity of clot formation altered by the anticoagulants as shown in the Phase I trial. In reversing the anticoagulation of UFH, LMWH, and the NOACs, aripazine provides an unmet medical need to the use of the NOACs as well as a better reversal agent for UFH and a single agent reversal for LMWH. A Phase II trial with multiple doses of both edoxaban and aripazine is being implemented. Although in its preclinical development different doses of aripazine were required for different anticoagulants, clinical trials will be carried out to establish that a single dose of aripazine can be used for anticoagulation reversal for all NOACs, UFH, and LMWH in their therapeutic range. A single intravenous dose of aripazine with no infusion requirements will be targeted as the standard dosage and administration. The product is stable over a wide range of temperatures and is available for immediate intravenous bolus injection. Aripazine's advantages include its small size, making immunogenic reactions unlikely; its use as a single bolus injection with no infusions required; its quick onset (~10 minutes in the Phase I trial); its reliance upon commonly used endpoints to show its efficacy, including cessation of bleeding and restitution of clot integrity; its reliance upon combining with another drug (an "exogenous receptor") to inactivate the anticoagulation rather than targeting an endogenous receptor (such as Factor Xa); its quick metabolism and renal clearance along with the anticoagulant; and the potential to be used as a single dose product for reversal of therapeutic anticoagulation from UFH, LMWH, fondaparinux, and the NOACs. Finally, although initial development targets aripazine for use in urgent or emergency settings, it also has the potential to be used in elective procedures wherein short-term reversal may be indicated for invasive procedures in order to minimize the time a patient is off anticoagulation.

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Professor Cowie's studies and reviews have been featured in a variety of peer-reviewed journals, including The Lancet, British Medical Journal, JAMA, Circulation, European Heart Journal, Heart and the European Journal of Heart Failure. *He has contributed chapters to many books, including the* Oxford Textbook of Medicine, *and has written a book for patients entitled* Living with Heart Failure – a guide for patients. *His research interests centre on health technology assessment, remote monitoring and new diagnostic and treatment approaches for heart failure.*

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Atrial fibrillation, ventricular tachycardia mechanism, atherosclerosis and heart failure are the main expertise fields for Dr. Dan. He has over 200 communicated and published papers and abstracts. Professor Dan has a very reach educational activity with over 450 medical conferences in Romanian and international congresses and symposia. He participated in many Clinical Trials as Principal Investigator, National Coordinator or member in steering committee.

Dr. Dan is Chief-Editor of the Romanian Journal of Internal Medicine *(indexed), associate editor of* the Journal of Royal Society of Medicine – Cardiovascular *and member in the editorial board of several Romanian and international journals. Dr. Dan is a fellow of American Heart Association (AHA) – Clinical Cardiology, Premium Professional – Silver of AHA, fellow of the European Society of Cardiology and member of the Scientific Documents Committee of the European Heart Rhythm Association.*

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Jean-Claude Daubert (Rennes, FRA)

Jean-Claude Daubert, MD, FESC, FACC, is professor of cardiology at the university of Rennes 1-School of medicine, France. He was the head of the department of cardiology and vascular diseases, and the cardio-thoracic centre at the Centre Hospitalier Universitaire of Rennes.

He was president of the French Society of Cardiology (2004–2005), the National College of Cardiology Professors (2007-2012) and the National Council of Universities (2012…)

His main research domains are: hemodynamics of cardiac pacing, cardiac resynchronisation therapy introducing the concept of atrial resynchronisation in 1989 and ventricular resynchronisation in 1993, electrical therapies for heart failure and cardiomyopathies and cardiac arrhythmias.

He was the chairman or initiator of several landmark studies in the field of electrical therapies in heart failure/ cardiomyopathies, in particular PIC (1997), MUSTIC (2001) and REVERSE (2008-9) studies. For his work, he received several international distinctions namely the Grüntzig award and ESC silver medal in 2001 and the Gold Medal of the ESC in 2011.

Dr Daubert is the author of more than 300 original papers or reviews published in peer-review journals.

Kristina Dunder (EMEA, SWE)

Dr Dunder graduated from Uppsala University (School of Medicine) in 1988. She specialized in internal medicine and endocrinology/diabetology and served as a medical doctor at the Uppsala Academic Hospital until 2005.

In 2004 she defended a thesis with the title "Clinical manifestations of coronary heart disease and the metabolic syndrome". Since 2005 Dr Dunder holds a position as a clinical assessor and senior expert at the Medical Product Agency in Uppsala, Sweden. She is also a member of the CHMP (Committee of Human Medical Products) at the EMA (European Medicine Agency) in London, UK.

Dr Dunder was one of the Rapporteurs for the update of the guideline Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus *which became effective November 2012, and is currently coordinating the ongoing update of the* guideline of medical products used in weight control.

Frank Eitner (Bayer, GER)

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Alan Fraser is Professor of Cardiology at the Wales Heart Research Institute, Cardiff University, UK, and Consultant Cardiologist at the University Hospital of Wales. He qualified in Edinburgh and was clinical research fellow at the Thoraxcentre in Rotterdam. He is a Past-President of the European Association of Echocardiography and currently chairs the Task Force on Medical Devices of the European Society of Cardiology. He attends the Medical Device Experts Group, and is a member of the Working Group on Clinical Investigation and Evaluation, of the European Commission. His research interests include heart muscle disease and the pathophysiology and diagnosis of heart failure. He is a member of the FP7 MEDIA research network studying heart failure with preserved ejection fraction.

ABSTRACT

The European Innovation Strategies

Alan Fraser (Cardiff, GBR)

A major objective of the current revision of the medical device regulatory framework in the European Union has been to preserve the capacity of the system to allow innovation and early market access for effective new devices, when there is unmet clinical need, at the same time as ensuring that clinical safety is paramount. Previously, the purpose of performing clinical investigations was to verify "that devices achieve the intended benefits to the patient as specified by the manufacturer"; in the draft legislation this has been amended to "the clinical safety and efficacy of the device". Flexibility will be preserved by enabling doctors to prescribe custom-made devices "exclusively to meet a specific patient's individual requirements and needs", and by introducing the concept of conditional approval so that any competent authority may authorize the placing on the market of a specific device before it has been fully evaluated, if this is judged to be in the interest of public health or patient safety. In these circumstances the manufacturer would be required to submit clinical data to the competent authority within a prescribed period thereafter, in order to be allowed to keep the device on the market. In the future, if the draft European regulations are approved, there will be a greater role for independent advice from clinical and scientific experts, and there will be a requirement to produce specific European standards concerning the regulatory approval of particular classes of medical devices. The importance of post-market surveillance will be strengthened, with independent review of the data produced by manufacturers. Innovation in medical technology is also a goal of the new EU research framework. In the longer term, there are several forces that may drive more international convergence in device standards and evaluation.

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John Funder (Melbourne, AUS)

John Funder first began working on aldosterone secretion and action as a PhD student in 1967. He is still deeply involved in aldosterone, mineralocorticoid receptors and primary aldosteronism, evidence of persistence but also perhaps of tunnel vision. During the time since he has published over 500 peer-reviewed papers, given over 200 invited international presentations, chaired the Endocrine Society's taskforce on Guidelines for Primary Aldosteronism (2006-2008), and is currently chairing the taskforce charged with their revision. In 2008 he was awarded the Novartis Prize of the Council for High Blood Pressure Research, and in 2003 the Robert H. Williams Leadership in Endocrinology Award of the Endocrine Society. He no longer has a laboratory, students or fellows, but a series of national and international collaborations, and writes multitudinous reviews, opinion pieces and editorial commentaries.

ABSTRACT

What is in the pipeline? Next generation MRAs and aldosterone synthase inhibitors

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Mineralocorticoid receptor antagonists (MRAs) have a long history, beginning with spironolactone over 50 years ago, the first generation progesterone-derived antagonist at mineralocorticoid receptors (MR) and androgen receptors (AR), and retaining agonist activity at progesterone receptors (PR). Spironolactone has relatively high affinity for MR, is largely plasma bound, has active metabolites and a long half-life. In contrast the second generation MR-selective agent eplerenone has much lower affinity for MR, negligible

affinity for AR and PR, no active metabolites and a short (4-6hours) half life, but is only modestly plasma bound. Optimally dosed it is ~60% as potent as spironolactone in vivo, without its sex steroid receptor engendered side-effects. Via their renal action both agents retain potassium, and thus particularly at higher doss may cause hyperkalemia as an obligate accompaniment.

In the pipeline we need both generation 3 (Gen 3) and generation 4 (Gen 4) MRAs. Gen 3 MRAs need to be non-steroidal, cheap to manufacture, as potent as spironolactone, as selective as eplerenone and with a relatively long patent life, Gen 4 agents need to be all of the above, and to be relatively tubule-sparing i.e. to be more potent at extrarenal sites than on renal principal cells, thus lowering the chance of hyperkalemia, an otherwise obligate side-effect. Peter Kolkhof, as discussant, will briefly detail the current pipeline for MRAs under development or in trials in Europe, Japan and the USA.

In considering the clinical uses to which Gen 3 and Gen 4 MRAs might be put there are a number of factors which must be borne in mind, as follows:

1. Currently ~10% of hypertensives are thought to have primary aldosteronism; an additional 20-30% (low renin hypertension, resistant hypertension) show evidence for a degree of autonomous aldosterone secretion/enhanced MR responsiveness. Such patients need Gen 3 MRAs, as Gen 4 may prove dangerous by provoking hypokalemia, which is in fact rather more dangerous than hyperkalemia;
2. MR evolved millions of years before aldosterone synthase, with cortisol the ligand and evolutionary driver. Most MR in the body - even in renal principal cells - are occupied but under normal circumstances not activated by cortisol. Cortisol however becomes a mineralocorticoid receptor agonist, mimicking the effect of aldosterone, under conditions of tissue damage, reactive oxygen species generation and redox change (or in principal cells, in the absence or blockade of 11BHSD2);
3. Current MRAs are not “blockers”, acting by denying agonist ligands access to MR, but act as inverse agonists - and thus are effective at doses considerably lower than those which would be required to exclude agonists;
4. MRAs are uniquely cardio/vasoprotective, whether the MR agonist be aldosterone (as in primary aldosteronism) or cortisol (as in heart failure or essential hypertension); and
5. MR are found in non-epithelial tissues (eg cardiomyocytes, macrophages, neurons), where their physiologic roles are only very lightly explored. Their pathophysiologic roles are commonly ascribed to aldosterone (wrongly except for primary aldosteronism), but in fact due to their activation in the context of tissue damage by normal circulating levels of cortisol, ~1000 times higher than those of aldosterone.

These data suggest novel roles for MRAs should be sought across a diverse range of situations, in addition the congestive heart failure and primary aldosteronism:

- Low renin hypertension and resistant hypertension - and all new hypertensives under the age of 70 with reasonable renal function;
- Chronic or acute inflammatory/fibrotic disease, ranging from chronic kidney disease to hepatic fibrosis to post-operative cochlear implant surgery;
- Autoimmune disease, from myasthenia gravis to rheumatoid arthritis to inflammatory bowel disease to multiple sclerosis; and
- possibly even in cancer.

The use of aldosterone synthase inhibitors has been dogged by specificity issues; on pathophysiologic grounds they are less likely to be useful than MRAs, given that the latter antagonize both aldosterone and cortisol (the latter in the context of tissue damage). The one caveat is if definite pathophysiologic roles can be demonstrated for actions of aldosterone via non-MR pathways. In this case the elevation of aldosterone secretion rate with higher doses of MRAs may prove an issue of importance, and thus represent a role for aldosterone synthase inhibitors; it should be noted that low dose MRA therapy appears to leave aldosterone secretion rate and plasma levels essentially undisturbed.

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Maurizio Gasparini (Rozzano, ITA)

Dr. Maurizio Gasparini graduated in Medicine and Surgery in 1980 and specialised in Cardiology in 1982. Assistant/ Senior Assistant Cardiologist from 1980 to 1997 at Niguarda Hospital in Milan. Since 1997 director of Electrophysiology and Pacing Unit at the Humanitas Clinical and Research Center Rozzano-Milano.

He published more than 300 papers or chapters on international Journals (205 papers indexed on Medline), with a citation index higher than 3400. Member of the steering committee of European Guidelines on Pacing and CRT, of the European Guidelines on implantation of loop recorder and AIAC Guidelines on treatment of AF; member of EHRA and national coordinator of the European CRT Registry. Areas of major interest are CRT (more than 1000 CRT implantation performed), paediatric ICD implantation, shock reduction in ICD, and AF ablation. Finally, Dr Gasparini is

the principal investigator of the Believe study, the Relevant study, the Advance CRT-D trial and Advance III trial. And a peer reviewer of JACC, AHJ, JCE, HR, Europace and in the Editorial board of Europace.

ABSTRACT

Evidence based progress in ICD therapy: New algorythms – better programming, subcutaneous ICDs

Maurizio Gasparini (Rozzano, ITA)

Despite the evidence-based efficacy of the ICD therapy, the debate continues on the risk/benefit ratio, particularly on the possible adverse effects of ICD shocks and device related complications that may affect quality of life.

In the latest years, have been significant improvement both in device technology and in physician knowledge, which have focused on minimizing painful shocks (appropriate and inappropriate) by better programming throughout longer detections and antitachycardia pacing (ATP).

Recently three trials have been published on this topic:

1. MADIT- RIT enrolled 1500 primary prevention patients showing that programming of ICD therapies for tachyarrhythmias > 200 bpm or with an extremely prolonged delay in therapy at > 170 bpm, compared with conventional 1-2.5 seconds delay programming, was associated with reductions in inappropriate therapy and all-cause mortality during long-term follow-up.
2. Advance III trial enrolled 1902 patients, both in primary and secondary prevention, undoubtedly showing that the use of a long detection interval (30/40 intervals) and the use of ATP during charging for any fast VT, resulted in a lower rate of ICD therapies, inappropriate shocks, and hospitalizations.
3. Finally the PROVIDE study, despite limited by unbalanced pts groups, confirmed reduction of ICD therapies as well as in all-cause mortality by using higher detection rates and longer detection intervals.

In conclusion, should be recognized in the upcoming guideline throughout the above mentioned trials the efficacy of ATP and long detection window in reduction of inappropriate and unnecessary therapy with the overall target of mortality reduction and furthermore quality of life improvement.

Even applying the best programming strategy, conventional endocardial ICD still may present "mechanical "complications involving transvenous leads; recently a subcutaneous implantable cardioverter-defibrillator (S-ICD) has been developed as an alternative system. A study on safety and efficacy at acutely terminating VT/VF has been published. However the limitation of patients eligible for this approach is self-evident, since candidates to S-ICD should neither required pacing nor had documented pace-terminable ventricular tachycardia. It should be emphasized that, at the moment, no randomized trial evaluated the efficacy of S-ICD. A word of caution should, therefore, be used for this technology in the absence of randomized trials comparing S-ICD to conventional endocardial system, at least in term of non-inferiority.

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Nancy L. Geller has been the Director of the Office of Biostatistics Research at the National Heart, Lung and Blood Institute of the National Institutes of Health since 1990. She directs a group of 12 statisticians who collaborate in the design, implementation, monitoring and analysis of multicenter clinical trials in heart, lung and blood diseases and sleep disorders and administers all statistical activities of the National Heart, Lung and Blood Institute. She has been or is involved in the design and analysis of a number of cardiovascular trials, including PEACE, AFFIRM, WHI (Women's Health Initiative), FREEDOM, ACCORD, the ongoing Ranolazine ICD trial (RAID), the recently completed COAG (Clarification of Optimal Anticoagulation through Genetics) trial and a recently completed trial of repair versus replacement of the mitral valve in severe ischemic mitral regurgitation. She has published over 200 papers in the statistical and medical literature. She is an Associate Editor of Biometrics and a member of the Editorial Board of Clinical Trials. She is a Fellow of both the International Statistics Institute and the American Statistical Association.

She was the winner of the 2009 Janet L. Norwood Award for outstanding achievement by a woman in the statistical sciences and was 2011 President of the American Statistical Association.

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Dr. Gheorghiade currently serves as Professor of Medicine and Surgery, Associate Director and Director of Experimental Therapeutics at the Center for Cardiovascular Innovation, Department of Medicine, at Northwestern University's Feinberg School of Medicine and Northwestern Memorial Hospital. He is also an Adjunct Professor of Medicine at Duke University. He graduated Magna Cum Laude from the University of Rome Medical School in 1972 and did his residency and fellowship in cardiology at Brown University.

Dr. Gheorghiade has served as a visiting professor in the United States and abroad. He has chaired or co-chaired more than 300 national and international meetings and has given more than 500 invited lectures. He has served or is currently serving on the editorial board of several journals including The American Heart Journal, The American Journal of Cardiology, Journal of the American College of Cardiology, *and* Circulation Heart Failure Journal. *He has also served as guest editor on several occasions for* The American Journal of Cardiology, The American Heart Journal, The American Journal of Medicine and Heart Failure Clinics. *He has chaired many international trials in heart failure including OPTIME-HF, ACTIV-HF, IMPACT, PRESERVD, HORIZON, COMPOSE, ASTRONAUT, RENO-DEFEND, IMPROVE-HF Bridge and Stresscopin Trials. He also co-chaired the global EVEREST Trial and the ECLIPSE Trial, and was a member of the Steering Committee of RADIANCE, FIRST, CARS, RITZ 4, and EPHESUS Trial. In addition, Dr. Gheorghiade was an active member of the Steering Committee in the OPTIMIZE-HF and IMPACT-HF registries. He is presently co-chairing SOCRATES, PARSiFAL and MUST-HF trials.*

Dr. Gheorghiade has authored close to 600 peer-reviewed publications and more than 300 abstract presentations at national and international meetings. He is the co-editor for two comprehensive textbooks on acute heart failure syndromes and has written several chapters in many textbooks including Kelley's Textbook of Internal Medicine, *and* Heart Failure: A Companion to Braunwald's Heart Disease, *and most recently authored the chapter on Acute Heart Failure Syndromes in the ninth edition of* Braunwald's Heart Disease.

ABSTRACT

Current management and future directions for the treatment of patients hospitalized for heart failure with low blood pressure

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Although patients hospitalized with heart failure have relatively low in-hospital mortality, the post-discharge rehospitalization and mortality rates remain high despite advances in treatment. Most patients admitted for heart failure have normal or high blood pressure, but 15–25 % have low systolic blood pressure with or without signs and/or symptoms of hypoperfusion. All pharmacological agents known to improve the prognosis of patients with heart failure also reduce blood pressure, and this limits their use in patients with heart failure and low blood pressure (HF-LBP). However, patients with HF-LBP have much higher in-hospital and post-discharge mortality. In these patients, a conceptually important therapeutic target is to improve cardiac output in order to alleviate signs of hypoperfusion. Accordingly, the majority of these patients will require an inotrope as cardiac dysfunction is the cause of their low cardiac output. However, the short-term use of currently available inotropes has been associated with further decreases in blood pressure and increases in heart rate, myocardial oxygen consumption and arrhythmias. Agents that improve cardiac contractility without this undesirable effects should be developed. To the best of our knowledge, the epidemiology, pathophysiology and therapy of patients with HF-LBP have not been addressed thoroughly. In June 2010, a workshop that included scientists and clinicians was held in Rome, Italy. The objectives of this meeting were to (1) develop a working definition for HF-LBP, (2) describe its clinical characteristics and pathophysiology, (3) review current therapies and their limitations, (4) discuss novel agents in development and (5) create a framework for the design and conduct of future clinical trials.

ABSTRACT

Soluble guanylate cyclase: a potential therapeutic target for heart failure

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The number of annual hospitalizations for heart failure (HF) and the mortality rates among patients hospitalized for HF remains unacceptably high. The search continues for safe and effective agents that improve outcomes when added to standard therapy. The nitric oxide (NO)—soluble guanylate cyclase (sGC)—cyclic guanosine monophosphate (cGMP) pathway serves an important*physiologic role in both vascular and non-vascular tissues, including regulation of myocardial and renal function, and is disrupted in the setting of HF, leading to decreased protection against myocardial injury, ventricular remodeling, and the cardio-renal syndrome. The impaired NO–sGC–cGMP pathway signaling in HF is secondary to reduced NO bioavailability and an alteration in the redox state of sGC, making it unresponsive to NO. Accordingly, increasing directly the activity of sGC is an attractive pharmacologic strategy. With the development of two novel classes of drugs, sGC stimulators and sGC activators, the hypothesis that restoration of NO–sGC–cGMP signaling is beneficial in HF patients can now be tested. Characterization of these agents in pre-clinical and clinical studies has begun with investigations suggesting both hemodynamic effects and organ-protective properties independent of hemodynamic changes. The latter could prove valuable in long-term low-dose therapy in HF patients. This review will explain the role of the NO–sGC– cGMP pathway in HF pathophysiology and outcomes, data obtained with sGC stimulators and sGC activators in preclinical and clinical studies, and a plan for the further clinical development to study these agents as HF therapy.

Edoardo Gronda (Milan, ITA)

Dr. Edoardo Gronda is a Cardiologist with international reputed expertise in heart failure diagnosis and management. His interest in heart failure started in 1984 when he staged 6 months at the London University Hospital Ontario (Canada), training on Heart Transplant program. Back in Italy he became one of the earliest Italian heart failure sub specialty expert, running till to 1999 the Heart failure, Heart Transplant Medicine Program at the Niguarda General Regional Hospital in Milano which has been awarded for quality by Bureau Veritas Quality International (BVQI, London Bureau Veritas Quality International, n°42269). In 2000 he became Director of Clinical and Heart Failure Cardiology Unit at IRCCS Humanitas in Milano and since 2010 became Director of Cardiology Division of Cardiovascular Department at IRCCS MultiMedica and San Giuseppe Hospital MultiMedica Group in Milano.

He is currently teaching Professor of Heart Failure Management at the School of Medicine of the Università degli Studi di Milano and at the School of Cardiology of Università degli Studi di Firenze.

He is one of the 3 Chairs of International Society for Heart and Lung Transplantation Guidelines released by the Society in 2006, and his name is present in the authorship of 101 indexed scientific publications.

ABSTRACT

Neuro Modulation Trials
Angina, arrhythmias, CKD, metabolic syndrome and other potential indications:
would neural modulation become a cure for all?

Edoardo Gronda, MD, IRCCS MultiMedica Milano Italy

Cardiovascular diseases are the prominent cause of death in the western communities. Pathophysiological mechanisms of cardiovascular diseases are complex and tightly related to mutual cardiovascular organs relationship.

When an injury or insult affects heart, kidney and/or vessels a complex interplay of several neuro-hormonal mechanisms become activated in order to try to sustain function, i.e.: a minor kidney injury will reflexly activate cardiac autonomic control in order to restore local perfusion by enhancing cardiac output. Perhaps the most prominent among these neuro-hormonal mechanisms is the adrenergic (or sympathetic) nervous system, whose activity and outflow are boosted with an immediate positive effect, mediated by local specific receptors stimulation that can work for a temporary need. However if tissue insult prolongs over time increased persistent activation of receptors in end organs exceeds appropriate range switching response from a positive compensatory effect to a hurting action that progressively affects organ function.

The critical message is that any single organ damage will lead to a global autonomic response that, in turn, may have detrimental consequences on all the other end-organs. As matter of fact, an excessive sympathetic response to an asymptomatic cardiac dysfunction may cause a major activation of neuro-hormonal response involving the kidney with obvious detrimental consequences. The final clinical picture will reflect the prevailing end organ damage so that, for instance, a concealed cardiac dysfunction might eventually result in a significant kidney disease.

It is also important to note that other not cardiovascular factors like glycemic hammer or insulin resistance can elicit high sympathetic reflexes leading to resistant hypertension endothelium damage and, ultimately, progression in the atherosclerotic disease.

It's relevant to note that any neuro-hormonal drug, although beneficial, has potential important drawbacks: beta blockers may enhance ischemic stroke incidence in hypertensive and in heart failure (HF) patients. Recently renin inhibition resulted in concerning results in diabetic patients, without to forget moxonidine, a central pharmacological inhibitor of autonomic system, which had consequence on mortality in treated patients.

Our recent observations in advanced HF patients, NYHA f. Cl. III documented that, despite optimized medical therapy, sympathetic activity (Muscle Sympathetic Nerve Activity, MSNA) was elevated, glycemic profile was unsatisfactory, and renal function moderately impaired. After autonomic modulation via baroreflex activation therapy (BAT) a rapid sustained decreased in MSNA was observed with persistence throughout 6 months observation. On note such response was coupled with impressive decrease in

number and length of HF hospitalizations in the 6 months follow up, with decreasing trend in renal dysfunction and in the need of heart failure drugs.

Despite the fact that evidence in the human beings is lacking, it's also important to highlight that in an animal model of coronary mycro-embolization systolic HF, BAT displayed significant effect in decreasing myocardium susceptibility to induction of arrhythmia with programmed electrical stimulation. These data are consistent with previous evidence of a powerful anti-fibrillatory effect of vagus nerve stimulation.

The kidney is a source and a target of the sympathetic nervous system activation. As a consequence, treating the kidney may save the heart. Overall, the paradigm of philosophical change is addressed by the aftermath of renal denervation (RDN) in patients with resistant hypertension. Such patients, thanks to the early autonomic balance restoration, displayed improved arterial compliance coupled with decreased heart rate and myocardial hypertrophy. Similarly after RDN HF patients enjoyed decreased daily intake of diuretic and/or neuro-hormonal drugs.

Last but not least RDN was associated with decreased insulin resistance in patients in which hypertension was part of the metabolic syndrome picture.

The global activation of neurohormonal response, which can be elicited by a single organ injury with immediate multi-organ consequences, might nowadays benefit of direct neural intervention and thus may overcome the limit of focal therapeutic interventions.

In conclusion, while excitatory reflex mediated by excessive sympathetic activation runs detrimental effects in end-organs, mostly driven by catecholamine pro-inflammatory action, the tapering of sympathetic drive and the synergic vagal activation can counteract and repair en-organs function and structure.

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Dr. Hauptman is currently Professor of Internal Medicine and Assistant Dean of Clinical-Translational Research at Saint Louis University. He holds an adjunct position at the School of Public Health, attends as Director of Heart Failure at Saint Louis University Hospital and directs the Clinical Trials Office at the School of Medicine, an entity that serves as the central regulatory entity for contracts, budgeting, invoicing and other tasks associated with clinical studies and trial management.

Dr. Hauptman graduated from Cornell University Medical College and completed internal medicine training at Brigham and Women's Hospital, two years of fellowship in cardiovascular diseases at Mount Sinai Hospital (New York) and a third year specializing in heart failure and transplantation. Subsequently he was on faculty at Harvard Medical School and attending physician in the Division of Cardiology at Harvard (1993-1998).He has received research grants from the American Heart Association and National Institutes of Health, and served as a reviewer for the National Heart Lung and Blood Institute of the NIH, a panel member of the Circulatory System Devices Panel of the Food and Drug Administration (US) and a member of multiple committees of the Heart Failure Society of America. He was an associate editor of the European Journal of Heart Failure *under the editorship of Professor Karl Swedberg and currently serves in that capacity at* Circulation: Heart Failure.

ABSTRACT

Neuromodulation Trials

Paul Hauptman (Saint Louis, USA)

A recent focus of heart failure research, autonomic imbalance, has led to new interest in reversing the effects of parasympathetic withdrawal. The defects associated with impaired parasympathetic nerve activity and the potential downstream mechanisms that mediate the maladaptive effects related to a decrease in vagal tone have been described. Pre-clinical and phase II experience in Europe with vagal nerve stimulation (VNS) has suggested that meaningful changes in structural and clinical outcomes is possible. Currently, a large open label randomized international study is underway (INOVATE-HF) with hard clinical endpoints; the technical approach and the current status of the study will be discussed.

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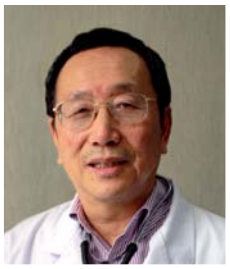
Peter HELD, MD, PhD, FACC is currently a Medical Science Director leading an AstraZeneca effort to improve the conduct and delivery of the company's large clinical outcome studies. He is currently responsible for several global ongoing or planned such studies in the cardiovascular and in the respiratory field. He has long experience from, and interest in the methodology and conduct of both traditionally run and simple focused trials. He has designed and led many global clinical development programs with a large number of new or established chemical entities, leading to successful demonstration of benefit and resulting in global regulatory approvals. He specialised in cardiology and internal medicine. Adjunct professor of clinical CV research at the University of Gothenburg 2001-2010.



Dayi Hu (Beijing, CHN)

Professor Dayi Hu, MD, FACC, FESC, is a Director of the Intervention Center at Peking University People's Hospital, Dean of Clinical Research Institute at Shanghai's Fudan University, immediate past President of the Chinese Society of Cardiology (CSC), President of the Chinese Society of Heart & Brain Diseases (CSHBD), President of the Chinese Society of Cardiovascular Rehabilitation(CSCR), the first President of the Chinese College of Cardiovascular Physicians (CCCP), and Board Member of World Heart Federation (WHF), Academician of The International Academy of Sciences for Europe and Asia (IASEA), International Council Member of American colleague of Cardiology (ACC), Member of ACC Heart Failure and Transplant Council, Board of Directors of the International Society of Cardiovascular Pharmacotherapy (ISCP).

Professor Hu graduated from Beijing Medical School (now Peking University Health Science Center) in 1970 and furthered his education both at SUNY-Oswego and University of Illinois from 1985-1987. Professor Hu has been a pioneer of radio-frequency ablation technology in the treatment of tachyarrhythmia. Since 1980, he had actively shared his work with more than 160 hospitals in China along with a few in India, Vietnam, and Japan. He has specialized in preventative cardiology, electrophysiology, pacemaker implantation and interventional therapy of coronary artery disease. He also focuses on the treatment and prevention of hypertension, coronary heart disease, heart failure, and arrhythmias. Currently, he actively participates in the management and prevention of cardiovascular disease and comprehensive interdisciplinary research on a national level. He is the principal investigator (PI) of the China Heart Survey, the Steer Committee member and many international clinical trials such as ROCKET, BEAUTIFUL, GARFIELD, SHIFIT, SAVE, ACE, MAGELLAN, SIGNIFY, ALECARDIO, Dal-HEART,TIMI 54, etc.

Professor Hu is an Editorial Consultant of JACC *Editorial Board, a member of the editor-in-chief of* Chinese Journal of Cardiology, *an international board member of* Journal of Clinical Cardiology, Journal of the American College of Cardiology, European Heart Journal, *and also of many other national and international medical journals.*

ABSTRACT

Where are the unmet needs?

The challenge of CV prevention: blood glucose, blood pressure and blood lipids

Dayi Hu[1], Linong Ji[1], Danyi Zhang[2],(on behalf of China Cardiometabolic Registries Advisory Board and CCMR-3B Study Steering Committee and Investigators)

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Due to urbanization, variations in diet and lifestyle, and the aging population, the prevalence of diabetes mellitus has nearly tripled in Chinaduring the last decade, rising from 2.5% in 1994 to 9.7% in 2007. Type 2 diabetics have a high risk of developing cardiovascular disease (CVD); diabetes with comorbid of hypertension and hyperlipidemia confers a much higher risk of CVD than diabetes alone. Consequently, early detection followed by effective treatment of complications in diabetics plays a key role in preventing their progression. We recently conducted a nationwide non-interventional study entitled "Nationwide Assessment of Cardiovascular Risk Factors: Blood Glucose, Blood Pressure, and Blood Lipid in Chinese Patients with Type 2 Diabetes" (referred to as the 3B Study). Thispopulation–based cross-sectional study evaluated the current level of control of CVD risk factors and treatment patterns indiabetic population.We have also initiated another observational study, evaluating the effectiveness of early treatment innewly diagnosedType 2 diabetics (NEW2D Study). Both studieswere conducted as part of the China Cardiometabolic Registries (CCMR), a platform designed to assess real-world clinical outcomes of cardiovascular and metabolic diseases in China. CCMR-3B study revealed that while there were close to 50% of the patients with type 2 diabetes reached proper glycemic control defined as HbA1c < 7%, only 5.6% reached all "3B" control (i.e. HbA1c<7%, blood pressure < 130/80 mmHg, total cholesterol < 4.5 mmol/L).An effective disease management strategy for patients with type 2 diabetes

aiming for reducing CVD risk, thatnot only addressing hyperglycemia but also hypertension and hyperlipdemia, is imperative.

Ewa Jankowska (Wroclaw, POL)

Ewa A. Jankowska, MD, PhD, FESC, is Professor of cardiology and head of Laboratory of Applied Research on Cardiovascular System in Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland, and Centre for Heart Diseases, Military Hospital, Wroclaw, Poland. She underwent clinical and research training in Wroclaw (under the supervision of Prof. P. Ponikowski), and also in Royal Brompton Hospital, National Heart & Lung Institute, Imperial College London (under the supervision of Prof. P.A. Poole-Wilson). She was the president of the Committee of Young Scientists, an advisory board of the Ministry of Science and Higher Education in Poland. Currently, she is the president of the "Club 30" of Polish Cardiac Society, the member of "Cardiologists of Tomorrow" nucleus of the European Society of Cardiology, and the member of the Online Educational Committee of the Heart Failure Association of the European Society of Cardiology. She is a co-author of more than 150 scientific papers in peer-reviewed journals, IF >300, with the following main areas of research: the role of peripheral mechanisms in the progression of heart failure (including cardiorespiratory reflex control, hormone derangements, deficiencies in anabolic hormones, cachexia), co-morbidities in heart failure (including cardiorenal anemia syndrome and iron deficiency), exercise training in heart failure, acute heart failure, experimental model of tachycardia-induced cardiomyopathy in pigs, male aging, andropausal syndrome.

ABSTRACT

Iron deficiency in heart failure: what can we expect from ongoing trials of ferric carboxymaltose therapy (EFFECT-HF, CONFIRM-HF)?

Ewa A. Jankowska, MD, PhD, FESC

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Iron deficiency (ID) is prevalent in patients with systolic heart failure (HF), both in those with and without anemia. The presence of ID exaggerates detrimental effects of concomitant anemia, but most importantly unfavourable consequences of ID are markedly seen in patients with HF with preserved erythropoiesis. ID is associated with poor quality of life, impaired exercise capacity, increased hospitalization rate and high mortality in patients with systolic HF. The FAIR-HF study demonstrated that i.v. ferric carboxymaltose lessens the symptoms of HF, improves quality of life and exercise capacity in these patients. The origin of ID and the pathogenesis of abnormal iron metabolism occurring in HF remain unclear. It has not been confirmed ID developing in patients with HF to be accompanied by augmented inflammation, and in fact, ID has been demonstrated to be associated with low (not high) circulating hepcidin.

There are several circulating biomarkers measured in peripheral blood (ferritin, transferrin saturation, soluble transferrin receptor, hepcidin) which are known to indirectly assess iron status in a general population, but their clinical applicability has never been validated in patients with cardiovascular disease. In particularly, their role in the biomarker-driven iron supplementation in patients with HF has never been proven. Taking into consideration the role of iron for extra-haematopoietic tissues which have high energy demand (e.g. myocardium, skeletal muscle), it seems reasonable to assess the clinical effects of iron supplementation also on their functioning (e.g. exercise capacity, muscle strength and endurance) beyond the effects on erythropoiesis. The EFFECT-HF and CONFIRM-HF trials have been designed to assess the impact of i.v. ferric carboxymaltose vs standard care (considering that some patients will be treated with p.o. iron in the EFFECT-HF trial) or vs placebo (in the CONFIRM-HF trial) in patients with symptomatic systolic HF on functional capacity assessed using either peak oxygen consumption or the distance during the 6-minute walk test. Importantly, the efficacy and safety of iron supplementation are to be related to baseline values and changes in several biomarkers of iron status.

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James Januzzi (Boston, USA)

Dr. James Januzzi is currently the Roman W. DeSanctis Endowed Distinguished Clinical Scholar in Medicine and Director of the Cardiac Intensive Care Unit at the Massachusetts General Hospital. He is Professor of Medicine at Harvard Medical School.

Dr. Januzzi is a teacher, researcher and active clinician. He is a frequent speaker at scientific meetings on the local, national and international level. Dr. Januzzi has contributed greatly to the understanding of cardiac biomarker testing, where his work with the natriuretic peptides and troponin has set international standards for use in diagnosis, prognosis, and management of patients suffering from acutely decompensated heart failure, chronic heart failure as well as those with acute coronary syndrome. Dr. Januzzi's research group has also pioneered first-in-human analyses of several novel biomarkers, including two with regulatory approval that are also incorporated into clinical practice guidelines (ST2 and Galectin-3). Additionally, he has performed extensive work in studies of biomarkers in acute kidney injury. He has published more than 400 manuscripts, book chapters, and review articles, has edited two text books on cardiac biomarker testing. He is on the editorial board of numerous scientific journals, including current service as an Associate Editor at the Journal of the American College of Cardiology: Heart Failure. He was the chairman of the NT-proBNP Consensus Panel, is the lead author of the Heart Failure Section for the Universal Definition of MI Biomarker Task Force, and is a section editor and member of the working group for the 2013 ACC/AHA Clinical Practice Guidelines for Heart Failure. He is an active clinician, with a busy consultative cardiology practice, and has been the cardiology consultant to the Boston Red Sox Baseball Club since 2005.

ABSTRACT

Biomarker aspects: which biomarker? How to judge best approach for application?

James L. Januzzi, Jr, MD, Boston, MA

A broad range of biomarkers are currently under evaluation for clinical use. Many have compelling links to the biology and pathophysiology of heart failure, but the transition from bench to bedside is complex, and a journey that many biomarkers cannot make, due to limitations in our understanding of their biology. We recently articulated strict expectations for how to evaluate a biomarker for clinical utility. These criteria will be discussed, along with future perspectives.

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Young-Hoon Jeong (Jinju, KOR)

Young-Hoon Jeong, MD PhD, is an associate professor of internal medicine at the Gyeong-Sang National University of Medicine from 2007. Dr. Jeong obtained his MD degree from the Chung-Ang University in South Korea in 1997. He subsequently did a fellowship in cardiology at the Asan Medical Center in South Korea, and worked as an exchange professor for the Sinai Center for Thrombosis Research in USA between 2010 and 2012. He was awarded the "Young Author Achievement Award" in 2010 by the JACC editorial board, and his papers were cited as "Most Important Papers in Antiplatelet Therapy" by 2011 Circulation Editors' Picks. He has been a member of the Platelet Research Group and ESC Working Group of Thrombosis. He has conducted studies about tailored antiplatelet therapy using pharmacogenetics and racial disparity, and invented the concept of "East Asian Paradox" and "thrombogenecity-based antithrombotic therapy". He has been devoted to evaluate the clinical benefit and pharmacodynamic effect of "Cilostazol", and published more than fifteen papers related with this content ("ACCEL" series). He is now focusing on choosing the different antiplatelet regimen according to the disease activity and ethnicity.

ABSTRACT

What does Cilostazol have to offer?

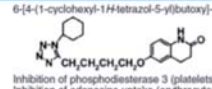
Young-Hoon Jeong (Jinju, KOR)

Current oral antiplatelet therapy mainly targets the inhibition of cyclooxygenase-1 (COX-1) and the P2Y12 receptor in patients with ACS or those treated with PCI. Despite proven clinical efficacy by potent P2Y12 inhibitor, the persistent ischemic event occurrence (-10%) suggests that dual antiplatelet therapy has reached a ceiling in its effect in attenuating thrombotic events and that some ischemic events are mediated by other pathways (non-COX-1 and non-P2Y12). Meanwhile, phosphodiesterases (PDEs) are potential targets for inhibition to attenuate adverse cardiovascular events in patients with coronary artery disease (CAD).

Cilostazol is a dual inhibitor of PDE3 and adenosine reuptake that may have an important role in reducing ischemic events associated with CAD. Because atherothrombosis is a systemic disease, proven benefit of cilostazol on stroke and peripheral artery disease may increase its clinical usefulness for long-term treatment. Cilostazol exerts not only antiplatelet actions, but also pleiotropic effects including

inhibition of neointimal hyperplasia, therefore preventing both in-stent restenosis and thrombosis. It also provides vasodilation, enhances endothelial function, decreases various inflammatory pathways, improves the lipid profile, and has cardioprotection against ischemia-reperfusion injury. The antiplatelte effect of prasugrel and ticagrelor are so strong in the selected patients that can increase the risk of clinically serious bleeding. Because adjunctive cilostazol to DAPT has not been increased the risk of serious bleeding compared with DAPT, its safey benefit must be considered in choosing the antiplatelet regimen. The adenosine therory extrapolating the mortality benefit of ticagrelor vs. clopidogrel has been suggested. However, the elevation of adenosine level in blood seems to be greater by classic PDE inhibitors (dypyridamone and cilostazol) than by ticagrelor. The clinical efficacy and safety of adjunctive cilostazol to DAPT in the high-risk patients must be tested compared with DAPT including potent P2Y12 inhibitor.

Table 1. Pharmacokinetics, Pharmacodynamics and Mechanisms of Cilostazol[4,18,20]

Drug name	6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone
Chemical structure	
Mechanism	Inhibition of phosphodiesterase 3 (platelets, VSMC, heart, and adipocytes)→increased cAMP Inhibition of adenosine uptake (erythrocytes, platelets, muscle cells, and endothelial cells)→increased adenosine
Metabolism	Extensively metabolized by liver *OPC-13015: mainly produced by *CYP3A4* *OPC-13213: mainly produced by *CYP3A5* and *2C19*
Maximal concentration	3–3.65h
Maximal effect	~6h (platelet inhibition)
Excretion	Urine (74%), feces (20%)

Target effect	**PDE3-dependent (cAMP)**	**PDE3-independent**
1. Antiplatelet effect	O	O (adenosine)
2. Vasodilatory effect (VSMC relaxation)	O	O (adenosine)
3. Antiproliferative effect (control of VSMC proliferation and migration)	O	O (adenosine)
4. Effect on endothelial dysfunction (NO release)	Δ	Δ (PGE$_1$, PGI$_2$, Sirt 1)
5. Antiatherogenic effect (decrease of adhesion molecules, control of inflammatory cells and cytokines, etc)	Δ	–
6. Control of dyslipidemia (decrease of triglyceride, and increased HDL-cholesterol and apolipoprotein A$_1$)	Δ (lipoprotein lipase)	–
7. Protection against ischemia-reperfusion injury (cytoprotection)	–	Δ (adenosine)
8. Positive chronotropic effect	O	–
Negative chronotropic effect	–	Δ (adenosine)

O, definite; Δ, proven by several studies; VSMC, vascular smooth muscle cell; cAMP, cyclic adenosine-monophosphate; *CYP*, cytochrome P450; PDE, phosphodiesterase; NO, nitric oxide; HDL, high-density lipoprotein; PG, prostaglandin; SIRT, sirtuin.

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David Kallend (MedCo, USA)

Following graduation from Kings College Hospital School of Medicine in London, Dr. David Kallend worked in various hospital departments in the UK, predominantly at the Royal Postgraduate Medical School Hammersmith Hospital, London, where his final post was Research Fellow in the Department of Surgery. In 1995 he joined the pharmaceutical industry. He initially worked as an International Research Physician on imaging studies for Schering AG in Berlin. Following this he joined AstraZeneca, working mainly on the development of rosuvastatin. He was also involved as an advisor to other cardiovascular programs and collaborations. From 2005 to 2012 he was the Global Clinical Leader and a Group Medical Director for dalcetrapib at Roche. During these last 18 years he has been involved with many clinical studies in the cardiovascular area and several regulatory approvals. His current role is Vice President and Global Medical Director for the lipid programs, Apo A-1 Milano and aPCSK9, at The Medicines Company.

ABSTRACT

Atherosclerosis trialists forum:
new lipid associated targets and improved pathway to successful clinical trials

Dr David Kallend
The Medicines Company, Zurich, Switzerland

New lipid associated targets for the treatment of atherosclerosis have been assessed with pharmacotherapy for several decades. The most successful have undoubtedly been the HMG-CoA reductase inhibitors or statins which lower total cholesterol, LDL-cholesterol and triglyceride and raise HDL-cholesterol. These changes in biomarkers have been associated with significant improvements in cardiovascular mortality and morbidity. Other lipid targets have been less successful in terms of improvements in cardiovascular outcomes despite significant changes in these biomarkers.

More recently, when added to a background of optimised therapy which includes statins, there have been failed outcomes studies which therapies such as niacin, fibrates and CETP inhibitors such as torcetrapib and dalcetrapib. The fact that these therapies have significant effects on biomarkers which are associated, at least epidemiologically,

with cardiovascular outcomes has added complexity to drug development in this area. Based upon this, unless a new therapy is a statin, approval for such a therapy is usually dependent on outcomes data which involves a lengthy and costly drug development. One exception to this may be the aPCSK9 therapies where LDL-C may be a route to approval in certain high risk populations such as familial hypercholesterolemia and statin intolerant patients. Retrospectively, once outcome benefit is shown for a new therapy then the biomarker may be validated, and may even help other therapies in the class gain a more rapid approval.

Imaging modalities have also been used to assess new therapies and these may eventually prove to be a better surrogate than biomarkers such as HDL-C, although LDL-C is still the gold standard and may be as reliable as any other biomarker. This is still the case for the statins.

Currently, these biomarkers can only be used prospectively when making decisions regarding the conduct of large Phase III outcomes trials. Until these surrogate biomarkers are clearly linked to improvements in outcomes and therefore validated by the regulatory authorities globally as a route to approval of new lipid modifying therapies, the development of new therapies for the majority of lipid targets will remain a lengthy and costly process.

Adnan Kastrati (Munich, GER)

Adnan Kastrati, MD, is Professor of Cardiology and Head, Catheterization Laboratory at the Deutsches Herzzentrum, Technische Universität, and Director, ISAResearch Center, Munich, Germany. Dr. Kastrati received his medical degree from the University of Tirana, Albania and completed his training in Internal Medicine and Cardiology in the University Hospital Center, Tirana, Albania. He served a fellowship in Interventional Cardiology in the University of Heidelberg and Technical University of Munich, Germany. He is a Fellow of the European Society of Cardiology. Dr. Kastrati has played a pivotal role in the design and conduction of a large number of randomized clinical trials, mostly identifiable by the "ISAR"-acronym.

Dr. Kastrati has written or contributed to more than 400 original publications mostly in high ranked medical journals. He serves on the Editiorial Board of main cardiology journals.

His main interests focus on reperfusion strategies in acute myocardial infarction, evaluation of new device technologies in interventional cardiology, peri-interventional antithrombotic therapy and genetics in cardiovascular medicine.

Jae Kim (Amgen, USA)

Dr. Jae B. Kim, MD, FACC, is a Clinical Research Medical Director in Global Development at Amgen where he is the Global Development Leader for Heart Failure. He has worked at Amgen for the last 4 years where he has held roles of increasing responsibility. He has experience in the clinical development of large and small molecules across early and late phase development.

Dr. Kim joined Amgen from the Cardiovascular Division of the Brigham & Women's Hospital where he served on the Faculty of Medicine at Harvard Medical School, was a Principal Investigator on the Systems Biology of Cardiomyopathies, and was an Attending Cardiologist at the Brigham & Women's Hospital. Dr. Kim developed and patented a method for next-generation DNA sequencing, and he was the very first to publish a deep-sequenced transcriptome of a cardiomyopathic heart.

Dr Kim received his B.A. Magna Cum Laude *in neurobiology from Cornell University. He received his medical degree from Cornell University, his postdoctoral fellowship at the Howard Hughes Medical Institute in the Department of Genetics at Harvard Medical School, and his clinical and research fellowships in Cardiovascular Disease at the Brigham & Women's Hospital and Harvard Medical School.*

Paulus Kirchhof (Birmingham, GBR)

Professor Paulus Kirchhof is a Chair in Cardiovascular Medicine at the University of Birmingham. His appointment includes a position as cardiology consultant at SWBH NHS Trust where he pursues general and interventional cardiology with a focus on atrial fibrillation and sudden death. He is also affiliated as a researcher to the Department of Cardiology and Angiology at University of Münster, Germany.

Professor Kirchhof graduated from Münster Medical School, Münster, Germany after studying Medicine at the Universities of Heidelberg, Germany; Münster, Germany; Lille, France; and Georgetown University, Washington DC, USA. He received postgraduate training in Internal Medicine, Cardiology, and Intensive Care Medicine at University Hospital Munster. He worked there as a senior general and interventional cardiologist until joining University of Birmingham in 2011.

Professor Kirchhof is an active member of several research consortia and professional organisations. Among others, he is a member of the Board of the German Atrial Fibrillation competence Network (AFNET), the Board of the European

Heart Rhythm Association, and is a member of the Committee for Practice Guidelines (CPG) of the European Society of Cardiology.

He has published 200 scientific articles in peer-reviewed journals, and received several research prizes, is an editorial consultant to the Lancet and deputy editor for Heart. His research tries to improve management of patient with cardiovascular disorders "from molecule to man". He has a special interest in atrial fibrillation and cardiomyopathies where his work extends from wet lab science to the conduct of international registries and controlled clinical trials. His research has been supported by the German Research Foundation (DFG), the European Union, Fondation Leducq, the German Ministry for Education and Research, and the British Heart Foundation, among others. He also contributes to the development, publication, and implementation of guidelines in Europe and in North America.

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Keld Kjeldsen (Copenhagen, DEN)

Professor, Chief Physician, D.Sc. Specialist in cardiology and internal medicine. Professor of clinical and experimental cardiology with focus on sudden cardiac death. Aalborg University, Denmark. Chief physician at Rigshospitalet (Copenhagen University Hospital) and Bornholms Hospital. Chairman of European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology. Scientific Committee Expert, European Medicines Agency (EMA), London, UK.

Head of Ion research laboratory at Rigshospitalet (Copenhagen University Hospital) and Danish Arrhythmia Research Centre.

Research interests: Cardiology, cardiovascular pharmacology, potassium, potassium-pump.

Author of around 200 papers and 2 books. Presenter of more than 150 lectures etc. nationally and internationally. Extensive experience as peer reviewer at scientific journals, from editorial boards, as chairman and organizer of meetings and congresses and as examiner of theses and research projects nationally and internationally. More than 3300 citations in Web of Science. H-index 33.

Extensive experience as chairman and organizer of educational courses.

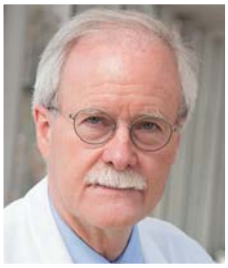
Christoph Koenen (BMS, FRA)

Christoph Koenen MD, MBA is currently heading up CV/Met medical affairs and clinical development for BMS in Europe within the GDMA organisation. Dr Koenen joined BMS in April 20011. He joined BMS from Novo Nordisk, where his last position was Vice President and Head of Medical Affairs Diabetes.

During his nine years with Novo Nordisk Dr Koenen worked on the development of several compounds for Novo Nordisk, including three different insulin compounds. His responsibilities included the design and execution of global research and development plans as well as the filing of three different insulin products. Before joining Novo Nordisk in 2002, Dr Koenen worked for GlaxoSmithKline. While at GlaxoSmithKline, Dr Koenen was involved in the development of anti-diabetic compounds.

Dr Koenen received his medical degree from Ruprecht-Karls University School of Medicine in Heidelberg, Germany in 1994. He also holds a Master of Business Administration from Schiller International University. In addition to attending Heidelberg Medical School, Christoph attended medical school in Johannesburg, South Africa, Basel Switzerland and Columbia, Missouri, USA.

Dr Koenen is a board certified internist and diabetologist.



Wolfgang Koenig (Ulm, GER)

Wolfgang Koenig, MD, PhD, FRCP, FESC, FACC, FAHA, is a Professor of Medicine and Cardiology at the University of Ulm Medical School, Ulm, Germany. He is Board certified in internal medicine, cardiology, and in intensive care medicine with special interest in invasive and interventional cardiology. At present he serves as a Consultant in Cardiology, and is the Director of the Preventive Cardiology Program and the Clinical Trial Unit (CTU) at the Department of Internal Medicine II - Cardiology of the University of Ulm Medical Center.

Dr. Koenig`s research interests involve the molecular basis of atherothrombogenesis including genomics, metabolomics, and other technologies. Further interests include type 2 diabetes, the metabolic syndrome, the clinical pharmacology of cardiovascular active compounds, and the clinical epidemiology of cardiovascular disorders, focusing on the identification and evaluation of new biomarkers for cardiometabolic diseases. Dr. Koenig has published more than 550 research papers and reviews. He has an H-Index

of 60. He is a member of the Editorial Board of Clinical Chemistry *and Associate Editor of Atherosclerosis. Presently he serves on the Steering Committee of various large international randomized clinical trials testing innovative targets in cardiovascular medicine.*

Joerg Koglin (Merck, USA)

Joerg Koglin, MD, PhD, is Executive Director, Section Head, Cardiovascular Clinical Research, at Merck Research Laboratories. He is board-certified in Internal Medicine and Cardiology. After more than 10 years as an academia-based physician with a junior faculty position at the Department of Cardiology, University of Munich, Germany, Joerg has worked in corporate R&D for over 10 years. Since joining Merck Research Laboratories in 2007 in the Late Stage Global Clinical Development organization, Joerg has been involved as the Clinical Lead and Development Team Lead in various early and late development programs for atherosclerosis, hypertension, ischemia/reperfusion, thrombosis and atrial fibrillation compounds and supporting the development of novel biomarker platforms to further enhance clinical development of cardiovascular drugs.

In his current role, Dr. Koglin is Section Head in the Cardiovascular Clinical Research Team providing clinical and medical oversight for all development programs around heart failure, pulmonary hypertension, and atrial fibrillation, and supports overall cardiovascular strategy development.

Peter Kolkhof (Bayer, GER)

Peter Kolkhof, PhD, is a Principal Scientist at Cardiology Research, Global Drug Discovery of Bayer HealthCare. He studied biology with emphasis on molecular biology, biochemistry and pharmacology and received his Doctorate in Natural Sciences from Cologne University in Germany. He joined Bayer in 1995 as laboratory head in the Institute for Cardiovascular Research and since then he directed research laboratories with focus on molecular biology, cell biology and in vivo pharmacology. Dr. Kolkhof is a preclinical project leader in the area of heart diseases research and an applicant of about 40 patents on novel chemical entities for the potential treatment of cardiovascular diseases. He is a member of the German Society of Cardiology and the European Society of Cardiology.

ABSTRACT

What is in the pipeline? Next generation MRAs

Peter Kolkhof (Bayer, GER)

Several pharmaceutical companies have implemented programs to identify especially novel non-steroidal MRAs that overcome the limitations of the available steroidal MRAs spironolactone and eplerenone [1].At least five novel MRAs from Pfizer, Eli Lilly, Mitsubishi, Daiichi Sankyo and Bayer have reached clinical phases in human. Most of these novel MRAs are in development for the indication diabetic nephropathy. A brief overview will be given on specific properties of these novel MRAs as published in preclinical in vitro and in vivo investigations [2-6]. The most advanced novel MRA is finerenone (BAY 94-8862) [7] which has been recently investigated in a clinical phase II study called 'ARTS' (MinerAlocorticoid-Receptor Antagonist Tolerability Study) among patients with HFrEFand CKD. In these patients, finerenone was at least as effective as spironolactone in decreasing BNP, NT-proBNP and urinary albumin, but it was associated with lower incidences of hyperkalemia and worsening of renal function [8].

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Stuart Kupfer (Takeda, USA)

Stuart Kupfer MD serves as Global Therapeutic Area Head of Cardiovascular and Metabolic Diseases at Takeda Pharmaceuticals International and is based in Deerfield, IL, USA. His areas of research include heart failure, hypertension, thrombosis, diabetes, obesity, and dyslipidemia. Dr. Kupfer previously served on the medical school faculty of Washington University in St. Louis, MO, USA where he conducted basic research in gene regulation of steroid hormone receptors and bone metabolism. Dr. Kupfer received his M.D. at the University of Florida in Gainesville, FL, USA and conducted his residency training at Yale-New Haven Hospital, New Haven, CT, USA and endocrinology fellowship at the University of North Carolina in Chapel Hill, NC, USA.

ABSTRACT

Examining the operational challenges of the EXAMINE trial

Stuart Kupfer (Takeda, USA)

Alogliptin is a dipeptidyl peptidase inhibitor developed by Takeda and approved for treatment of type 2 diabetes

(T2D) in the United States (US), Europe, and Japan. Prior to approval in the US, the Food and Drug Administration (FDA) required Takeda to rule out unacceptable cardiovascular (CV) risk of alogliptin according to the 2008 draft guidance.[1] In order to meet this requirement, Takeda sponsored EXAMINE, a randomized, double-blind, multinational outcomes trial to evaluate CV safety of alogliptin compared with placebo in patients with T2D and recent acute coronary syndromes.[2] The primary endpoint was a composite of major adverse cardiovascular events (MACE): CV death, myocardial infarction, and stroke. The early interim primary endpoint analysis of EXAMINE met the threshold for FDA approval – i.e. the upper boundary of the one-sided repeated confidence interval for the hazard ratio was less than 1.8. In the final analysis of 621 MACE events, alogliptin was proven to be non-inferior to placebo based on the FDA-specified margin of 1.3.[3] During the EXAMINE trial conduct, special precautions were implemented to protect the study blind and data integrity, particularly with respect to activities associated with the early interim analysis and NDA submission.

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Carolyn Lam (Singapore, SGP)

Dr Carolyn Lam, MBBS, MRCP, MS, FACC, FESC, is an Associate Professor of the Yong Loo Lin School of Medicine, Singapore; a Consultant Cardiologist at the National University Heart Centre, Singapore; and the Director of the first Women's Heart Health Clinic in Singapore. She graduated from the Faculty of Medicine, National University of Singapore, did her Cardiology Fellowship at the Cardiac Department of NUH, and pursued her Research Fellowship at the Cardiorenal Laboratory, Heart Failure Fellowship at the Division of Cardiovascular Diseases, and Advanced Cardiology and Master of Biomedical Sciences at Mayo Clinic, Rochester MN. She returned to Singapore in 2010 on the National Medical Research Council's Clinician Scientist Award, concurrently holding appointments as Assistant Professor of Medicine, College of Medicine, Mayo Clinic, and Adjunct Assistant Professor, Section of Preventive Medicine & Epidemiology, Boston University School of Medicine.

Dr Lam is the principal investigator of an ongoing nation-wide heart failure study in Singapore (the Singapore Heart Failure Outcomes and Phenotypes [SHOP] study) and a multinational Asian study of patients with heart failure across 11 Asian countries (Asian Sudden Cardiac Death in Heart Failure [ASIAN-HF] study). She is on the Executive Committees of several global heart failure trials. She started the first Heart Failure with Preserved Ejection Fraction Programme and Women's Heart Health Clinic in Singapore, was awarded the L'Oreal Women In Science Award (2012) for her work in women's cardiovascular disease, was named an InterAcademy Medical Panel Young Physician Leader at the World Health Summit in Berlin (2012), and is currently recipient of the Senior Investigator Clinical Scientist Award (2013). She is the editor-in-chief of the ASEAN Heart Journal.

ABSTRACT

Acute heart failure and heart failure with preserved ejection fraction: the next frontier
Insight from epidemiology

Carolyn S.P. Lam

Despite widespread recognition of the large and growing global public health burden of acute heart failure (AHF) and heart failure with preserved ejection fraction (HFpEF), clinical management guidelines for both these heart failure syndromes have not changed since the 1970's, since no new therapies have been shown to improve outcomes. The recent failure of large-scale clinical trials in AHF and HFpEFunderscores the need for better understanding of the epidemiology, clinical course and outcomes of these syndromes.

Epidemiologic studies have traditionally been viewed as tools to understand the burden of disease, using conventional indices such as incidence, prevalence, hospitalization and death rates. More recently, epidemiologic studies have been utilized to gain insights into disease mechanisms, clinical sub-types, disease trajectories and cause of death. The knowledge gained allows a deeper understanding of patient characteristics, disease pathophysiology and development of outcomes, which in turn can guide patient selection, identification of pathophysiologic targets, and the design of future clinical trials in AHF and HFpEF.

Furthermore, heart failure clinical trials are increasingly becoming global trials, in order to meet the need for large numbers of patients over short periods of recruitment. At the same time, the global burden of cardiovascular disease has shifted to developing regions, where data are notably lacking, and where, importantly, patient populations may differ. For instance, Atherton et al recently showed remarkable differences between Asian patients in the ADHERE-Asia Pacific study and Western patients in the US-based ADHERE registry, with important implications for global trial design. Global epidemiologic studies can aid by providing the fundamental knowledge base needed for effective large-scale clinical trial development in AHF and HFpEF.

Andrea Laslop (EMA, AUT)

Andrea Laslop joined AGES, the Austrian Agency for Health and Food Safety, on January 1st, 2006. She is heading there the Scientific Office, which constitutes the link to the European Medicines Agency (EMA) with a focus on the different types of centralised European procedures during drug development, marketing authorisation applications and life-cycle management. Since 2003 she is a member of the EMA Scientific Advice Working Party, in 2007 she also became alternate member of the Committee for Human Medicinal Products of the EMA, where she is representing Austria now as the full member since 2009.

Prior to this Andrea Laslop worked as an associate professor of pharmacology and toxicology at the Medical University of Innsbruck, Austria, where she earned her MD and later on specialized as a pharmacologist. Her professional career included several sojourns for joint research projects at the NIMH in Bethesda, the Albert Einstein College of Medicine in New York and the Clinical Research Institute of Montreal.

Martin Lefkowitz (Novartis, USA)

Martin Lefkowitz, MD, is currently Cardiovascular Therapeutic Area Head at Novartis Pharmaceuticals Corporation. Over his 15-year career with Novartis, Dr. Lefkowitz has been involved in the clinical development of compounds primarily in cardiovascular medicine, including the design and execution of major outcome trials such as ACCOMPLISH and PARADIGM-HF. He has largely worked in cardiovascular medicine with a focus on heart failure, hypertension and coronary artery disease. He received a medical degree from New York University and did his internal medicine training at the University of Michigan. Subsequently he completed a fellowship in nephrology at the University of Pennsylvania. Dr. Lefkowitz was in the clinical practice of nephrology prior to joining the pharmaceutical industry.

Cecilia Linde (Stockholm, SWE)

Cecilia Linde, MD, PhD, is Professor and former Head of Cardiology of the Karolinska University Hospital in Stockholm, Sweden. Her research focuses CRT in heart failure. She was a co-chairman in the MUSTIC study the first randomized controlled study ion CRT in severe to moderate heart failure and is the principal investigator of the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study, which was to first to show a benefit of CRT in mild heart failure. She is presently the PI of the ongoing MiracelEF study focusing on CRT in mild to moderate heart failure and LVEF 36-50%. Dr Linde is the author of more than 200 papers, reviews and meeting abstracts in a wide variety of fields including CRT, haemodynamic monitoring and the molecular biology of arrhythmias, and she serves on the editorial board of several journals. She has been a board member of the European Heart Rhythm Association (EHRA), an official branch of the European Society of Cardiology. She has been involved in the EHRA Task Force for guidelines in pacing and CRT published 2007 updated 2010 and is a member of the scientific committee of the European cardiac resynchronization therapy survey. She is chair of the scientific program committee for EHRA Europace Cardiostim in Milan 2015 and a member of the Board EHRA.

ABSTRACT

Thrombosis trialists workshop: competing new therapies in atrial fibrillation and heart failure

What is the role of catheter ablation and LAA closure? Registries and ongoing trials

Cecilia Linde (Stockholm, SWE)

Atrial fibrillation is common in the general population and increases with age. Thus 15% of 80 year olds have AF as evidenced from the Swedish patient registries. Even more patients may have silent paroxysmal or persistent AF. The stroke-risk increases by accompanying disease and risk factors according to the CHADS2VASC score. The HAS BLED score helps in balancing the risks of bleeding against the benefits of stroke prevention when deciding on oral anticoagulants.

Only 50% of patients with atrial fibrillation are on medication with oral anticoagulants. Moreover of patients prescribed warfarin due to a previous ischemic stroke more than half stop taking it over a 2 year follow up.

Patients are thus very reluctant to take warfarin or have a contraindication. Contraindications also apply for the new anticoagulants due to comorbidities, renal failure of concomitant medication with drug interactions. Therefore there is a need for alternative treatment to reduce thromboembolic risk in such patients.

More than 90% of thrombi are believed to have originated in the left atrial appendage (less in the > 80 yr old). It would thus seem appealing to occlude the left atrial appendage to impair thrombus formation. For patients with contraindication for OAC LAA occlusion by special devices

such as the WATCHMAN, AMPLATZER or APC may be an alternative therapy even though randomized trials with morbidity and mortality as endpoints are lacking.

Pulmonary vein ablation for atrial fibrillation may be curative and is indicated for patients intolerant to antiarrhythmic drugs in the guidelines. There is remaining uncertainty as to how long a time OAC are needed after a successful ablation especially in view of the relatively high relapse rate in which a large proportion needs 2 ablation procedures for successful results. Moreover, the long lasting effect of maintenance in sinus rhythm is unclear and thus it may be difficult to decide on when OAC therapy can be interrupted.

The purpose of this discussion is to discuss current evidence for LAA occlusion devices and to some extent discuss results in ablation for atrial fibrillation.

Ray Lipicky (North Potomac, USA)

attending by conference call

Raymond John Lipicky, MD is the Director of LIPICKY, LLC (a consulting company) having retired (March 2002, after 21 years of service) from the US Food and Drug Administration (FDA) where he held the position of Director, Division of Cardio-Renal Drug Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research. Previously, he was on the faculty of University of Cincinnati, College of Medicine (for 14 years) where he held the positions of Professor of Pharmacology and Professor of Medicine and Director, Division of Clinical Pharmacology at the time he joined FDA. He is a graduate of the University of Cincinnati College of Medicine, trained in Internal Medicine and Cardiology. He also had an appointment as Visiting Scientist at the Marine Biological Laboratory (Woods Hole, MA) where, for about 30 years, he had a summer laboratory pursuing an interest in drug effects on electrically-excitable membranes, although his laboratory is no longer active.

Dan Longrois (Paris, FRA)

Dan Longrois is Professor of Anaesthesia and Intensive Care at Bichat-Claude Bernard Hospital (Assistance Publique-Hôpitaux de Paris), Paris, France. trained in anaesthesiology and intensive care, and obtained a PhD in cardiovascular pharmacology at Paris VI University.

A postdoctoral Fellow at the Cardiovascular Division of the Brigham and Women's Hospital at Harvard Medical School, Boston, MA, USA, Dr Longrois was Chair of the Departments of Anaesthesia and Intensive Care in Nancy, France, between 2004 and 2008. He has been a member of the Scientific Committee of the French Society of Anaesthesia and Intensive Care and of the Cardiovascular sub-committee of the European Society of Anaesthesia, and is a past-President of the French Society of Perfusion.

Dr Longrois' research interests include the cellular and molecular mechanisms of inflammation in cardiovascular diseases and the interaction(s) between inflammation and peri-operative stress.

ABSTRACT

How can vasodilators save lives in acute heart failure?

Dan Longrois (Paris, FRA)

Recent meta-analyses on inotropes (dobutamine), inodilators (milrinone, levosimendan) and studies on vasodilators suggest that dobutamine and milrinone are at best neutral (but may be deleterious) whereas levosimendan and vasodilators have beneficial effects on survival in patients with acute heart failure (AHF) syndromes. The aim of this essay is to attempt to explain these results through a novel conceptual framework of cardiocirculatory (patho) physiology.

Many clinical studies in AHF were based and interpreted on a 'cardiocentric' framework. The three above-mentioned categories of drugs are thought to increase cardiac output (CO) through increased ejection volume by increasing inotropism (inotropes and inodilators) or decreasing systemic vascular resistance (inodilators and vasodilators). We complement this 'cardiocentric' framework with a more integrated one based on: (i) the effects of drugs on venous return (VR), equal to CO (VR is the difference between mean systemic and right atrial pressures divided by venous resistance; maintenance of adequate VR depends on the stressed blood volume); inodilators and vasodilators may decrease the stressed volume and therefore may decrease VR; (ii) the coupling of the left ventricle–aorta and right ventricle–pulmonary artery (dependent on the compliance of the large arteries), which is increased by inodilators and vasodilators in the absence of measurable effects on arterial systemic/pulmonary pressures); (iii) the vascular waterfall phenomenon, which explains that inodilators and vasodilators, by decreasing intra-organ arterial resistance, can improve organ perfusion even in previously mildly hypotensive patients (in the absence of cardiogenic shock).

The challenge is to transform these concepts into clinical tools to guide therapy in AHF syndromes.

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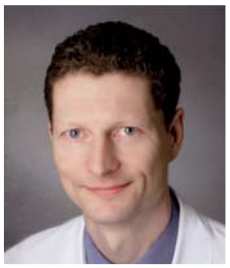

Matthias Lorenz, (Frankfurt, GER)

Matthias Lorenz studied Human Medicine at Saarland and Heidelberg universities from 1992-2000, and specialized in Neurology in 2008. He acquired a postgraduate degree in medical biometry and statistics in 2008 (GR-IBS). He received the venia legendi *for Neurology in 2009.*

Since 2000 he is involved in stroke and vascular medicine both clinically and scientifically. He is an expert in acute stroke medicine, vascular ultrasound and cardiovascular epidemiology. His current position is senior physician at the Department for Neurology at the University Hospital Frankfurt / Main (Head: Prof. Helmuth Steinmetz). He is the Principal Investigator and main coordinator of the PROG-IMT project (Individual progression of carotid intima media thickness as a surrogate for vascular risk), a multinational collaborative IPD meta-analysis project.

ABSTRACT

Established measures of atherosclerosis: angiography, IVUS, and IMT

Matthias Lorenz, (Frankfurt, GER)

CIMT, measured at one occasion, is predictive of future CVD events, independent of all other cardiovascular risk factors. For the use in RCTs, it is logical to use the individual change in CIMT as a 'surrogate endpoint' instead, mostly expressed as 'annual CIMT progression'. It has not yet been shown convincingly, that CIMT progression is a surrogate of vascular event.

In the general population, CIMT progression has not been shown to be predictive of future CVD events, in an IPD meta-analysis on 70% of the world data (1). There may be heavy methodological limitations to explain this null finding. Analyses to assess this association in at-risk populations are currently underway. However, this scientific issue differs from the criteria of surrogacy.

For the question of surrogacy, a publication-based review from Espeland et al. (2) was the only attempt for many years. Based on seven statin trials, the criteria of surrogacy of CIMT progression were assessed. Looking closely, one key criterion of surrogacy relies on unadjusted estimates from one single trial.

In 2010, two larger meta-analyses were published on the same issue (3, 4). Costanzo et al. (3) used published estimates of 41 RCTs, including trials of lipid lowering, antihypertensive, antidiabetic, antioxidant and hormone-replacement interventions. Using meta-regression techniques, the authors were unable to show a significant association between the effect of the intervention on IMT progression, and the effect of the intervention on cardiovascular events.

Goldberger et al. (4) used the published results from 28 RCTs for meta-regression. Inconsistent with Espeland's results (2), they found no significant association between IMT progression and nonfatal MI in trials testing statins, but a significant association in 'nonstatin trials' (antihypertensive, antidiabetic, vitamin substitution, hormone replacement, or antioxidant intervention).

In summary, the data about the association of IMT progression and vascular endpoints remain inconclusive. The issue may be finally resolved when the results from stage 3 of the PROG-IMT project become available.

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Felippe Martinez (Cordoba, ARG)

Felipe Martinez is Professor of Medicine and teaches at Cordoba National University, Argentina (since 1994). He is the Director of the Instituto Damic-Fundacion Rusculleda (since 1993). President Elect, International Society of Cardiovascular Pharmacotherapy, Former President, Argentinean Federation of Cardiology (2002-2003). Co-chairman, Scientific Program, World Congress of Cardiology (2008).

He has published more than 130 scientific articles, edited two books, and has been an invited speaker in more than 200 international meetings in 23 countries. Dr. Martinez has participated in 25 steering committees and also has been a member of executive committees and endpoint committees of international clinical trials. In many of those studies the Institution managed by him has been the Coordinating group for Latin America.

Peter McCullough (Novi, USA)

After receiving a bachelor's degree from Baylor University, Peter A. McCullough, MD, M.P.H., F.A.C.C., F.A.C.P., F.C.C.P., F.A.H.A., F.N.K.F. completed his medical degree at the University of Texas Southwestern Medical School in Dallas. He went on to complete his internal medicine residency at the University of Washington in Seattle, cardiology fellowship including service as Chief Fellow at William Beaumont Hospital, and master's degree in public health at the University of Michigan. He recently served as the Chief Academic and Scientific Officer of the St. John Providence Health System in Southeast Michigan. He is an internationally recognized authority on the role of chronic kidney disease as a cardiovascular risk state with over 1000 publications including the "Interface between Renal Disease and Cardiovascular Illness" in Braunwald's Heart Disease *Textbook. In 2013, he was honored with the International Vicenza Award for Critical Care Nephrology for his outstanding contribution and dedication to the emerging problem of cardiorenal syndromes. Dr. McCullough is the current Chair of the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), the nation's largest community screening effort for chronic diseases. He is the co-editor of* Reviews in Cardiovascular Medicine *and serves on the editorial boards of multiple specialty journals.*

ABSTRACT

Atrasentan for the treatment of diabetic nephropathy: how to control the risk of heart failure?

Peter A. McCullough, MD, MPH

Patients with chronic kidney disease (CKD) are at high risk for the development of both systolic and diastolic heart failure because of longstanding left ventricular pressure overload, volume overload, and cardiomyopathy. In addition, patients with CKD have more extensive and progressive atherosclerosis with a decreased myocardial capillary density resulting in both epicardial coronary and microvascular ischemia. Atrasentan (endothelin receptor type A antagonist) has been tested in Phase II trials of patients with coronary disease at doses of 10 mg per day and despite improvements in endothelial function, there were unacceptable rates of peripheral edema. This agent has been tested at much lower doses, 0.75 mg p.o. qd, and has been found to reduce proteinuria in patients with diabetic nephropathy. Thus, at this dose, the SONAR Trial (Study Of Diabetic Nephropathy with Atrasentan) is underway testing atrasentan 0.75 mg p.o. qd in patients with diabetic nephropathy with the primary outcome of doubling of serum creatinine or the onset of ESRD [needing chronic dialysis, renal transplant, or renal death. To mitigate against the risk of heart failure the trial will exclude patients with a previous hospitalization for heart failure or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure. In addition, those with a baseline blood B-type natriuretic peptide >200 pg/ml will be excluded. Finally, all subjects will have exposure to the active drug during a 6 week enrichment period, and if the BNP at that time is ≥ 300 pg/ml, subjects will exit the study. Along with protocol guided use of renin-angiotensin system blockade and good clinical practice for patients with proteinuria, it is hoped that these measures will reduce the risks for the development of heart failure over the course of this trial.

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Alexandre Mebazaa (Paris, FRA)

Alexandre Mebazaa is Professor of Anaesthesiology and Critical Care Medicine at the Hôpital Lariboisière, University Paris 7, France. Professor Mebazaa qualified from the Louis Pasteur University, Strasbourg, France, and subsequently obtained a doctorate on the effect of endothelial cells on the calcium responsiveness of the cardiac myofilament from the Lariboisière School of Medicine, Paris. His research interests include mechanisms of contractile impairment during acute heart failure. He acted as member or Chair of several Steering Committee including SURVIVE, an European trial comparing the effects of levosimendan and dobutamine on mortality in severe acute heart failure. He is also heavily involved in several European and global registries on circulatory failure. He authored or coauthored more than 100 papers and is Lead-Editor of the "Acute Heart Failure" book. He is acting as Vice-Chair of Department of Anesthesiology and Critical Care in Paris, and Chair of Educational Board of Paris 7 Medical School.

Michele Mercuri (DSI, USA)

Michele Mercuri, MD, PhD, Vice President, Global Clinical Development, Daiichi Sankyo, graduated in Medicine and Surgery from the University of Perugia, Italy, and obtained a PhD in Neurobiology of Aging from the University of Modena, Italy. From 1988 to 1996, Dr. Mercuri was at the Bowman Gray School of Medicine of Wake Forest University in Winston Salem, NC, USA, where he was an Associate Professor and co-Director of the Division of Vascular Ultrasound in the Center for Medical Ultrasound. Dr. Mercuri published extensively on the Non Invasive Imaging of Carotid Atherosclerosis. In 1997, Dr. Mercuri joined to the Metabolism Clinical Development Division of Merck Research Laboratory (Rahway, NJ, USA) to work with Dr. Jonathan Tobert and the clinical development of lovastatin and simvastatin. He moved on to work on the development of several drug candidates modulating lipid, glucose and other risk factors for atherosclerosis. His drug development work continued at Novartis Pharmaceuticals (East Hanover, NJ, USA) where he worked from 2003 to 2008 prior to moving to his current job as the Cardiovascular Therapeutic Area Head and global leader of the edoxaban Development Program at Daiichi Sankyo (Edison, NJ, USA).

ABSTRACT

New oral activated factor X inhibitors and thrombin inhibitors for subjects with Atrial fibrillation

Michele Mercuri, MD, PhD, Vice President, Clinical Development, Daiichi Sankyo Pharma Development, Edison, NJ, USA

Atrial fibrillation (AF) occurs in 1-2% of the population. There are over 6 million cases of AF in the European Union and it is the commonest sustained cardiac arrhythmia. The prevalence of AF increases with age, from 0.5% at 40–50 years, to 5–15% at 80 years. Current recommendations for antithrombotic therapy for persistent non-valvular (NV) AF are based on risk factors for stroke and systemic thromboembolism (SEE). The risk factors cardiac failure, hypertension, age, diabetes, prior stroke or transient ischemic attack (TIA) can be combined into the CHADS2 score. Scores of ≥2 are considered moderate to high risk, and chronic anticoagulation therapy is indicated. Currently licensed anticoagulants in the EU comprise the vitamin K antagonists (VKA), with dose adjustment to achieve an International Normalized Ratio (INR) of 2 to 3; *dabigatran,* a thrombin inhibitor, and *rivaroxaban* and *apixaban*, Factor Xa inhibitors (Xa-i), which are collectively referred to as Novel Oral Anti-Coagulants (NOACs), have also received market authorization. Recently, *edoxaban*, the newest among the Xa-i and already licensed in Japan, have also reported data. The development programs for all the NOACs were based on a non-inferiority study design using a VKA as the reference since this treatment has been shown to be the most effective active control and it is widely used in clinical practice. The efficacy of VKA from pooling historical placebo-controlled studies is manifested as an estimated 80% reduction of strokes and SEE when compared to placebo. As it is for all anti-thrombotic, VKA therapies carry an increased risk of bleeding and importantly serious bleeding. The NOACs have shown a clinically better bleeding profile. VKAs are also extremely effective in the treatment of Venous Thromboembolism (VTE) and its recurrence. VTE is a single pathophysiological process that combines the clinical manifestations of DVT and Pe with an estimated incidence of 0.16% to 0.27% per annum and over 1.5 million cases of VTE and 0.5 million VTE-related deaths in the European Union alone). The NOACs have also been studies in this area and are also becoming available for VTE patients. Treatment with a VKA has been demonstrated to be highly effective in both AF and VTE. However, VKA therapy does have a number of limitations: it has a delayed onset of action, numerous drug and food interactions, and an unpredictable pharmacological response and narrow therapeutic index requiring ongoing laboratory monitoring. Treatment with VKA also carries a risk of major or clinically significant bleeding. In routine clinical practice, only 50% of patients treated with VKA have an appropriate time in therapeutic range (TTR).Given the limitations of VKAs, there is considerable unmet medical need for NOACs such as edoxaban that preserve the efficacy of the VKA while addressing its limitations.

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Marco Metra (Brescia, ITA)

Prof. Metra is associate professor of cardiology at the University of Brescia and directs the institute of Cardiology of the University and Civil Hospital of Brescia, Italy. He received his medical degree in 1981. He has a post-graduate fellowship in Internal Medicine and in Cardiology. He was a research associate at the Committee on Clinical Pharmacology of the University of Chicago, Illinois, (Director, Prof. Leon I. Goldberg) in 1985, returning to the University of Brescia in 1986.

Prof. Metra has been principal investigator and member of the Executive or Steering Committees of many trials in patients with heart failure. His research is focused on heart failure with, as main areas of interest, □-blocker therapy, cardiopulmonary exercise testing and, more recently, the assessment and treatment of acute heart failure. He has co-chaired with Prof. Teerlink the phase IIB Pre-RELAX-AHF and the phase III RELAX-AHF trials and is chairing the RELAX-AHF-2 trial, having mortality as primary end-point in more than 6500 patients with acute heart failure. All these trials regard the effects of the new agent serelaxin in the patients with acute heart failure. Prof. Metra is also member of the Executive Committee or data Monitoring Committee of many major trials regarding the treatment of heart failure.

A board member of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) from 2001 to 2008, Prof. Metra served as secretary of the executive board from 2004 to 2006. He has also been a member of the ESC's Committee for Practice Guidelines (years 2004 to 2008), and has been co-chair with Prof. Dickstein of the 2008 meeting of the HFA of ESC, held in Milan in June 14-17, 2008.

He is author of more than 280 articles in peer-reviewed journals (current H index, 58).

Scott Meyer (Boston Scientific, USA)

Scott Meyer, PhD is currently Director, New Markets for the Cardiac Rhythm Management division of Boston Scientific. He has over 13 years of industry experience in translational technology development inluding preclinical and clinical investigations across a wide range of cardiovascular applications including heart failure, myocardial infarction, atrial fibrillation, and hypertension. Dr. Meyer holds a B.S. in Biomedical Engineering from Marquette University and M.S. and PhD degrees in Biomedical Engineering from Duke University.

ABSTRACT

Neural modulation trials: industry perspective

Scott Meyer (Boston Scientific, USA)

Increased sympathetic activation and reduced parasympathetic tone (as reflected by reduced baroreflex sensitivity and/or decreased heart rate variability) are important pathophysiological contributors to the progression of HF irrespective of aetiology, and are associated with poor outcome in patients with CHF. Preclinical evidence in large animal models of left ventricular dysfunction has demonstrated that chronic vagus nerve stimulation improves cardiac function and promotes reverse ventricular remodelling, although the exact mechanism of action is not well established. The NECTAR-HF (**NE**ural**C**ardiac *Ther***A**py*fo***RH**eart Failure) trial is a randomized, single-blind, Phase II study designed to evaluate whether right vagal nerve stimulation is safe and might attenuate cardiac remodelling, improve cardiac function and increase exercise capacity, in symptomatic HF patients with LV systolic dysfunction and dilation, receiving optimal medical therapy. Designing a feasibility study to evaluate neuromodulation therapy for heart failure presents unique challenges. In the NECTAR-HF trial, specific challenges included: (1) endpoint selection – reliance on surrogate measures at 3 or 6 months vs measures to support mechanistic plausibility (e.g. HR reduction target); (2) inclusion of a control group with an active implantable device; (3) subject blinding due to laryngeal motor response to stimulation; (4) patient selection / risk stratification. Specific design tradeoffs were made based on a desire to generate the most robust data possible while limiting sample size for the investigational therapy. Given the challenges presented, there is opportunity for continued partnership between academic and industrial partners to refine our understanding of neuromodulation therapies in cardiovascular disease in order to maximize the potential of these therapies.

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Gilles Montalescot (Paris, FRA)

Gilles Montalescot is Professor of Cardiology at the Pitié-Salpêtrière Hospital in Paris, France where he heads

the Cardiac Care Unit. He is a practicing Interventional Cardiologist and has extensive experience in basic and clinical research. He is the director of the INSERM research Unit UMRS 937 on Thrombosis.

Dr Montalescot has been an investigator for many of the new drugs developed in the past 15 years as well as for many of the new interventional technologies. Dr. Montalescot is a senior scientist and has been the lead investigator of many national or international randomized trials including ADMIRAL, ARMADA, ALBION, STEEPLE, ARCHIPELAGO, ABOARD, ACAPULCO, ATOLL, ARCTIC, ACCOAST, ATLANTIC and ALBATROSS trials. Dr Montalescot is the chairman of the ACTION study group, an Academic Research Organization based at Pitié-Salpêtrière Hospital in Paris.

He has served on several task force committees on antithrombotic drugs and acute coronary syndromes and is the current chairman of the Stable Coronary Artery disease guidelines of the European Society of Cardiology. Dr Montalescot has received several awards in his country including the J. Valade Prize from the Fondation de France and the J. Escalle award from the National Academy of Medicine. He is a member of several editorial boards and has published over 400 peer-reviewed original articles in journals such as The NEJM, JAMA, Lancet *and* Circulation*. Internationally, Dr. Montalescot has also been an invited speaker at plenary sessions of all the major congresses such as the European Society of Cardiology, The American College of Cardiology or the American Heart Association.*

Claudio Mori (Vifor Pharma, CHE)

Claudio Mori is Medical Affairs Director Cardiology & New Therapeutic Areas and Medical Lead for Medical Affairs Studies at Vifor Pharma Ltd, Zurich, Switzerland. He graduated from the University of Zurich Medical School, Switzerland. After basic research in Microbiology and clinical experience in General and Internal Medicine, always focusing on Cardiology, he joined the pharmaceutical industry as Medical Advisor Cardiovascular at Bristol Myers Squibb GmbH, Baar, Switzerland. Before moving to Vifor Pharma he worked as Regional Medical Liaison Rheumatology in Spain/Portugal for Centocor B.V., Leiden, Netherlands. In Vifor Pharma, he started in Clinical Development being responsible or involved for Cardiology (FAIR-HF, CONFIRM-HF, EFFECT-HF), Nephrology (FIND-CKD) and Gastroenterology (FERGICore, FERGIMain) studies, started to build up the Medical Affairs functions and subsequently got appointed as Medical Affairs Director Cardiology and Nephrology. He worked in different therapeutic areas which lead to his current position as Medical Affairs Director Cardiology & New Therapeutic Areas and Medical Lead for Medical Affairs Studies. Claudio Mori is interested in the role and treatment of the comorbidity iron deficiency (anemia) particularly in chronic heart failure and chronic kidney disease and the link to the Cardio-Renal Iron Deficiency (Anemia) Syndrome (CRIDS) and other for iron deficiency relevant diseases. He is member of the Heart Failure Association (HFA), the European Renal Association - European Dialysis Transplant Association (ERA-EDTA), the American Heart Association and the American Society of Nephrology (ASN).

ABSTRACT

Iron deficiency in heart failure: what can we expect from ongoing trials of ferric carboxymaltose therapy (EFFECT-HF, CONFIRM-HF)?

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Iron deficiency (ID) and anemia are common in patients with heart failure (HF) and are associated with worse symptoms and adverse outcomes in this population.[1,2] While ID is known to be the most common cause of anemia, recent evidence indicates that iron deficiency by itself is an independent predictor of reduced quality of life, impaired exercise capacity and poor outcome in patients with HF, irrespective of anemia status.[2-8] Recent data showed a prevalence of around 50% in all HF patients, whereas more than 75% of the anaemic patients had ID.[2,5,8] Several treatment options for the management of ID and anemia are available, including blood transfusion, erythropoiesis-stimulating agents and iron substitution. In particular, evidence of clinical benefits of treating ID with intravenous (i.v.) iron therapy in HF patients has been steadily accumulating,[9-12] culminating in the FAIR-HF study of 459 iron-deficient HF patients, with and without anemia. This study showed that, compared with placebo, i.v. ferric carboxymaltose therapy for 24 weeks significantly improved Patient Global Assessment, New York Heart Association functional class, quality of life (QoL) and exercise capacity. Subgroup analyses revealed that the observed favourable outcomes were independent of the presence of anemia at baseline. Treatment with i.v. ferric carboxymaltose demonstrated a favourable tolerability profile, with similar rates of adverse events and a trend towards a lower rate of first hospitalisation compared with placebo.[6,13] Results of the FAIR-HF study are also introduced in the recent released ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic HF 2012, where ID is, for the first time, recognized as a co-morbidity of HF and considered to be a potential therapeutic target in HF patients. This guidelines also recommend to routinely assess and monitor the iron status in patients suspected having HF and mention a possible definition of ID (ferritin < 100µg/L or ferritin 100-299 µg/L when transferrin saturation < 20%).[13] Several other studies are planned or ongoing (EFFECT-HF, CONFIRM-HF, iCHF)[14,15,16] to confirm and fully elucidate the efficacy and safety profile of available i.v. iron therapies, in particular ferric carboxymaltose, in HF patients with ID.

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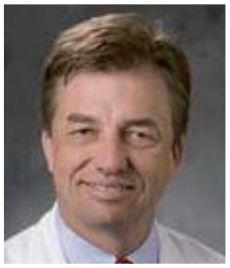
Kiyoshi Nobori (PMDA, JAP)

Kiyoshi Nobori, MD, PhD, is currently a Reviewer of Pharmaceuticals and Medical Devices Agency (PMDA), Japan. Prior to joining PMDA, he served as an Assistant Professor in Cardiology Division at Akita University in Japan (2006-2011). Dr. Nobori received his MD from Shinsyu University in Japan. He received his PhD from Tokyo Medical and Dental University, and his postdoctoral fellowship at Center for Cardiovascular Development, Baylor College of Medicine, Houston, TX.



Christopher O'Connor (Durham, USA)

Dr. O'Connor is the Director of the Duke Heart Center and Chief of the Divisions of Cardiology and Clinical Pharmacology at Duke University Medical Center. He is a Fellow of the ACC, the AHA, and the ESC. He has served on over 90 CEC and DSMC committees in 25 years and served as Chair or Co-Chair on more than 15 of these committees. He has an extensive record of successful mentorship of trainees and has published over 400 manuscripts. He has served as PI or Co-PI for over 20 national and international clinical trials with an extensive record of NIH/NHLBI and industry grants. He previously served as PI of the NIH Heart Failure Network and is now a Co-Investigator and PI of the Core Skills Development Training Grant, focused on the training of future CV investigators. He was PI of the recently completed ASCEND-HF Trial, the largest acute heart failure trial ever conducted. He has served as a PI for a number of other cardiovascular trials, including the NHLBI sponsored HF-ACTION Trial, the largest prospective randomized trial examining the effects of lifestyle intervention on outcomes in heart failure patients. Dr. O'Connor has also been the lead investigator in the WIZARD Trial; the SADHART Trial; the ACTIV Trial; and the RITZ 4 trial. Dr. O'Connor's research interests include: acute heart failure; co-morbidities in heart failure; clinical trials; biomarkers; and novel pharmacological and non-pharmacological approaches for the treatment of heart failure. Dr. O'Connor completed his undergraduate and medical school training at the University of Maryland. He completed his Internal Medicine residency and Cardiology Fellowships at Duke University Medical Center. He is a Professor of Medicine and Associate Professor in Psychiatry and Behavior Sciences.

Gunnar Olsson (previously Astrazeneca, SWE)

Graduated from Karolinska Institutet (medical school) in 1978 for medical degree. Licence to Practice Medicine 1980 (post-internship), Registrar 1980-86, Consultant 1986-1989.

PhD 1984, Specialist in Cardiology and Internal Medicine 1985, Associate Professor in Cardiology 1986, Adjunct Professor at Karolinska Institutet, Stockholm 1998-2010.

Honorary Doctorate in Medicine (honoris causa) at Gothenburg University 2004.

Medical Director (Cardiovascular) in Astra 1989, Various leadership roles in Astra/AstraZeneca R&D, and Vice President & Head of Cardiovascular and Gastro-intestinal in Global R&D 2003-2013. Approximately 125 publications in the field of cardiovascular medicine.

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Professor Burkert Pieske, FESC, FAHA, FACC, is Chair of Cardiology at the Medical University Graz (www.kardiologie-graz.at)and Director of the Ludwig-Boltzmann-Institute for Transational Heart Failure Research (www.heart.lbg.ac.at) in Graz, Austria. Professor Pieske is Past-President of the Austrian Society of Cardiology (2011-2013), and Member of the Executive Board of the Heart Failure Association of the European Society of Cardiology (HFA/ESC).He was President of the Heart Failure Congress of the HFA/ESC in Lisbon 2013.

Professor Pieske´s research focuses on molecular and cellular mechanisms, diagnosis and therapy of heart failure and arrhythmias. Professor Pieske serves as Principal Investigator or member of Steering Committees in a number of Phase II and Phase III clinical trials, and is partner in several European Research Networks with focus on Heart Failure, Atrial Fibrillation, and Biomarkers. His current focus is on new diagnostic approaches and novel therapies for heart failure with Preserved ejection fraction.

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Ileana Piña (New York, USA)

Ileana L. Piña, MD, MPH, received her Doctor of Medicine from University of Miami in 1976, followed by an internal medicine residency (University of South Florida) and cardiology fellowship (University of Miami). Between 1982 and 2006, Dr. Piña served as a director at several institutions, in which she initiated cardiopulmonary testing of heart failure patients and established a cardiac rehabilitation program. From 2006 to 2009 she completed a Quality Fellowship at the Cleveland VA and in 2010, obtained a Masters in Public Health.

Dr. Piña served as principal investigator in multiple heart failure trials, including PRECISE, ELITE and ATLAS, co-investigator for VEST and Val-HeFT, and served on the DSMB of WARCEF. She is a former member of the Heart Failure Society of America Executive Council and former Chair of NHLBI, via the HF-ACTION study and Clinical Trials Committee. A recent recipient of the prestigious AHA Chairman's Award (November 2013), Dr. Piña continues in her efforts to further AHA's strategic goals. She is currently on the Get With the Guidelines and Target HF committees and the Go Red for Women committee (AHA).

In July 2011, Dr. Piña joined Albert Einstein College of Medicine and Montefiore Medical Center as Professor of Medicine and Epidemiology & Population Health, and Vice Chief for Academic Affairs, respectively. Her primary role is to reduce re-admission rates for heart failure patients, as she continues to co-direct the National Heart Failure Training program, a CME activity. To date, Dr. Piña continues her involvement with the FDA as a consultant for devices.

Bertram Pitt (Ann Arbor, USA)

Bertram Pitt is a professor of medicine emeritus at the University Of Michigan School Of Medicine. Dr. Pitt obtained his MD degree from the University of Basel in Switzerland in 1959. He subsequently did a fellowship in cardiology at the Johns Hopkins University School of Medicine and remained on the faculty there until 1977 when he left to direct the division of cardiology at the University of Michigan School of Medicine. He has been chairman or co-chairman of a number of clinical trials in cardiology including: SOLVD; ELITE I and II; Prevent; Rales and Ephesus. He is currently chairman of the steering committee of the NHLBI TOPCAT trial examining the effect of spironolactone in patients with HF and preserved LV systolic function; co-chairman of the Emphasis-HF trial examining the role of eplerenone in patients with NYHA Class II HF; chairman of Break-DHF; co-chairman of STOP-CKD; co-chairman of Exceed; co-chairman of Escape-SHF and Escape-DH F; chairman of a study evaluating the role of an aldostereone synthase inhibitor in patients with HF and is a member of the executive committee of the Accomplish trial. In addition, he serves as the chairman of the DSMB for the NHLBI HF-Action trial and has over 500 articles in peer reviewed journals.

Dr. Pitt has been a member of a numerous medical journal editorial boards. He has also been a member of a number of medical organizations and has served as an advisor to the clinical trials branch of the NHLBI and a member of the FDA cardio-renal advisory board. He has been awarded the James B. Herrick Award by the Council of Clinical Cardiology of the American Heart Association and has been elected to the Society of Scholars of the Johns Hopkins University.

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Dr Pochet is VP Global Clinical Trials, Cardiac Rhythm Management division, Boston Scientific Education. He holds a PhD in Biomedical Engineering.

Stuart Pocock (London, GBR)

Stuart J. Pocock is Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine.

His primary research interest concerns clinical trials, both as regards methodological developments and applied collaboration in major trials. He also has interests in observational epidemiology especially pharmaco-epidemiology. His particular methodological areas of expertise include: standards for the statistical reporting of trials and epidemiological studies, the statistical ethical and organizational principles for data monitoring including early stopping guidelines, the presentation of time-to-event (survival) data, the pros and cons of non-inferiority trials, problems of multiplicity in trial reporting, eg, subgroup analyses, multiple outcomes and covariate adjustment, the development of prognostic risk scores, and the use/interpretation of meta-analyses.

Professor Pocock runs a statistical centre for the design, conduct, analysis and reporting of major clinical trials, especially in cardiovascular diseases. He is also a consultant statistician for a wider range of clinical trials in which expert statistical advice is needed, and serves as a statistical member of many trial data monitoring and steering committees.

He collaborates internationally especially with the Centro Nacional de Investigaciones Cardiovasculares in Madrid, and the Cardiovascular Research Foundation and Mount Sinai School of Medicine in New York. He is a frequent lecturer on a variety of clinical trials issues.

Krishna Prasad (MHRA, GBR)

Manager, CV team, Expert Assessor/Cardiologist
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Dr Prasad MB, BS, MD, FRCP, has a dual role at the MHRA, the UK regulatory Agency, as a unit manager and an Assessor. He is also a practicing cardiologist with a special interest in cardiovascular genetics and personalized medicine. He is a member of the Cardiovascular Working party of the CHMP/EMEA and the Co-rapp (EU/CHMP representative) for the ICH process relating to the E-14 guidance document. He has also been member of the pharmacogenomics working party of CHMP since its formal inception. In addition, prior to joining the MHRA, he worked as a BHF supported Research Fellow and Lecturer in Cardiology. His special areas of interest are heart failure, arrhythmias and sudden death where he was involved in research as an academic, with a number of publications. Dr Prasad's areas of special interest outside of cardiology are Pharmacogenetics/pharmacogenomics, stratified medicine and drug innovation and he has been author on abstracts, publications including peer review papers, book chapters and editorials. He has an interest in development of regulatory guidance and in enhancing the interaction between academia, regulators and the other stakeholders.

ABSTRACT

Antithrombotics

NOACS are in the news and are becoming viable alternatives to something we have got used for nearly half a century, i.e., warfarin. The three main agents, Apixaban, Rivaroxaban and Dabigatran all have shown a level of similarity and certain advantages over warfarin particular clinical situations. Notwithstanding the above, they still have some way to go to meet the overall clinical experience with warfarin (of over 50 years) even collectively. The discussion will focus on the main issues that regulators grapple with, when newer agents such as these new anticoagulants are being evaluated. The issues to focus are on comparisons on mechanism of action, pharmacogenomics and its impact on safety and efficacy, use of combinatorial end points and overall evidence base. For example, when efficacy measures are combined with safety end points and concept of net clinical benefit is used, this requires careful consideration of these individually and carefully. Last but not the least, reversal of the anticoagulant effect comes into focus if and when serious bleeding events are considered. The most challenging aspect as regulators is to harmonize all the product information for the 3 approved anticoagulants and to continue to do so for the new AC to come. It's especially important that they are comparable between them so that clinicians can easily decide which one is the best treatment option, for that purpose we are in constant communication between the assessment teams to work on that direction

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Arthur Mark Richards (Singapore, SGP)

Professor Richards holds appointments in both Singapore and New Zealand including Director of Cardiovascular Research Institute (CVRI) and Professor in the Department of Medicine, National University of Singapore (NUS), Professor in Medicine at the University of Otago, Christchurch. He is director of the Christchurch Heart Institute, University of Otago, and Professor of Cardiovascular Studies for the Heart Foundation of New Zealand.

Prof Richards has been actively involved in both basic and clinical research into the neurohormonal control of the circulation in health and disease for 30 years. He has led pioneering work in elucidation of the biology of the cardiac natriuretic peptides and their clinical application in diagnosis, prognosis, monitoring and management of treatment of heart failure.

Peer-reviewed publications 555 including 412 original articles. Life Time H Index 66, Post 1995 H Index 51, Total citations ~18,000.

ABSTRACT

What have we learned so far?
An update of the strength and limitations of the recent guided therapy trials
Biomarkers

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Aims: Trials of biomarker-guided treatment of heart failure have been characterized by variable sample size, demographics (especially age), duration of follow up,

peptide target, selected end-point and outcomes. Never the less repeated meta-analyses of pooled summary trial data have indicated benefit.We performed an individual patient data meta-analysis to evaluate the effect of NP-guided treatment of heart failure on all-cause mortality.

Methods and Results: Eligible randomized clinical trials were identified from searches of Medline and EMBASE databases and the Cochrane Clinical Trials Register. The primary pre-specified outcome, all-cause mortality was tested using a Cox proportional hazards regression model that included study of origin, age (<75 or ≥75 years) and left ventricular ejection fraction (LVEF, ≤45% or >45%) as covariates. Secondary endpoints included heart failure or cardiovascular hospitalization.

Of 11 eligible studies, 9 provided individual patient data and 2 aggregate data. For the primary end-point individual data from 2000 patients were included, 994 randomized to clinically-guided care and 1006 to NP-guided care. All cause mortality was significantly reduced by NP-guided treatment (Hazard Ratio=0·62 [0·45-0·86]; p=0·004) with no heterogeneity between studies or interaction with LVEF. The survival benefit from NP-guided therapy was seen in younger (<75 years) patients (0·62 [0·45-0·85]; p=0·004) but not older (≥75 years) patients (0·98 [0·75-1·27]; p=0·96). Hospitalization due to heart failure (0·80 [0·67-0·94]; p=0·009) or cardiovascular disease (0·82 [0·67-0·99; p=0·048) was significantly lower in NP-guided patients with no heterogeneity between studies and no interaction with age or LVEF.

Conclusion: NP-guided treatment of heart failure reduces all-cause mortality in patients aged <75 years and overall reduces heart failure or cardiovascular hospitalization.

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Lothar Roessig (Bayer, GER)

Lothar Roessig received his MD from the Hannover Medical School, Germany. He is board certified in Cardiology and in Internal Medicine, and Lecturer in Medicine at the Goethe University of Frankfurt, Germany. As senior cardiologist and member of the faculty at the University Hospital Frankfurt he participated as clinical investigator in numerous cardiovascular trials until 2007 when he moved into clinical research industry. Since October 2009 he is appointed at Bayer Health Care as Global Clinical Leader in heart failure development. He leads at Bayer the soluble guanylate cyclase stimulator in heart failure studies (SOCRATES). Lothar Roessig authored more than 40 international scientific publications, peer reviewed for various cardiovascular journals, and was finalist of the American Heart Association Samuel A. Levine Young Clinical Investigator Awards.

Yves Rosenberg (NHLBI, USA)

Dr. Rosenberg, MD, M.P.H. is Chief of the Atherothrombosis and Coronary Artery Disease Branch, Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute, National Institutes of Health, in Bethesda, Maryland. Dr. Rosenberg obtained his MD from the University of Lyon, France, and is Board certified in Preventive

Medicine. He also has an MPH from the Johns Hopkins School of Hygiene & Public Health, and a MS in Clinical Pharmacology. Dr. Rosenberg's main research interests are the design and conduct of large multicenter phase III clinical trials; the methodology of trials of treatment strategies and comparative effectiveness trials. As a Program Director at NHLBI for the last 18 years he has led and participated in the development, conduct, analysis and reporting of more than a dozen major international clinical trials, the results of which have usually been incorporated in clinical guidelines and are influencing today's practice of cardiovascular medicine in the United States and all over the world. Dr. Rosenberg is currently the lead NIH Project Scientist for a randomized trial of genotype-guided warfarin therapy (COAG), the first large scale (1,015 participants) NIH trial of genotype-guided therapy and for the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) an 8,000 participants, 400 sites trial. Dr. Rosenberg served as a member of the Society for Clinical Trials Board of Directors.

Patrick Rossignol (Nancy, FRA)

Patrick Rossignol, MD, PhD, is a Nephrologist and Vascular medicine specialist, Professor of Therapeutics at the University of Lorraine, France. Since 2007, he has a position of deputy Director in Nancy University Hospital Inserm Clinical Investigation Center, which is headed by Professor Faiez Zannad, researcher in Inserm UMR_S1116, and is consultant in the University Hospital Heart Failure and Hypertension Unit (ESH excellence Centre) as well as in hemodialysis clinics within a Disease Management program. He is mainly involved in clinical research, especially concerning circulating biomarkers, in the settings of heart failure, hypertension, hemodialysis and vascular diseases. He is also involved in translational basic research studies on the mechanisms of transition of hypertension and metabolic disorders to the cardiorenal syndrome. He is a EURECA-m (cardiorenal working group of ERA-EDTA) member since its creation in 2009 and was elected as board member in 2013. He is the PI of a doubleblind (spironolactone vs. placebo) CV outcome RCT in hemodialysis (ALCHEMIST), funded by the French Ministry of Health, and steering committee member of 4 international randomized clinical trials, including one led by EURECA-m.

Christian Ruff (Boston, USA)

Christian T. Ruff, MD, MPH, is an Associate Physician in the Cardiovascular Division at Brigham and Women's Hospital in Boston, MA an Instructor in Medicine at Harvard Medical School, and an investigator in the TIMI Study Group. He graduated from Harvard University with a degree in Neurobiology in 1998. He earned his medical degree at the Johns Hopkins University School of Medicine in 2003 and his masters of public health at the Harvard School of Public Health in 2010. Dr. Ruff completed his internal medicine residency and cardiovascular medicine fellowship at the Brigham and Women's Hospital. As an investigator in the TIMI Study Group, Dr. Ruff is the co-chairman of the Clinical Events Committee and has led a broad array of projects, ranging from small studies of biomarkers and genetic variants to large clinical trials. Dr. Ruff has specific expertise in risk stratification in atrial fibrillation and implementation of novel antithrombotic therapy for stroke prevention. He was a lead co-investigator for the ENGAGE AF-TIMI 48 study evaluating the investigational factor Xa inhibitor edoxaban for the prevention of stroke in patients with atrial fibrillation and has been selected to serve as the Chairman for the Stroke Prevention in Atrial Fibrillation Consensus Initiative for the North American Thrombosis Forum.

ABSTRACT

ENGAGE AF-TIMI 48 Primary Results

Authors: Robert P Giugliano, Christian T Ruff, Eugene Braunwald, Sabina A Murphy, Laura T Grip, Brigham and Women's Hosp, Boston, MA; Joshua M Betcher, Quintiles, Morrisville, NC; Shirali P Patel, Quintiles, Durham, NC; Indravadan Patel, James Hanyok, Minggao Shi, Michele Mercuri, Daiichi-Sankyo, Edison, NJ; Elliott M Antman, Brigham and Women's Hosp, Boston, MA

Background: Edoxaban is an investigational, oral, once-daily anticoagulant that specifically and reversibly inhibits factor Xa with rapid onset, linear pharmacokinetics, and half-life of 8-10h. In a phase 2 study of 1146 patients with atrial fibrillation (AF) followed for 3 months, bleeding was dose-related and lower with once-daily compared to twice-daily dosing.

Methods: ENGAGE AF-TIMI 48 (NCT00781391) was a randomized, double-blind, placebo-controlled, study of 21,105 subjects with moderate to high risk (CHADS2 ≥2) AF comparing warfarin (target INR 2.0-3.0) to two dosing regimens of *edoxaban*. At randomization, subjects were stratified based on $CHADS_2$ and *edoxaban* dose adjustment for drug clearance (based on renal function, use of strong P-gp inhibitors, body weight). Dosing could also be dynamically adjusted throughout the trial. Blinding was maintained through the use of a sham INR algorithm. The primary endpoints were a composite of stroke and systemic embolism (efficacy); and International Society on Thrombosis and Haemostasis (ISTH) major bleeding (safety). Cardiovascular events and overall mortality were also assessed.

Results: Baseline characteristics are shown in Table 1. The primary and key secondary endpoints will be available in August 2013 and presented at the meeting.

Conclusion: ENGAGE AF-TIMI 48 is the single largest phase 3 trial of a novel anticoagulant in AF and will provide definitive evidence of the efficacy and safety of two dosing regimens of edoxaban compared to well-managed warfarin.

Demographics	
Median Age [inter quartile range], years	72 [64-78]
Women (%)	38
AtrialFibrillation History	
Naiveto Vitamin K antagonists (%)	41
Paroxysmal (%)	25
Persistent (%)	23
Permanent (%)	52
Qualifying Risk FactorsforStroke	
Prior stroke or TIA(%)	28
Age ≥75 years (%)	40
Prior heart failure (%)	57
Diabetes (%)	37
Hypertension (%)	92
$CHADS_2$ 2-3 (%)	76
$CHADS^2$ 4-6(%)	24
Prior myocardial infarction (%)	12
History of peripheral arterial disease (%)	4
Dose adjustment at randomization (%)	25
Region	
North America (%)	22
Latin America (%)	13
Western Europe (%)	13
Eastern Europe (%)	34
Asia/Pacific (%)	16

David Rutledge (Abbott Vascular, USA)

Dr. David Rutledge is a clinical trial scientist bringing over 25 years' experience with international regulatory submissions to agencies such as US FDA, China FDA, Japan PMDA, EMA, Korea FDA, Australia TGA, and CDSCO of India. He has both management and professional experience on both pharmaceutical and device program teams involving products within the cardiovascular, gastrointestinal, respiratory, and AIDS therapeutic areas. As a former Professor/Chairman in academia, IRB member and investigator, he understands the role of a PI as a sponsor-investigator in clinical trials. He was inducted as a Fellow of the American Heart Association in 1995. Dr. Rutledge served on two FDA panels which led to publishing a device-drug combination Guidance Document on Coronary Drug-Eluting Stents (March 2008). He was a speaker for the FDA's Post-Approval Studies for Medical Devices Workshop (June 2009) and then served as a panel member for the Methodologies for Post-Approval Studies of Medical Devices Workshop (September 2009). In 2010, he accepted a 4-year appointment from the United States Department of Health & Human Services to serve as the Industry Representative on the FDA's General Hospital and Personal Use Devices Advisory Committee in FDA's Center for Devices and Radiological Health (CDRH). He also served on the June 27th, 2013, Gastroenterology-Urology Devices Panel of CDRH. Dr. David Rutledge is currently Director, Worldwide Clinical Research with Abbott Vascular.

ABSTRACT

Cardiovascular medical device innovation: barriers and solutions

David Rutledge (Abbott Vascular, USA)

Health care is a heavily regulated industry with expectations, guidelines, regulations, and laws designed to protect patients. Medical device innovation is challenged by matching innovation with unmet medical needs. Evidence necessary for approvals varies across geographies leading to erratic, inconsistent, and expensive regulatory pathways. Discussion of therapeutic effect, surrogates, trial design, size, local product registration/approval process, threshold of US/EMEA/Asia data, reimbursement challenges, need for imaging, number of physician/engineering specialty teams, training, and audit potential is required. Communicating initial results is vital, because even failed trials may prove valuable in the long run, but not if the data is locked away. Developing mechanisms to collaborate among multiple stakeholders is necessary to provide optimal medical innovation in a changing global environment.

Naoki Sato (Tokyo, JAP)

Naoki Sato, M.D., Ph.D., FESC, FJCC, did his residency for two years at Nippon Medical School Hospital in Japan and had trained cardiac catheterization and intervention for another three years. He had done basic research regarding sympathetic nervous system in heart failure using pacing induced heart failure models and also regarding aging under the direction of Prof. Stephen F. Vatner at Harvard Medical School for four years. He was Melvin L. Marcus Young Investigator Award Finalist in Cardiovascular Integrated Physiology at 67th Scientific Sessions in American Heart Association and also had The Samuel A. Levine award from American Heart Association, Massachusetts affiliate. After that, he belonged to intensive and cardiac care unit of Nippon Medical School for 12 years. At present, he is the director of internal medicine, cardiology, and intensive care unit in NMS Musashi-Kosugi Hospital. He is a fellow of European Society of Cardiology and a member of American Heart Association. He works as a councilor of many Japanese Societies. Dr. Sato's researches focus pathophysiology and managements of heart failure. He is especially interested in organ-interactions in heart failure. Dr. Sato is the primary investigator of the ATTEND (acute decompensated heart failure) registry, which is the largest registry of Asia area.

Dan Schaber (Medtronic, USA)

Dan Schaber, PharmD, is Vice-President Heart Failure Clinical Research, Medtronic Inc. In this role, he is responsible for providing overall leadership and direction on a worldwide basis for new product approval, new indication approval and post market approval clinical research in heart failure.

Dr Schaber has more than 25 years' experience in the pharmaceutical and medical device industry. He joined Medtronic in 1987 from the University of Minnesota and Minneapolis Children's Medical Center where he was an Assistant Professor of Clinical Pharmacy. Since coming to Medtronic he has held management positions in the clinical research, product development, regulatory and marketing organizations of Cardiac Rhythm Management. From 1995 thru 1998 Dr Schaber was on an expatriate assignment in Switzerland where he served as the Business Director for the Tachyarrhythmia and EP Systems businesses. In 1998 he returned to the U.S. where he has held senior leadership positions in Cardiac Rhythm Marketing, Bradyarrythmia Therapy, Program Leadership for the implantable hemodynamic monitor and Clinical Research Strategy. He holds a Doctor of Pharmacy degree from the University of Minnesota and was Pediatric Clinical Pharmacy Fellow at Minneapolis Children's Medical Center.

Patrick Serruys (Rotterdam, NED)

Prof. Patrick W. Serruys, with respected h-index – 118 *is a professor of Interventional Cardiology at the Interuniversity Cardiological Institute of the Netherlands (1988-1998), and Erasmus MC. Since 1980 he was a Director of the Clinical Research Program of the Catheterization Laboratory, ThoraxCenter atErasmusUniversity, and since 1997 the Head of the Interventional Department, ThoraxCenter, Erasmus MC (University Medical Center Rotterdam),Rotterdam, The Netherlands.*

He is a Fellow of the AmericanCollege of Cardiology and a Fellow of the European Society of Cardiology and scientific council of the International College of Angiology.

In 1996 he received the TCT Career Achievement Award and in 1997 he was awarded the Wenkebach Prize of the Dutch Heart Foundation. In 2000 he was awarded the Gruentzig Award of the European Society of Cardiology. In 2001 he held the Paul Dudley White Lecture at the American Heart Association in the USA. In 2004 he received the Andreas Gruentzig Award of the Swiss Society of Cardiology. In 2005 he held the 4th International Lecture at the AHA and Mikamo Lecture at the Japanese heart Association. In 2006 he received the highest award of the Clinical Council of the American Heart Association: the James Herrick Award. In 2007 he received the Arrigo Recordati International Prize (Italy) and the ICI Achievement Award (bestowed by the President of Israel – Shimon Perez). In 2008 he received the Einthoven Penning (Leiden). In 2009 he became Doctor Honoris Causa from the University of Athens. In 2011 he received the Lifetime Achievement Award, bestowed by the AmericanCollege of Cardiology, in recognition of many years of service and invaluable contributions to the ACC. At the end of 2011 Prof. Serruys received the Ray C. Fish Award, bestowed by the Texas Heart Institute, for outstanding achievement and contribution to cardiovascular medicine. In 2012 he received a Golden Medal of the European Society of Cardiology.

Kaori Shinagawa (PMDA, JAP)

Dr. Kaori Shinagawa, MD, PhD, majored in internal medicine, with an emphasis on cardiology. After graduating from National Saga Medical School in 1992, she conducted medical examinations and patients treatments including clinical electrophysiological studies as a cardiologist. She received her doctoral degree of Medical Science in 2000. Her main research field was to investigate the electrophysiological mechanisms and pharmacological treatment of atrial fibrillation, and she was a postdoctoral fellow of Dr. Stanley Nattel's laboratory at Montreal Heart Institute from 1999 to 2002. She worked as a cardiologist at Eiju general hospital from 2002 to 2005. Since March 2005, she has been working at the Pharmaceuticals and Medical Devices Agency (PMDA). She is currently Senior Scientist for Clinical Medicine, PMDA. She has been involved mainly in the review and consultation of new cardiovascular drugs, and creating new guidelines for Japanese drug application. She has also been involved in International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use□ICH□activities since 2005 including E14 topic. She has authored over six papers for a variety of cardiovascular journals. Dr. Shinagawa's findings have been featured in Circulation, J Am Coll Cardiol, PACE, and Cardiovascular Res.

She also received Kimura Memorial Award from the Japanese Heart Rhythm Society in 2000.

Walter Singleton (ISIS, USA)

Dr Walter Singleton, MA, BM, BCh, is Chief Medical Officer at Isis Pharmaceuticals, Inc. in Carlsbad, California, a position he has held for the past 5 years.

Dr Singleton has more than 35 years' experience in the Pharmaceutical Industry, principally in the field of development of new drugs and guiding them effectively through the stages of clinical development and regulatory approval.

He received his Medical degrees at the University of Oxford and completed postgraduate training in Internal Medicine and Cardiology, with a specialty of Cardiovascular Clinical Pharmacology, at the Leeds University Medical School in U.K. during which time he participated as an investigator on numerous clinical trials in Angina, Hypertension and Heart Failure.

Dr Singleton began his pharmaceutical industry career with Pfizer, serving for 10 years in European Clinical Research and 5 years in the company's New York Headquarters, eventually as Senior Vice President of Medical and Pharmaceutical Development for Pfizer's US Division.

After this he moved to the California Biotech arena, serving as Vice President of Medical and Pharmaceutical Development Gensia Inc, biopharmaceutical start-up company in San Diego, with responsibility for planning and executing two concurrent programs from preclinical development through NDA. In 1995 he left Gensia to form a consultancy providing expert input into clinical development programs primarily for start-up and emerging biotechnology and biopharmaceutical companies.

For the past 5 years he has been Chief Medical Officer at Isis, having worked with the company on a consulting basis for a short time prior to that appointment.

James Snider (Critical Diagnostics, USA)

James V. Snider, PhD, is President of Critical Diagnostics, an early-stage healthcare company dedicated to the development of an important new category of diagnostic and prognostic markers that are useful both for the early detection and guiding therapy of both myocardial infarction (heart attack) and heart failure. During his tenure at Critical Diagnostics James has led the program leading to FDA clearance for the Presage ST2 Assay as well as additional products soon to be introduced.

Prior to joining Critical Diagnostics, Dr. Snider spent over three years as the Executive Vice President of Business & Operations for IntelligentMD ("IMD"), an early-stage medical device company that focuses on the essential elements of disease diagnostics and therapeutic intervention. While at IMD he guided the company through three rounds of fundraising, staffing and resourcing for two product development projects and several business development deals. Prior to joining IMD, Dr. Snider spent eight years in a series of marketing and product development positions at Applied Biosystems (ABI).

Before joining ABI, Dr. Snider was a Senior Scientist at Biotech Research Laboratories, a contracts and service research company specializing in retroviral technologies. Dr. Snider performed his post-doctoral research as a fellow in the Biological Response Modifiers Program at the Frederick Cancer Research and Development Center of the National Cancer Institute. He holds a BS in chemistry from Grand Valley State University, a PhD in chemistry from the University of South Carolina and an MBA in technology management from the University of Phoenix.

Scott Solomon (Boston, USA)

Scott D. Solomon, MD, is Professor of Medicine at Harvard Medical School, and Director of Noninvasive Cardiology and Senior Physician at Brigham and Women's Hospital. He also directs the Cardiac Imaging Core Laboratory and the Clinical Trials Endpoints Center at Brigham and Women's Hospital, and directs the Cardiac Imaging Center for the NHLBI sponsored Atherosclerosis Risk in Communities (ARIC) study and Hispanic Community Health Study – Study of Latinos (HCHS-SOL).

Dr. Solomon's research interests have focused on changes in ventricular structure and function following myocardial infarction, modifiers of risk and influences of outcome in patients following myocardial infarction and with chronic heart failure, cardiovascular safety of non-cardiovascular therapies, and factors that influence the transition from hypertension to heart failure. He has combined clinical trials with cardiac imaging, and has played a leading role in many international clinical trials in heart failure, hypertension and myocardial infarction, including the SAVE, HEART, VALIANT, CHARM, PEACE, OVERTURE, MADIT-CRT, ALOFT, ALLAY,, TREAT, RED-HF, ALTITUDE, PARADIGM, FREEDOM, TOPCAT trials. He chaired the VALIDD, EXCEED, ASPIRE, PARAMOUNT trial. Dr. Solomon has directed the Harvard Medical School Cardiovascular Clerkship and the echocardiography training program at Brigham and Women's Hospital for a decade. He has authored more than 250 original peer-reviewed articles, review articles and editorials, two textbooks of cardiac imaging, an iphone atlas of echocardiography, and the echocardiography sections for the next edition of Braunwald's Heart Disease *and Harrison's* Principles of Internal Medicine. *He is Cardiology Section Editor at Up To Date and serves as Associate Editor at Circulation.*

Harald Sourij (Oxford, GBR)

Harald Sourij graduated (sub auspiciis presidentis reipublicae) 2004 from the Medical University of Graz, Austria where he subsequently did his training in General Medicine and Endocrinology and Metabolism.

In 2010 he moved to Oxford, UK and joined the Diabetes Trials Unit to work with Professor Rury Holman on diabetes outcome trials and served as the Clinical Lead for the EXenatide Study of Cardiovascular Event Lowering (EXSCEL). In 2013 he returned to an Associate Professor position at the Medical University of Graz, Austria, but remains also affiliated with the Diabetes Trials Unit in Oxford.

His research activities focus mainly on diabetes and its cardiovascular complications. He has published over 40 peer-reviewed manuscripts and book chapters. In his current clinical role he works as a consultant in diabetes outpatient and inpatient care of the Division of Endocrinology and Metabolism in Graz, Austria.

Harald Sourij is a member of the Austrian, British and European Diabetes Association and of the Diabetes & Cardiovascular Disease Study Group of the EASD. He served as the Secretary and Board Member of the Austrian Obesity Association (2005-2007 and 2010-2012). Since 2013 he is Associate Editor of Trials.

ABSTRACT

Other ongoing diabetes CV safety trials. The various scenarii of interim or no interim results for approval

Harald Sourij, MD

In December 2008, the US Food and Drug Administration (FDA) issued guidance requiring thorough assessment of cardiovascular safety for new antidiabetic drugs to be licensed for the treatment of type 2 diabetes. Prior to this guidance, the approval of antihyperglycemic drugs was based on the ability of a drug to lower plasma glucose or hemoglobin A1c (HbA1c), both surrogate markers primarily for microvascular diabetic complications. However, prompted by concerning, but inconclusive, evidence of cardiovascular harm attributed to Rosiglitazone the regulatory authorities (FDA and EMA) demanded a change of the approval pathway for new antidiabetic drugs and to make the demonstration of cardiovascular safety mandatory for new drugs to be licensed. In a first step sponsors need to perform a meta-analysis to assess the cardiovascular risk and to demonstrate an upper bound of a two-sided 95% confidence interval for the estimated cardiovascular risk to be below 1.8. However, as long as the two-sided 95% confidence interval for the estimated cardiovascular risk is above 1.3, an adequately powered and designed post-marketing trial is necessary.

As a consequence during the following three years 16 cardiovascular outcome trials investigation antihyperglycaemic agents were commenced. This new requirement also led to the design of more "pragmatic" trials, characterized by a focused clinical question, streamlined data collection, and minimal face-to-face participant contact which appear to be particularly well suited for late phase trials of well-tolerated agents with reasonable safety profiles.

Recently an outcome trial (Canagliflozin Cardiovascular Assessment Study, CANVAS) investigating the cardiovascular safety of canagliflozin, an SGLT-2 inhibitor caused some discussions since the sponsor included data from an interim analysis of the CANVAS trial in the approval submission. Further discussion will be needed as to whether it is appropriate to use interim analyses of an ongoing trial for drug approval and to make the interim results publicly available and how this might impact and bias the further conduct of the trial.

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Bart Staels (Lille, FRA)

Bart STAELS is professor (Classe Exceptionnelle), Faculty of Pharmacy, University of Lille II, France; and Head of the new founded Inserm Unit UMR1011 - Institut Pasteur de Lille, France (2010-) with laboratories (around 75 persons) on the campus of the Institut Pasteur de Lille, and the Research Pole of the University of Lille 2, France. He is member of the Research Scientific Council of the Institut Pasteur de Lille and President of the Scientific Advisory Board of Genfit SA. Honorary Professor at the University of Groningen, The Netherlands (2009-2014); European correspondent of the National Academy of Pharmacy, Paris, France (06/2011)and Senior member of the Institut Universitaire de France (from 2011).

Pr. Staels' research focuses on molecular pharmacology of cardiovascular and metabolic diseases, including dyslipidemia and type 2 diabetes.

ABSTRACT

Identifying new targets for lipid management in atherosclerosis.

B. Staels

UMR1011 INSERM; Institut Pasteur de Lille; Univ Lille 2, Lille, France

Although *'the high-density lipoprotein cholesterol (HDL-c) promise'* was held high, it has suffered major blows over the

last few years. We will focus our presentation on the recent developments in the field of targeting drugs to modulate HDL metabolism against the threatening background of failures of major trials and a lack of evidence that increasing HDL-c protects against atherosclerosis. Arguably, inhibition of cholesterol ester transfer protein, antagomirs against miR33, ApoA-I mimetics, delipidated HDL and PPARa or PPARa/d agonistshold, on the basis of the current data, most promise. Key is that those patients with low HDL- and increased triglycerides are to be treated and that, in the post-statin era, personalized medicine is inevitably on the horizon.

Christina Stahre (Astrazeneca, SWE)

Christina Stahre, MD, currently works as Senior Research Physician at AstraZeneca R&D Cardiovascular and Metabolic Diseases in late development She has been the study physician for the SAVOR saxagliptin CV outcomestudy since 2011. She has almost ten years of experience from pharma industry work including safety responsibilities for AstraZeneca´s cardiovascular drugs both on the market and under development. Before joining the pharma industry she had 20 years of clinical experience and specialised in Anesthesia and Intensive care with obstetric anaestesia as subspeciality, holding the position as head of Obstetric and Gynaecology Anesthesia at the Sahlgrenska University Hostpital until 2004. In parallel she also works as a Diving and Search and Rescue physician in the Swedish Navy.

Evan Stein (Cincinnati, USA)

Evan A Stein, MD PhD FRCP(C) FCAP, received his medical degree and PhD from the University of Witwatersrand in Johannesburg, South Africa. He recognized and described the high gene frequency of Familial Hypercholesterolemia and in 1972 started the first lipid clinic in South Africa. He completed his specialist training in Medical Biochemistry at McMaster University Medical Center, Canada and was on the full-time faculty at the University of Cincinnati, Ohio, for 11 years as tenured Professor of Pathology and Laboratory, and remains on faculty as Voluntary Professor. In 1988 he formed the Metabolic and Atherosclerosis Research Center, and Medical Research Laboratories and relocated his clinical and laboratory groups.

Dr Stein has had a number of committee appointments to the National Institutes of Health since 1986, including the General Clinical Research Centers, NCEP Standardization Committee, Data and Safety Advisory Board of the NHLBI Program on Genetics in Hypertension from 1999-2003. From 2006-2010 he served on the FDA Clinical Chemistry and Clinical Toxicology Advisory Panel.

ABSTRACT

The atherosclerosis trialists forum: new lipid associated targets and improved pathway to successful clinical trials monoclonal antibodies – for lipid lowering or for cv prevention indication?

Evan A Stein MD PhD Cincinnati

Recent trials with monoclonal antibodies (mAb) to PCSK9 have demonstrated they are the most effective LDL-C lowering agents yet developed, decreasing LDL-C approximately 60% in virtually all patient groups, whether on diet alone or on maximal statin±ezetimibe background therapy.In two large phase 2 programs of over 900 mAb treated patients the drugs have been well tolerated, highly complied with despite SC administration and have been associated with minimal adverse effects.

Low density lipoprotein cholesterol (LDL-C) is one of the most validated targets in clinical medicine. Large randomized, outcome trials have demonstrated a clear relationship between reducing LDL-C and cardiovascular disease (CVD) risk, which has been maintained to LDL-C levels of <1.8 mmol/L. To assess the benefit of even lower LDL-C it is important to recognize that; 1) CVD risk reduction is related to absolute reduction in LDL-C, not to percent change. 2) baseline LDL-C still drives CVD events in 'control' group.1) The 'rule of thumb' is 1 mmol/L decrease in LDL-C = 20% reduction in CVD events in 2-3 years.

Thus a 50% reduction in LDL-C results in different CVD event reduction depending on baseline LDL-C; a. mean baseline LDL-C of 2.1 mmol/L (~80 mg/dL) predicts CVD risk reduction = 20% in 2-3 years; b. mean baseline LDL-C of 3.2 mmol/L (~125 mg/dL) predicts CVD risk reduction = 30% in 2-3 years2) For same global risk baseline LDL-C of 3.2 confers 1/3 greater annual risk of CVD than 2.1 mmol/L. Thus, the higher the entry LDL-C the 'bigger bang for the buck', which means less patients and shorter duration (and lower cost) for a successful CVD outcome trial.

A third and unique factor for a CVD outcome trial with a PCSK9 mAb is the very large LDL-C reductions and ability to reduce LDL-C well below prior levels in prior trials. This is especially important with the routine use of more effective statins and higher doses in high risk CVD patients as standard of care and results in baseline LDL-C as seen in recent trials of 2 mmol/L or less (e.g. HPS2-THRIVE, AIM-HI, dalOutcomes). The addition of PCSK9 mAb in such patients and LDL-C reductions of 50-60% results in mean LDL-C below 1 mmol/ Land many patients well below this level.Complicating these low LDL-C levels is the recent evidence that the most common method for measuring LDL-C, calculation using the Friedewald formula, is inaccurate as LDL-C decreases below 1.8 mmol/L and significantly underestimates LDL-C below 1 mmol/L. The potential impact of underestimation of LDL-C is two-fold; first, concern about safety resulting in down titration of mAb dose or less frequent dosing and second distortion of the true relationship between LDL-C reduction and CVD risk reduction.

In summary while mAb to PCSK9 provide an exciting and very effect method to reduce LDL-C they also present new challenges in designing and conducting CVD outcome trials.

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Gregg Stone (New York, USA)

Gregg W. Stone, MD, FACC, FSCAI, is Professor of Medicine at the Columbia University Medical Center, Director of Cardiovascular Research and Education at the Center for Interventional Vascular Therapy at New York-Presbyterian Hospital, and Co-Director of Medical Research and Education at the Cardiovascular Research Foundation in New York, NY. Dr. Stone has served as the national or international principal investigator for more than 60 national and international multicenter randomized trials, has authored more than 1750 book chapters, manuscripts and abstracts published in the peer-reviewed literature, and has delivered thousands of invited lectures around the world. Dr. Stone's areas of expertise include interventional therapies of acute coronary syndromes and myocardial infarction; drug-eluting stents; antiplatelet and antithrombotic pharmacotherapies; percutaneous heart valves, new device angioplasty including distal embolic protection, thrombectomy, vascular brachytherapy and stent grafts; intravascular imaging; saphenous vein graft therapies; chronic total occlusions; vulnerable plaque; contrast nephropathy; clinical trial design; and regulatory issues. Dr. Stone, along with Dr. Martin B. Leon, is the director of Transcatheter Cardiovascular Therapeutics (TCT), the world's largest symposium devoted to interventional cardiology and vascular medicine, directs the annual National Interventional Cardiology Fellow's Course, and co-directs several other annual courses, including Optimizing Complex PCI Outcomes, The Left Main and Chronic Total Occlusion Summit, and Transcatheter Valve Therapies. Dr. Stone's medical practice is devoted to interventional cardiology at New York-Presbyterian Hospital/ Columbia University Medical Center.

Dr. Stone previously held similar positions at Lenox Hill Hospital in New York and the Washington Hospital Center in Washington, DC. Previously he was the Director of Interventional Cardiology at the Cardiovascular Institute at El Camino Hospital and Stanford University Medical Center in California.

Dr. Stone completed medical school at Johns Hopkins University Medical Center, in Baltimore, MD, and his internship and residency at the New York Hospital-Cornell Medical Center in New York City. He completed his general cardiology fellowship at Cedars-Sinai Medical Center in Los Angeles, CA, under Dr. Jeremy Swan, and subsequently a dedicated fellowship in advanced coronary angioplasty with Dr. Geoffrey O. Hartzler in Kansas City, MO.

Ahmed Tawakol (Boston, USA)

Dr. Tawakol is Co-Director of the Cardiac MR PET CT Program at the Massachusetts General Hospital, Harvard Medical School. His work focuses on multi-modal imaging of atherosclerosis, incorporating molecular imaging approaches. A hypothesis that is central to his research is that assessment of plaque biology and function provide an important supplement to the classical structural information. His group played a major role in developing PET/CT imaging of atherosclerosis: 1) performed the pre-clinicaland studies to show that FDG PET/CT measurements correlate with atherosclerotic inflammation 2) demonstrated that the signal correlates with high-risk arterial plaque morphological features and plaque progression, and 3) has shown that individuals with increased arterial signal are at an increased risk for subsequent cardiovascular disease events.

Additionally, Dr. Tawakol has played a primary role in developing multi-modality imaging methods for implementation in trials evaluating novel treatments. His team has trained scores of institutions on the performance of arterial FDG PET/CT imaging, and has shown that the trained sites can provide excellent quality data for multi-center trials. He currently serves as study Chairman and Core Lab Director for several on-going multi-center trials (MCT) evaluating interventions targeting plaque inflammation.

Ferran Torres (EMA, ESP)

Ferran Torres, MD, PhD, medical doctor (1988), clinical pharmacology medical specialty (1992), PhD (methodological and statistical issues of sequential clinical trials, 1998), with more than 20 years' experience in the design and analysis of clinical studies in the hospital and university settings (1992).

More than 115 published papers in indexed scientific journals with a cumulated IF of >600 (1993 to Jun-2013). [Pubs from 2000-] Associate professor at the Biostatistics Unit, Faculty Medicine, Universitat Autònoma de Barcelona (UAB, 1994).

Scientific Director of the Biostatistics and Data Management Core Facility, IDIBAPS - Hospital Clinic Barcelona (2007).

Medical and statistical consultant to the Spanish Medicines Agency (AEMPS, 1999); member of the Scientific Advice Working Party (SAWP, 2008-) and the Biostatistics Working Party (BSWP, 2009) groups at the European Medicines Agency (EMA).

Active collaborator of the ECRIN network: Spanish representative to the Data Management group (2003); Permanent External Reviewer of the ECRIN standard procedures (2013).

Interested in Orphan diseases and collaboration with EURORDIS network. Coordinator and professor to several training, doctorate courses and masters of methodological-statistical issues on clinical investigation.

Freek Verheugt (Amsterdam, NED)

Freek W.A, Verheugt, MD, F.E.S.C., F.A.C.C., F.A.H.A. is Professor of Cardiology at the Heart-Lung Centre of the University Medical Centre of Nijmegen and Chairman of the Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam, The Netherlands.

Professor Verheugt gradua¬ted from the University of Amsterdam in 1974 and wrote a thesis on platelet and granulo¬cyte antigens and antibodies. He trained in cardiology at the Thoraxcenter of the Erasmus University in Rotterdam. He has been a Professor at the University of Colorado Health Sciences Center in Denver, U.S.A., and at the Free University in Amsterdam. He was President of the Netherlands Society of Cardiology between 1999 and 2001.

Professor Verheugt has published over 430 papers in peer-reviewed international journals including New England Journal of Medicine, Lancet, Circulation, Journal of the American College of Cardiology and European Heart Journal, of which is an Editorial Board Member. He is an editorial adviser of Lancet, New England Journal of Medicine and Circulation. He has over 20,000 citations and a Hirsch index of 60. His main fields of scientific interest are pharmacological and interventional treatments of acute coronary syndromes and atrial fibrillation.

ABSTRACT

Combination of AF and ACS: the potential role of NOACs

Prof. Freek W.A. Verheugt
Amsterdam, The Netherlands

The objective of antithrombotic therapy in atrial fibrillation (AF) is prevention of stroke or systemic thromboembolism. For acute coronary syndromes ACS) the purpose of antithrombotic therapy is prevention of further coronary thrombosis and/or rethrombosis, that may lead to (re) infarction and death.

For AF oral antiplatelet therapy hardly modifies the risk of stroke[1], whereas oral anticoagulation with vitamin-K antagonists (VKA) is very effective against stroke or systemic thromboembolism. The flip side of oral anticoagulation therapy in AF is the catastrophic complication of intracranial haemorrhage.

For ACS it is the other way around: oral antiplatelet Ischemic is very effective in reducing myocardial infarction and death, and VKA is hardly used although is effective alone[2,3], or in combination with aspirin provided INR is above 2.0[4].

In the era of invasive ACS management dual antiplatelet therapy and VKA are mandatory[5], but the risk of bleeding is very high. Better options are the omission of aspirin[6] and/or the introduction of safer anticoagulants[7,8]. Both strategies and their combinations will be discussed.

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Alphons Vincent (Medtronic, CHE)

Alphons Vincent, MD, is currently Director Medical Programs and Education for the Cardiac Rhythm Disease Management division of Medtronic in Europe. He has been with Medtronic for 23 years and held several positions in marketing, business, clinicals, medical affairs and education. His experience includes positions in Vitatron, a pacemaker company within the Medtronic corporation, and further Cardiac Surgery, Subcutaneous Diagnostics and Monitoring and Cardiac Rhythm Disease Management. He is a graduate (MD) of the medical school at the University of Nijmegen (The Netherlands) and holds bacholor degrees in management information systems and economics at the University of Tilburg (The Netherlands). In his current role he is responsible for physician advisory boards, scientific symposia, clinical study strategy and medical physician education. He plays a coordinating role in managing the relationships with key opinion leaders in Europe.

Adrian Voors (Groningen, GER)

Adriaan Voors is Professor of Cardiology and specialized in heart failure. Since July 2003, Dr Voors works as a Cardiologist in the University Medical Center Groningen. In 2007, he became Established Clinical Investigator of the Netherlands Heart Foundation and President of the Working group of Heart Failure of the Dutch Society of Cardiology. In May 2010, he became Professor of Cardiology at the University Medical Center Groningen. Professor Voors works as a clinical cardiologist, teaches cardiology to students at the University of Groningen, and is/was supervisor of 25 PhD students. He (co)authored more than 250 peer-reviewed papers and several books and chapters, mainly on heart failure, and he is deputy editor of the European Journal of Heart Failure and an editorial board member of the Journal of the American College of Cardiology, Netherlands Heart Journal and Cardiovascular Drugs and Therapy. Professor Voors is project leader of a large scale European FP7 project on personalized medicine in heart failure patients. In 2013 he founded G-CURE (Groningen- Cardiology University Research Enterprise), a company aimed at supporting early phase drug development for heart failure. Finally, he has a large experience in the design and conduction of phase II/III clinical trials in heart failure (principal investigator of 7 phase II heart failure trials, executive/steering committee member of another 15 phase II/III heart failure trials, and member of the data safety monitoring board of 4 phase II-III heart failure trials).

Rolf Wachter (Göttingen, GER)

Rolf Wachter is an assistant Professor of Cardiology and clinically working as a cardiology consultant. He is responsible for the clinical trial unit and the outpatient clinic for severe heart failure of the Clinic for Cardiology and Pneumology, University of Göttingen, Germany and is running the center for therapeutic-resistant hypertension of Göttingen University in collaboration with Michael Koziolek, a nephrologist. He studied medicine in Göttingen and Paris with internships in South Africa and at Huntington Memorial Hospital, Pasadena, CA and received his MD in 2000. He is in the board of directors of the German Heart Failure network (www.knhi.de) and a principal investigator of the German Center for Cardiovascular Research (www.dzhk.de). His three areas of research interest are: (1) Heart failure with a special interest in heart failure with preserved ejection fraction (HFpEF), where he and his team run a large observational study (Diast-CHF) and, in collaboration with Burkert Pieske and Frank Edelmann, the RCTs Aldo-DHF (published in JAMA 2013) and Ex-DHF trial(ISRCTN 42524037). (2) Undiagnosed atrial fibrillation in patients with cerebral ischemia, which include the observational Find-AF study family and the ongoing Find-AF randomised trial (NCT01855035). (3) Baroreceptor stimulation in hypertension and heart failure, where his team overseas roughly 50 patients with implanted baroreceptor stimulators. He is a member of the German Cardiac Society, a fellow of the European Society of Cardiology (FESC) and a professional member of the American Heart Association (AHA) and has published more than 60 papers in peer-reviewed journals.

Scott Wasserman (Amgen, USA)

Dr. Wasserman, MD, FACC, is an Executive Medical Director in Global Development at Amgen where he is responsible for the clinical development of novel cardiovascular therapeutics in the Cardiovascular Therapeutic Area. Since joining Amgen in June 2005, Scott has taken new therapies, including small and large molecules, from phase 1 through phase 3 clinical development. He set program strategy and led numerous critical programs in heart failure, osteoporosis, fracture healing, and dyslipidemia. In addition, Scott expanded Amgen's cardiovascular capabilities, shaped our cardiovascular portfolio, and built our Cardiovascular Therapeutic Area team. Most recently, Scott's efforts focus on the design, execution, and delivery of the global

evolocumab clinical trials program and registrational strategy.

Prior to joining Amgen, he was on faculty at Stanford University in the Division of Cardiovascular Medicine where he was the principal investigator on NIH-funded research that examined endothelial gene expression and served as an attending cardiologist at the Palo Alto Veterans Administration Hospital. Dr. Wasserman received his M.D., Magna Cum Laude from Harvard Medical School and his B.S., Magna Cum Laude from Haverford College. He completed his postgraduate training in Internal Medicine and Cardiovascular Medicine at Stanford University and is board certified in both disciplines. Scott did post-doctoral cardiovascular research at COR Therapeutics and Millennium Pharmaceuticals and served as a consultant for 5AM Ventures and Crestview Capital Funds.

Stephan Windecker (Bern, CHE)

Prof. Windecker currently serves as physician-in-chief and director of invasive cardiology at the Department of Cardiology, Swiss Cardiovascular Center Bern, Switzerland. He also is an executive board member of the Clinical Trials Unit (CTU) at Bern University Hospital and co-director of clinical research in the department of cardiovascular diseases.

Prof. Windecker's principal activity surrounds clinical services in the section of invasive cardiology. He is involved in clinical research and evaluation of new devices. His principal research interest focus on the evaluation of intracoronary devices for the treatment of coronary artery disease. He also has an interest in research related to structural heart disease including transcatheter aortic valve implantation, PFO as well as percutaneous left ventricular assist devices. He is involved in continuous medical education and teaching of medical students, housestaff, fellows, and tutor for interventional cardiologist.

Prof. Windecker is currently President-Elect of the European Association of Percutaneous Coronary Interventions (EAPCI). He is a fellow of the European Society of Cardiology (FESC).

Holger Woehrle (Resmed, GER)

Holger Woehrle is VP Clinical Research/Medical Director Europe for Resmed. Since 2006 he has been responsible for clinical research and the execution of major global clinical trials. Responsible for Medical Affairs in Europe. Developed the ResMed Science Center to support local investigators with research logistics and the ResMed Academy for external clinical training.

Consultant in the lung center Ulm and their sleep and ventilation center (since 2007). Head of the sleep and ventilation center, board certified specialist in internal medicine, specialist in sleep medicine.

University Hospital Ulm (till 2006): Head of the emergency room, head of the sleep lab, associate lecturer for internal medicine, state degree in medical didactics.

Faiez Zannad (Nancy, FRA)

Faiez Zannad, MD, PhD is Professor of Therapeutics at the Medical Faculty of the Henri Poincaré University of Nancy. He obtained his MD as a Cardiology specialist in 1979 from the Faculté de Médecine de Nancy. He is currently Head of the Division of Heart Failure, Hypertension and Preventive Cardiology/department of Cardiovascular Disease of the academic hospital of Nancy, and Director of the Clinical Investigation Center (CIC), mutually funded by the academic hospital and the INSERM and of a research group at an INSERM Unit (U961, Cardiac Fibrosis, Stiffness and cardiovascular risk) at the Faculté de Médecine. He is national coordinator of the network of 15 Clinical Investigation Centres working in the cardiovascular field in France. He is coordinating a Joint Research Program on transition from Hypertension to Heart Failure, in the 6th FP EU funded Network Excellence "InGeniousHyperCare". He conducts his research, in the area of physiopathology and pharmacotherapeutics of hypertension and heart failure.

Dr Zannad is currently Co-Editor in chief of Fundamental and Clinical Pharmacology, the official journal of the European Federation of Pharmacological Societies (EPHAR) and a member of the Editorial boards of a number of journals in the field of Cardiology, Hypertension and Cardiovascular Pharmacology.

He has contributed more than 300 scientific publications and published several books on cardiovascular pharmacotherapy and on Heart Failure. He is chairman and organizer of several international meetings: "CardioVascular Clinical Trialists (CVCT) Forum and Workshop" (Cannes and Paris, with Bertram Pitt and Desmond Julian); "Acute Heart Failure Syndromes" (Cannes and Chicago, with Mihai Gheoghiade) and "Biomarkers in Heart Failure" (Cannes, with Kirkwood Adams).

Dr. Zannad is involved in a number of major cardiovascular clinical trials, as a Principal Investigator and/or as a chair or member of several Steering Committees, Critical Event Committees and Data Safety and Monitoring Boards –

- Chairman: FOSIDIAL, EMPHASIS-HF, NECTAR-HF; ARTS, COMMANDER-HF,
- Member of Executive Steering Committee: CIBIS II, RALES, VALIANT, RECOVER, MOXCON, EPHESUS, EVEREST, AURORA, ASTRONAUT, AXIOM-ACS, HF ACTION; PEARL-HF, ALBATROSS, REMINDER, SERVE-HF, ALCHEMIST; EXAMINE; PARAGON, STAR-HF, DENER-HTN,
- Steering Committee Member: APSI, FIRST, CIBIS I, CAPRICORN, ASCEND-HF,
- Critical Event Committee: CAPRICORN, RESPECT, SCOUT, EchoCRT,
- Data and Safety Monitoring Board: HEAAL, ASPIRE.

ABSTRACT

Results of and lessons from the first CV safety trials of oral diabetes drugs, in the new FDA regulation environment: clinical perspective, the cardiologist view

Faiez Zannad (Nancy, FRA)

Glycemic control is an inadequate surrogate marker of cardiovascular event reduction in patients with type 2 diabetes. Clinical trials to date have been unsuccessful in identifying a therapeutic approach that addresses the underlying problem in diabetes (glycemic control) and reduces cardiovascular risk. The potential for some agents to increase the risk of cardiovascular events has led to substantial changes in regulatory requirements for new anti-diabetic therapies. These requirements, while key to ensuring the cardiovascular safety of new agents, fail to emphasise the need to show clinical benefits, such as less visual impairment, less need for dialysis, or fewer cardiovascular events and deaths. Changes in test results such glycemic control, serum creatinine, micro-albuminuria or retinopathy are inadequate surrogates.

The findings of a meta-analysis with rosiglitazone published in 2007 caused some controversy, despite the data-quality and resulting methodologic limitations of the analysis, are believed to have contributed to the change in the U.S. Food and Drug Administration (FDA) regulatory requirements for new anti-diabetic therapies.

Two trials have been published recently, (SAVOR and EXAMINE) which yielded similar results, suggesting that saxagliptin and alogliptin, respectively, are safe and do not increase CV events (MACE). While the patient populations differed slightly (primary and secondary prevention vs. post ACS populations, respectively), the results are similar. However, some differences on the effects on heart failure (HF) events may stir controversy. SAVOR but not EXAMINE showed a significant increase of HF hospitalization rates with active study drug. The incidence of HF is often similar to that of myocardial infarction in patients with diabetes and in some studies, higher. Thiazolidinediones have been associated with an increased risk for heart failure. In the RECORD trial, rosiglitazone was associated with a higher risk of death or heart failure hospitalization. The debate on HF safety will need cooperation across trialists, with potentially a meta-analytic approach. Mechanistic plausibility needs also to be investigated.

It is possible that cardiovascular safety (i.e. not producing more cardiovascular events) will dominate future research of anti-diabetic medicines, potentially at the expense of obtaining efficacy data (i.e. prevention of cardiovascular events). This would be an unfortunate consequence since drug approval should be based on improvements in outcomes that are important to patients, as well as safety.

Regulators should consider the potential advantages of offering extended patent-protection in order to encourage companies to conduct long-term trials in diabetes and many other long-term medical conditions. Cooperative efforts among physicians, clinical trialists, regulators, and sponsors are needed to address unresolved issues including re-defining therapeutic targets that are meaningful to patients with diabetes, determining the appropriate length of follow-up for future trials, and considering the ethical and operational challenges of non-inferiority designs.

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ABSTRACT

Biomarkers to guide care in heart failure - The HOMAGE approach

Faiez Zannad (Nancy, FRA)

HOMAGE (Heart OMics in AGEing) is a 6-year European Research network (Collaborative Project) supported by the European Commission under the Health Cooperation Work Programme of the 7th Framework Programme.

As more people survive into old age, the prevalence of heart failure (HF), one of the most common and debilitating diseases in older people, will rise still further. Delaying or preventing HF will have great benefit to those at personal risk, their families, society and the economy. HOMAGE aims to provide a biomarker (BM) approach that will help identify:

i. Patients at high risk of developing HF before the onset of symptoms

ii. Subsets of patients who are more likely to respond to specifically targeted therapies (personalized medicine).

In available cohorts, we will identify the most promising 'omics based BM profiles for the pre-symptomatic diagnosis and future prediction of HF in patients at risk. The predictive value of the BMs for other co-morbidities commonly associated with HF and ageing will also be investigated.

Furthermore, in a prospective trial, we will investigate the potential for targeting preventive therapy at patients with the greatest likelihood of response and the lowest risk of adverse effects. Our selection of innovative 'omics-based BMs is based on knowledge of biological pathways of the disease, which may facilitate identification of 'Biotargets' for future therapies. On the economic side, HOMAGE will act as an economic catalyst for European SMEs in the field of cardiovascular and ageing BMs, estimated to peak annual turnovers of up to 800 M€.

The HOMAGE is set to deliver clinically relevant and industrially applicable clinically validated omics-based BMs that will quantify pathological activity in disease pathways that may lead to HF enabling early detection of risk and effective and efficient targeting of treatments at groups of patients that will have the largest net gain.

HOMAGE objectives are:

1. To validate the association of 'omics based BMs with the risk of developing HF and co-morbid conditions in cross-sectional at risk and population cohorts.
2. To demonstrate the incremental value of 'omics based BMs, over the existing predictive models alone or integrated with established clinical phenotypes and existing BMs.
3. To investigate an innovative 'omics BM-based therapeutic strategy.

ABSTRACT

Can mineralocorticoid receptor antagonist be kidney friendly?

Faiez Zannad (Nancy, FRA)

Despite their proven benefits in large-scale, prospective, double-blind, randomized trials and recommendations for their use included in international guidelines, adoption of optimal therapy including Mineralocorticoid receptor antagonists (MRAs) is slow and mainly hindered by concerns over the risk of hyperkalemia, especially in the elderly and in patients with concomitant CKD and diabetes.

Beyond spironolactone and eplerenone, there is a need for more selective, better-tolerated MRAs. The next generation of MRAs has entered the clinical trial development phase (ARTS trials with finerenone, Mitsubishi agent). How to position them vis-a-vis the available MRAs in heart failure needs creativity in designing novel trials with more focused patient populations.

Finerenone is a next-generation non-steroidal MRA that has shown improved selectivity for the MR over other steroid hormone receptors compared with spironolactone and improved affinity for the MR compared with eplerenone in pre-clinical studies.5 In comparative studies using pre-clinical models of hypertension-driven HF and renal dysfunction, finerenone has been found to confer more pronounced cardiorenal end-organ protection than the steroidal MRAs.

The MRA Tolerability Study (ARTS) was designed to assess the safety and tolerability of finerenone in patients with HFrEF and mild or moderate chronic kidney disease (CKD), and to select doses for further study in phase III clinical trials.

This randomized, controlled, phase II trial consisted of two parts. In part A, the safety and tolerability of oral finerenone [2.5, 5, or 10 mg once daily (q.d.)] was assessed in 65 patients with HFrEF and mild CKD. In part B, finerenone (2.5, 5, or 10 mg q.d., or 5 mg twice daily) was compared with placebo and open-label spironolactone (25 or 50 mg/day) in 392 patients with HFrEF and moderate CKD. Finereneone was associated with significantly smaller mean increases in serum potassium concentration than spironolactone (0.04–0.30 and 0.45 mmol/L, respectively, P, 0.0001–0.0107) and lower incidences of hyperkalaemia (5.3 and 12.7%, respectively, P ¼ 0.048) and WRF. BAY 94-8862 decreased the levels of B-type natriuretic peptide (BNP), amino-terminal proBNP, and albuminuria at least as much as spironolactone. Adverse events related to finerenonewere infrequent and mostly mild. Therefore, in patients with HFrEF and moderate CKD, finerenone 5–10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in decreasing biomarkers of haemodynamic stress, but it was associated with lower incidences of hyperkalaemia and WRF.

The ongoing ARTS-HF trial aims at assessing finerenone given orally at different doses, to evaluate whether it is safe and can help the well-being of patients with worsening chronic heart failure and either type II diabetes with or without chronic kidney disease or kidney disease alone. These treatment doses will be compared to eplerenone.

The ARTS-DN trial will assess finerenone given at different doses, to evaluate whether it is safe and can help the well-being of patients with type 2 diabetes and diabetic nephropathy. These treatment doses will be compared to placebo.

Prevention of heart failure is another potential area where novel MRAs might be helpful. Metabolic syndrome, diabetes, CKD, resistant hypertension and a whole host of potential indications offer important opportunities for novel agents action on the aldosterone pathways.

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ABSTRACT

NOACS for heart failure with sinus rhythm: rationale and design of the COMMANDER-HF trial

Faiez Zannad (Nancy, FRA)

Heart failure (HF) is a prothrombotic disease and thrombosis may be associated with increased morbidity and mortality. For the last 15 to 20 years, more research has centered around the hypercoagulable state that occurs in HF patients. It has been observed in clinical studies that subjects with HF have higher circulating levels of pro-coagulants. In addition, autopsy studies of subjects with HF who died suddenly during a clinical trial had a high rate of myocardial infarction (MI) or acute coronary events. Studies and guidelines have reported that the prognosis after an index hospitalization for HF is poor with a 50% readmission rate at 6 months and a 25% to 35% mortality rate at 12 months. Although the results of previous studies with warfarin have demonstrated that anticoagulation is associated with reduced rates of important clinical events in patients with HF, results of these studies have not been conclusive. In a recent Phase 3 study of rivaroxaban in acute coronary syndrome (ACS), rivaroxaban was shown to reduce the incidence of the primary endpoint (cardiovascular [CV] death, MI, or stroke) in a subset of subjects with a history of HF (see Table 1 of the protocol). This supports the hypothesis that rivaroxaban may help reduce thrombotic events in patients with HF that can lead to death, MI or stroke. Thus, a large prospectively designed study with a novel anticoagulant is warranted to adequately address whether or not rivaroxaban can reduce the risk of death, MI, and stroke in patients with chronic HF and significant coronary artery disease (CAD), following a hospitalization for exacerbation of their HF. This study is designed to be a pivotal Phase 3 study, with adequate power to determine if the use of the Factor Xa inhibitor rivaroxaban in addition to standard HF therapy can reduce the risk of important clinical outcome events (ie, all-cause mortality [ACM], MI, and stroke) in patients with chronic HF and significant CAD. The addition of another therapeutic approach to reduce the risk of morbidity and mortality in chronic HF patients would fulfill a substantial unmet medical need. This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven, superiority study of rivaroxaban with clinical outcome assessments in subjects with chronic symptomatic HF (3 months or longer) and significant CAD. The subject population comprises men and women age 18 and over who have a diagnosis of previous MI or significant CAD with a left ventricular (LV) dysfunction (left ventricular ejection fraction [LVEF]) ≤40%). Only subjects hospitalized for decompensated HF (known as the index hospitalization) will

be eligible for enrollment at hospital discharge (and up to 7 days after discharge) if they are in stable condition.

The primary efficacy outcome is the composite of ACM, MI, or stroke. The principal safety outcome is the composite of fatal bleeding or bleeding into a critical space. Additional bleeding outcomes are bleeding events requiring hospitalization, and ISTH major bleeding events.

A total of 984 primary efficacy outcome events are targeted to demonstrate the superiority of rivaroxaban compared with placebo. A sample size of approximately 5,000 subjects will be enrolled.. Subjects will receive double-blind treatment (oral rivaroxaban 2.5 mg or matching placebo b.i.d.). The maximum dose of ASA will be 100 mg. Dual antiplatelet therapy is allowed where indicated.

The trial started enrolling patients in August 2013.

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ABSTRACT

TOPCAT, lessons learnt and implications for clinical practice and for the design and conduct of future trials

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The very first HFPEF trials were complex to perform took very long to enroll patients or had neutral results. More recent trials adopted different strategies attempting to better define patient populations enrolled in the trials.

TOPCAT results are unknown at the time of drafting this abstract, but will be known at the time of the CVCT 2013 forum.

Whatever the results of TOPCAT, this study will add to the experience gained from the few trials in HFPEF and will therefore help answer the following questions:

Is it possible to homogenize the heterogeneous HF-PEF population?

- What approaches are most promising (e.g., biomarkers, hemodynamics, echo parameters, omics, other)?
- How to better target a primary pathophysiology?
- How soon after heart failure admission should patients be ideally enrolled?
- How to deal with the confounding role of concomitant comorbidity?
- What are the implications for industry?

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POSTERS

Primary prevention population cohort: Budakalász cardiovascular health examination survey

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Objective: Determination of novel biomarkers of subclinical vascular diseases is a main target of primary prevention efforts. The Framingham study provides important association data between risk factors and cardiovascular disease in a US cohort. No reliable morbidity data exists however on Central-european, especially on Hungarian population.

Method: Semmelweis University started a cardiovascular screening programme involving the adult population (>20y) in a Central-Hungarian town The Budakalász Cardiovascular Health Examination Survey. The complete adult population (8.000 inhabitants) of the selected town is targeted in our voluntary programme, and parallel a 5% (400 persons) representative sample have been selected for screening. Repetition of the screening is planned in every five years. Protocol includes health questionnaire based on the European Health Indicators Monitoring (ECHIM) survey and FINDRISK score, non-invasive tests (body height and weight measurements, resting blood pressure and ankle-brachial index), digitally recorded ECG and venous blood biobanking (serum, plasma and DNA).Cardiac- and carotid ultrasound is performed on all participants. Carotid duplex scans are **analysed** offline for semi-automatic intima-media thickness measurement. Low-dose cardiac CT for coronary calcium and cardiac fat determination is also performed in certain age groups (>35yin males and >40y in females). Comprehensive psychological tests (BIG5, TLE, Zung, STAI, PANAS, RSS, etc.) are performed optionally.All information about samples and data collected is stored in a coded clinical database.

Results and conclusion: By September 2013, 2227 inhabitants have been screened (male: 912 (41.0%), average age 55.3 (+/- 14.8) years. Our goal is to complete the protocol on the majority of the adult population in the selected town. By performing longitudinal follow-ups and analyzing associations between cardiovascular risk factors, morbidity and mortality our study would be effective to detect the relevant cardiovascular risk factors in a primary prevention Central-European cohort while may ameliorate the population's health-consciousness.

Serial measurements of matrix metalloproteinase-9 in stratification of arterial hypertension patient

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Objective: To investigate the predictive value of serial measurements of circulating matrix metalloproteinase-9 level in hypertensive patients during 12 months after ischemic stroke.

Method: 102 patients with mild to moderate arterial hypertension within 3 weeks after ischemic stroke were included in the study. The circulating matrix metalloproteinase-9 (MMP-9) level was assessed at baseline and after six months of baseline. Clinical interviews were conducted every 3 months for 1 year after receiving blood samples. As clinical end-points we determined follow cardiovascular outcomes: recurrent stroke or TIA, ischemic heart disease, sudden death, diabetesmellitus, cardiovascular events, including chronic heart failure and the need for hospitalization for these reasons.

Results: 102 mild-to-moderate arterial hypertension patients (67 men and 35 women; mean age, 58.38 years [95% CI = 54-72 years]) were included in this study in 3 weeks after first clinical signs of ischemic stroke. All included patients were hypertensive, 45.1% were dyslipemic, 42.2% were smoked, and 14.7% had a history of mild diabetes mellitus. We found right-side injury of brain in 63.7% cases; in 34.3% and 2% left-side and two-side injuries were defined. During observation period 58 cumulative clinical events occurred.

Discussion: It has been showed that increased MMP-9 concentration within six months after ischemic stroke has positively associated with incidence of cardiovascular events, when compared with individuals without increased circulating levels of MMP-9. Adjusted odds ratio for the occurrence of cumulative cardiovascular events in hypertension patients with MMP-9 at baseline more 1001.0 ng/ml, when compared with lower concentrations of one was 2.78 (95% CI=2.41-2.95; P=0.001), and an increased sixth month circulating MMP-9 over 956.5 ng/ml, when compared with lower concentrations of one was associated with adjusted odds ratio 3.02 (95% CI=2.72-3.57; P=0.001).

Conclusion: We found that circulating MMP-9 level is an independent predictor of 1 year cumulative cardiovascular events in patients with hypertension after ischemic stroke.

Interrelationship between circulating osteoprotegerin and subclinical coronary atherosclerosis

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Objective: To evaluate the interrelation between circulating OPG and coronary vasculature damage in type 2 diabetes mellitus patients with known coronary artery disease.

Method: 126 subjects with stable diabetes mellitus 2 type with previously angiographic documented CAD were enrolled to the study. All patients were graduated into two groups depended calculating very high risk cardiovascular events and other. Assessment of risk was performed with contrast multispiral CT- angiography. Patients with Agatston' coronary calcium score (CCS) ≥ 320 units were stratified as high risk (n = 72) and all other patients as low risk patients (n = 54). OPG plasma levels were measured with ELISA.

Results: Analysis of the results showed that in a cohort of patients examined the mediana of circulating OPG was 3849.51 pg/mL (95% CI = 3282.23-4413.79 pg/mL). No significant differences in OPG levels were observed regarding age, sex, initial BP, hyperlipidaemia. Circulating OPG level in high risk subjects was significantly higher when compared with low risk patients (5295.86 pg/mL [95% confidence interval (CI) = 4856.90-5734.82 pg/mL] and 2230.85 pg/mL; 95% CI = 1860.57-2801.13 pg/mL; P<0.0001).

Discussion: Results from this study underline the importance of this biomarker use for screening procedure in diabetic populations aimed to specify of coronary vasculature damage severity and probably to recalculate cardiovascular risk.

Conclusion: We demonstrated that OPG plasma level can associate with vessel-wall thickening, percent atheroma volume, and Agatston' score index value in type 2 diabetes mellitus patients with previously angiographic documented CAD.

Link between lowed proangiogenic circulating mononuclear cells and cardiovascular risk factors

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Background: Multiple cardiovascular risk factors (MCRFs) in cardiovascular diseases, such as chronically increased blood pressure, hyperlipidemia, hyperuricemia, hyperglycemia, and obesity, have a negative impact on the heart exposed to ischemia. Many studies have demonstrated the presence of circulating endothelial progenitor cells (EPCs) in the peripheral circulation.

Objective: To evaluate the correlation between MCRFs and proangiogenic CMCs in asymptomatic coronary artery disease (CAD) patients.

Method: 126 subjects (54 male), aged 48 to 62 years, with asymptomatic CAD documented previously with angiography, and 25 healthy volunteers were enrolled in the study. The flow cytometric technique was used for predictably distinguishing cell subsets that depend on the expression of CD14, CD34, Tie-2, CD45, and CD309 (VEGFR2).

Results: The analysis of the outcome obtained shows a trend of an increase in circulating CD45–CD34+ CMCs and a reduction in CMC population defined as CD14+CD309+ and CD14+CD309+Tie2+ in known asymptomatic CAD patients in comparison with healthy volunteers. Substantial correlations between CD45–CD34+ and conventional cardiovascular risk factors (hs-CRP, T2DM, serum uric acid and hypertension) were found in the patient cohort. The concentrations of CD14+CD309+ and CD14+CD309+Tie2+ CMCs had effect on such factors as T2DM (RR = 1.21; 95% CI = 1.10–1.40; P = 0.008), hs-CRP > 2.54 mg/L (RR = 1.29; 95% CI = 1.12–1.58; P = 0.006), Agatston score index (RR = 1.2095% CI = 1.15–1.27; P = 0.034), and occurrence of three and more cardiovascular risk factors (RR = 1.31; 95% CI = 1.12–1.49; P = 0.008).

Discussion: Hematopoietic-derived EPCs have an effect on angiogenesis and tissue repair following several injuries. Therefore, traditional EPC populations, such as CD34+VEGFR-2+ and CD34+VEGFR-2+CD133+, are not related to severity of coronary artery disease or clinical outcome in the patients with atherosclerosis.

Conclusion: Lowed circulating CD14+ CD309+ and CD14+CD309+Tei2+ CMCs are related to a number of cardiovascular risk factors in asymptomatic patients with known CAD.

The long-term ethnicity survival effect on 12-years outcome in an ACS population

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Objective: To evaluate the application of relative survival to a large long-term observational study in coronary heart disease (CHD) among different ethnicities and potential advantages compared with all-cause survival methods. Survival after myocardial infarction (MI) is generally assessed using all-cause or cause-specific methods. Neither method is able to assess the impact of the disease or condition of interest in comparison with expected survival in a similar population. Relative survival, the ratio of the observed and the expected survival rates, is applied routinely in cancer studies and may improve on current methods for assessment of survival in CHD studies. To this end we analyzed using both methods the outcome of the 3 major Asian ethnic groups (Chinese, Indian and Malay) admitted after an index ACS event in Singapore.

Method: We studied 15,151 patients hospitalized for AMI (STEMI/NSTEMI) with a median follow-up of 7.3 years (maximum 12 years) in six publicly funded hospitals in Singapore from 2000 to 2005. Overall and cause-specific cardiovascular (CV) mortality until 2012 were compared among 3 major ethnic groups that represent large parts of Asia. The relative survival ratio (RSR) of all 3 ethnic groups was calculated and compared by dividing the "unexposed reference group survival ratio" matched by age, gender and ethnicity in the same period to analyze the relative exposure impact of an ACS event on survival. Furthermore, the relative excess risk (RER) was calculated since it removes the background risk using the reference population (Chinese). The RER was calculated by subtracting the crude mortality rate ratio in the minority ethnic groups (Malays or Indians) by the majority ethnic group (Chinese). Baseline characteristics were summarized as frequencies and Kaplan–Meier curves reflecting the cumulative adjusted mortality per ethnicity. Multivariate Cox model was made and adjusted in two different levels for all pre-treatment variables and for both pre and in-hospital variables.

Results: The median GRACE score was highest among Chinese, followed by Malay and Indians: 144 (25th percentile 119, 75th percentile 173), 138 (115, 167), and 131 (109, 160), respectively.

Sudden cardiac death risk factor identification in hypertensive patients

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Objective: Sudden cardiac death is defined as an unexplained death within 24 hours after onset of symptoms or earlier. It is a traumatic event for the patient's family. Ways of acting are limited and prevention is of primary importance. For long, its prevention has been confounded with coronary artery disease prevention. However, recent studies suggest that sudden cardiac death might be a distinct condition, whose occurrence cannot be diminished by using blood pressure lowering medication. Further research for risk factors for sudden cardiac death is necessary to identify situations in which a preventive strategy would be particularly relevant.

Method: The patients (16 058) included were enrolled in five randomized, controlled clinical studies, available through the INDANA research program (COOPE, MRFIT, EWPHE, STOP, SYSTEUR studies). These studies assessed the benefits of antihypertensive treatments against placebo or absence of treatment in hypertensive patients. The endpoint was the occurrence of sudden cardiac death. Various covariates were taken into account, including age, sex, smoking, history of atrial fibrillation, of heart failure, of myocardial infarction and of stroke, systolic blood pressure, diastolic blood pressure, body mass index, blood glucose, cholesterol, creatinine level, potassium level, heart rate. Baseline factors were related to risk of sudden cardiac death by logistic regression, adjusting for trial and treatment group. The model, builds on 2/3 of the patients, was converted to a risk score, validated on the remaining third of patients.

Results: In a multivariate analysis, we found that the risk for sudden cardiac death multiplied 1.95 (95% CI: 1.87, 2.03) every 10 years of age (p = 0.001), by 4.16 (95% CI: 1.45, 11.89) in men compared to women (p = 0.007), by 1.91 (95% CI: 1.21, 3.00) in smokers compared to non-smokers (p = 0.005). The rise of 1 cmHg in systolic blood pressure multiplied by 1.14 (95% CI: 1.13, 1.16) the risk for sudden cardiac death (p = 0.03), and of 1 mmol / L cholesterol by 1.36 (95% CI: 1.11, 1.67) (p = 0.002).

Conclusion: This study shows that in hypertensive patients, the covariates including age, sex, smoking, systolic blood pressure, high cholesterol, which are risk factors for coronary events, are risk factors for sudden cardiac death.

Can 6-minute walk test predict the development of cardiac events in STEMI patients post fibrinolysis?

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Objective: This study was performed to assess the added value of the 6-minute walk test (6MWT) in the risk-stratification methods for patients with ST -segment elevation myocardial infarction (STEMI) treated with fibrinolysis.

Method: 100 consecutive patients with STEMI who received fibrinolysis at Assuit University Hospital were enrolled in our study.We calculated the TIMI and GRACE risk scores, ST-segement resolution 90 min. after fibrinolysis, infarction size using total Creatine Kinase and eligible patients underwent 6MWT before discharge.

Results: Patients were divided into 3 groups according to level of 6MWT distance. Mean age was 61 years, 71.9% of our patients were males, 2/3 of our patients had anterior MI. only 10.5% of our patients had successful thrombolysis. Among the study population, the median 6MWT distance was 370 meters (interquartile range 162-462). Compared to patients in level 1 (>450m), patients in level 3 (<300m) were more likely to have clinical risk factors of hypertension, diabetes and impaired renal function test. The patient's mean TIMI score was 3.4 + 2.2. The patient's mean GRACE score was 150.5 + 27.7. There was a significant negative correlation between 6 MWT distance and GRACE risk score (r= - 0.80, p<0.001). 51% had major adverse cardiac events (MACE) at 3 months of follow-up including 16% died. Multivariate logistic regression analysis identified the GRACE risk score and 6MWT distance levels as the best predictors of the MACE at 3 month of follow up of STEMI patients after fibrinolysis, The incidence of MACE were 2 times higher in patients with a high risk 6MWT and GRACE risk scores (OR= 2.66, 95%CI= 1.1-4.9 & OR= 2.46, 95% CI=1.15-5.9).

Conclusion: In patients with STEMI treated with fibrinolysis, the addition of 6MWT to traditional risk factors improved risk prediction of cardiovascular events at follow up.

Heart 'omics' in AGEing (HOMAGE): design and research perspectives

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On behalf of the Heart 'omics' in AGEing (HOMAGE) investigators

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Objective: Heart failure (HF) is common in older people and its prevalence is increasing. The Heart 'omics' in AGEing (HOMAGE) project aims to provide a biomarker approach that will improve the early diagnosis of heart failure. A large clinical database, based on (1) cross-sectional and prospective studies of patients with overt disease or at risk, (2) population studies or (3) patients enrolled in randomised clinical trials, will be constructed to validate the association of 'omics'-based biomarkers with the risk of developing HF and co-morbidities.

Method: Studies are eligible for inclusion, if they received ethical approval, have baseline information about on cardiovascular risk factors available and if the subsequent follow-up includes fatal and nonfatal outcomes, including HF. Patient cohorts, population studies and randomised controlled trials are eligible for inclusion in the common database.

Results: Currently, the HOMAGE database includes 44,167 subjects, from 20 studies in 9 European countries. Data from healthy subjects were obtained from 2 population studies in Belgium and France (n=7929). The database also consists of patients with heart failure (n=4260), from 4 cohorts in France, UK, and Spain. Eight cohorts in patients with cardiovascular risk factors (n=4666) from France, Austria, the Netherlands and Italy were also included. Finally, data from 6 randomised controlled trials (n=27,312) in patients with heart failure patients, hypertensive patients and patients with high cardiovascular risk, from Austria, Ireland, the Netherlands, UK and Scotland, were included in the HOMAGE database. At this moment, follow-up data are available in 13 of the 20 studies (n=42,038).

Conclusion: The constructed database can be a useful resource in identifying candidate biomarkers that play a role in the mechanism underlying the onset and development of HF.

Eligibility for renal denervation experience from ENCOReDCentres: baseline characteristics of ongoing trials

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Objective: To investigate the proportion of patients eligible for renal denervation (RDN) and the reasons of non-eligibility in expert centres involved in the European Network COordinating Research on renal denervation in treatment-resistant hypertension (ENCOReD).

Methods: The medical files of patients referred for RDN from 9 European centres were reviewed according to a standardized questionnaire focused on basic characteristics, proportion of patients eligible for RDN and reasons of non-eligibility.

Results: This analysis included altogether 410 patients. Mean age of patients was 62 years and the average office blood pressure at screening was 173/95 mmHg. Patients were taking on average 4.7 antihypertensive drugs. 71% of patients were referred by specialists and 29% by general practitioners. The proportion of patients eligible for RDN according to the Symplicity HTN-2 criteria (E1) and the centre's criteria (E2) were 43% and 39%, respectively. The main reasons of non-eligibility were normalization of blood pressure after treatment adjustment (57%), anatomical reasons (18%) and renal dysfunction (14%).

Conclusion: In 410 resistant hypertensive patients screened in the ENCOReDcentres, approximately 40% are eligible for RDN. The primary reason for non-eligibility is blood pressure under control after treatment adjustment, which highlighted the importance of optimizing drug treatment in resistant hypertension patients and a careful screening procedure for RDN.

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Cardiovascular target values in a Hungarian primary prevention screening programme

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Objective: Our goal was to assess the awareness of population about cardiovascular diseases and related medication habits in a primary prevention screening program in a central-Hungarian town.

Method: Budakalász Health Examination Survey is a comprehensive cardiovascular voluntary screening program, targeting the adult population (>20years, ~8000 inhabitants). Examination consists of health interview survey, recording medical history and medication and non-invasive tests such as echocardiography, carotid ultrasound, body height and weight, resting blood pressure and ankle-brachial pressure index measurements (health examination survey). Venous blood biobanking and laboratory tests are part of the screening. Cardiovascular risk assessment is performed.

Results: By September 2013, 2227 inhabitants were screened (male: 41.0%, average age 55.3 (+/- 14.8)) years. Body mass index was above 30 in 32.3% of participants. According to health questionnaire 87.1% of them considered themselves obese. Medical history as reviewed by a physician, included hypertension in 1044 patients (47.1%), among them 88.5% were on anti-hypertensive regime, measured blood pressure, however was in normal range only in 36.4%. In the not-treated group only 59% of patients were aware of their disease (according to health interview survey). Hyperlipidaemia was previously known in 779 persons (35.1%), among them 50.8% persons takes statin daily. In contrast, at time of screening 44.6% had elevated total cholesterol level and 73.6% of the treated group had it in normal range. Pathological ankle-brachial index, an indicator of peripheral artery disease (PAD, normal range: 0.9-1.2) was found in 15.2%, but only 4.4% had PAD in past medical history. Average Framingham risk score for cardiovascular disease in 10 years of the population was 15.8% +/-13.3, and for CV death risk was 9.5% +/-8.2.

Conclusion: According to our results, awareness of the population and general practitioners should be raised. Also, our survey is effective to detect relevant cardiovascular risk factors and may ameliorate health-consciousness.

Thirty-day readmission following percutaneous coronary intervention in Malta: registries and surveys

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Objective: This study aimed to identify the 30-day readmission rate following percutaneous coronary interventions (PCI) in Malta, to determine the predictors that lead to readmission following PCI, as well as the underlying reasons for readmissions. This study has already been performed in New York State; a comparison of the readmission rate would thus be beneficial.

Method: The Maltese population constitutes approximately 375,000. In view of the small population a retrospective cross-sectional study was performed whereby the readmission rate over a period of four years, from 1st January 2008 to 31st December 2011, was assessed. This was possible in view that there is only one public hospital in Malta which caters for the whole population. Exclusion criteria included patients who had a previous PCI within 30 days, patients who had CABG surgery before PCI in the same admission, patients who died during the index hospitalization, and non-Maltese residents. Demographic factors, underlying co-morbidities, reason for primary readmission, coronary angiography findings, number of diseased vessels, number of stents deployed, intraventricular pressures, ejection fraction, as well as readmissions within 30 days and their respective reasons were noted from three databases: the Catheterisation Suite database, the hospital database for admitted patients, and database for electronic case summaries. Data were analysed using SPSS version 20.0. A total of 2814 PCI were performed during the four- year period studied. Of these, 477 were primary PCI for the management of ST-elevation myocardial infarction while the rest were performed electively, on both in-patients and out-patients. Subjects that died during the index hospitalization were excluded (n= 30) as well as non-Maltese residents.

Results: A total of 253 patients (8.99%) were readmitted within 30 days while 28 patients had staged PCI. 10.9% of patients undergoing primary PCI were readmitted while the admission rate in the remaining patients undergoing PTCA was 8.60%. The majority of the admissions were secondary to a cardiac cause (65.61%). In the population studied, no difference was shown in the admission rate with regards age (p= 0.61), gender (p= 0.69), number of stents deployed (p= 0.55), left ventricular function (p= 0.085), left ventricular systolic pressure (p= 0.10) and Left ventricular end-diastolic pressure (p= 0.44). However, the number of diseased vessels was shown to be significantly associated with the readmission rate (p= 0.037).

Conclusion: A lower 30-day readmission rate is noted in the Maltese population following PCI as compared to residents in New York. However, the population studied is much smaller and it is impossible to compare the complexity of the lesions tackled. In the study population, the number of diseased vessels was found to be associated with readmission rate. Major adverse cardiovascular events at 1 year might indicate further which patients benefit most from close monitoring following percutaneous coronary interventions.

The INcreaseOfVAgal Tone in Heart Failure (INOVATE-HF) Trial: Study Update

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Objective: Increased activation of the sympathetic nervous system with withdrawal of parasympathetic tone contributes to the deleterious clinical progression in patients with heart failure. The INOVATE-HF trial is assessing the safety and efficacy of the CardioFit® vagal nerve stimulation (VNS) system that is intended to restore the imbalance between the parasympathetic and sympathetic nervous systems in symptomatic heart failure (HF) patients receiving optimal medical therapy (including beta adrenergic antagonists).

Method: INOVATE-HF is an ongoing multi-center, open label trial enrolling up to 650 subjects at a up to 100 global centers. Subjects are randomized in a 3:2 ratio (active treatment: optimal medical management) and are followed at 3 month intervals for 18 months, then at 6 month intervals.Key inclusion criteria include left ventricular ejection fraction <40%, LVEDD between 55 and 80 mm and New York Heart Association functional class III despite optimal medical therapy. Patients with bi-ventricular pacemaker must have had it for at least 12 months.Key exclusion criteria include severe renal or liver dysfunction, untreated pacemaker indication, chronic atrial fibrillation, and significant anemia. The primary efficacy end point is all-cause mortality and heart failure hospitalization.There are 2 safety end points (freedom from procedure and system related complication events through 90 days post implant and the comparison of serious events between the 2 study arms after 90 days). Data from multiple secondary objectives will be assessed including echocardiographic, QoL, ECG, biomarker, functional and adverseevents. Hypothesis testing will determine whether the hazard rate is improved for the treatment group using a one-sided log-rank test.Three interim analyses are planned in addition to the planned analysis after approximately 376 primary events.

Results: INOVATE-HF is currently enrolling and following subjects at over 75 U.S. and European sites.Secondary objectives are designed toprovide additional evidence of the clinical benefits, as well as supportive insights into the mechanism of action of CardioFit® therapy.

Conclusion: Currently there are no therapies that specifically address restoring parasympathetic tone on cardiac function and structure in patients with HF. INOVATE-HF is the first large pivotal trial of VNS for the treatment of symptomatic HF through augmentation of parasympathetic tone.If proven effective and safe, this novel therapy is envisioned to be a synergistic, complementary adjunct to existing medical therapy that would impact the current treatment paradigm.

Understanding of Chest Pain in Microvascular Disease Proved by Cardiac Magnetic Resonance Image (UMPIRE)

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Background: Microvascular angina (MVA) is characterized by anginal chest pain, an abnormal stress test, and normal coronary arteries on coronary angiography. Although the exact pathogenesis remains to define, endothelial dysfunction contributes to it. To date, there exists no specific therapy for this disease entity. Phosphodiesterase-5 inhibitor improves the endothelial function and subsequently mircovascular circulation.

Objective: To identify whether udenafil offers benefits in treatment of MVA in female patients women with MVA, who have perfusion defect in cardiac magnetic resonance image (CMR), but normal coronary arteries.

Method: The 'Understanding of Chest Pain in Microvascular Disease Proved by Cardiac Magnetic Resonance Image: (UMPIRE)' trial is a multi-center, prospective, randomized, placebo controlled trial, designed to evaluate the effect of udenafil on myocardial ischemia and symptoms in female patients with MVA. The myocardial ischemia will be quantified by myocardial stress perfusion defect in CMR. A total of 70 patients with proven perfusion defect in adenosine-stress CMR will be randomly assigned to udenafil treatment group (daily 100 mg) or placebo group for 3 months. The primary end point is the improvement in perfusion defect size >25% in adenosine-stress CMR from baseline. The secondary endpoints include improvement in perfusion defect size <25%, chest pain frequency, ST-depression in stress test, Duke score in stress test, quality of life (QoL) assessment by SF-36 questionnaire, sexual dysfunction assessment by BISF-W self-questionnaire, and biomarkers for endothelial function.

Discussion: The UMPIRE trial is the first randomized controlled trial to evaluate the efficacy of udenafil in female MVA patients. If udenafil demonstrates cardioprotective effects, it may provide a novel therapeutic option to reduce myocardial ischemia and improve cardiac function in female MVA patients.Trial registration: ClinicalTrials.gov: NCT 01769482

Impact of smoking on platelet function testing in patients taking clopidogrel for ACS

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Objective: The variable response to clopidogrel is multifactorial, cigarette smoking is thought to be one of them, as smoking is a known inducer of CYP1A2, one of the predominant isoenzymes responsible for activation of clopidogrel. Purpose of the study was to find out the impact of cigarette smoking on clopidogrel-induced effects.

Method: In a prospective study 90 patients with acute coronary syndrome that underwent coronary angioplasty with drug eluting stents were consecutively enrolled. Of these ninety patients 26 (28.8%) patients were smokers. Patients received clopidogrel 300mg as loading and 75mg per day as maintenance dose. The loading dose of clopidogrel was administered from 1 to 7 days before the procedure. Pre-procedure arterial blood sample was taken from every patient for assessment of platelet function (Verify Now P2Y12 point-of-care assay).

Results: The mean percentage of inhibition was higher in smokers (23.8 ± 18.3) as compared to non smokers (12.9 ± 13.1) by two sample T test with p value =0.01. Similarly the mean P2Y12 reaction units (PRU) was found to be significantly higher in non smokers at 213±72 than in smokers who had mean PRU of 152±66 (p>0.00). Five in-hospital clinical events were encountered, including 3 cases of recurrent angina and 2 cases of sub acute stent thrombosis. Notably 4 of these patients including the 2 cases of stent thrombosis were smokers.

Conclusion: Clopidogrel therapy, in particular PFT % inhibition, may be more effective in current smokers compared with nonsmokers.

Similarities and differences in patient characteristics and design methodology between heart failure registries versus randomized clinical trials

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Objective: The generalizability of heart failure RCTs to the broader population has been questioned. Several large scale registries are shedding insight into the outcomes of heart failure patients in a real life setting. The objective of this analysis is to examine the differences between RCT and registry data for modern heart failure therapies.

Method: A literature search of EMBase, MEDLINE, PUBmed, Google Scholar, Cochrane reviews, articles identified 49 peer reviewed articles that addressed a comparison between RCTs and registry data.

Results: RCTs of ICD demonstrated significant differences compared to national registries yet no difference in mortality between RCT and registry patients was noted. Registry data suggests that utilization of evidence-based therapies has been slow in the community setting and this is a global phenomenon. Several small RCTs, several observational studies, and a large clinical registry demonstrated an improved survival using statins in advanced HF yet two large RCTs failed to show benefit. By constructing a simultaneous registry alongside the RCT, deficiency in delivery of care of non-trial patients can be identified.

Conclusions: While RCTs are still considered the gold standard for proof-of-concept, there is concern that such results are not applicable to the general public. In addition it is difficult to reconcile the benefit of drugs that work in the general public and not in clinical trials. Furthermore, while evidence may accrue from RCTs, there appears to be a delay in knowledge translation to non RCT clinical locations, further hampering the initiation of beneficial therapies.

Microcirculation features in diabetic patients with hypersecretion of c-peptide: a non-invasive study versus control subjects

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Background: It is known insulin resistance is associated with endothelial dysfunction andperipheral vascular disease in afflicted individuals. In clinical practice of endocrinologist in some cases the problem of the defects of hypoglycemic therapy errors lies in the development of contrinsular reactions in response to hyperinsulinism. Due to the rapid hormone destruction in the in the blood serum the definition of insulin secretion is difficult.

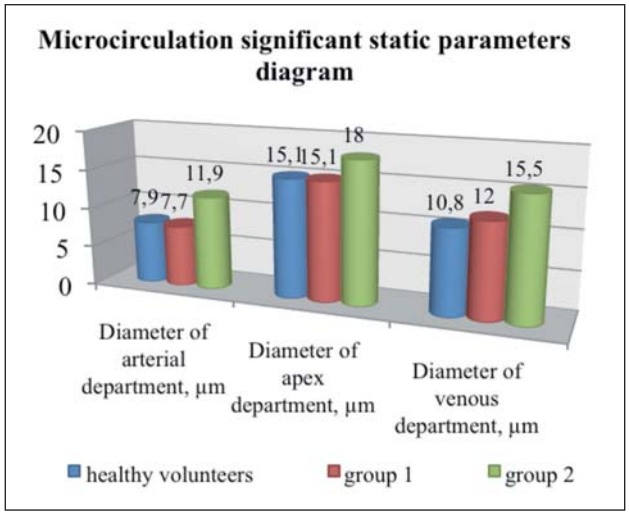
Objective: To assess microcirculation features in diabetic patients with hypersecretion of c-peptide.

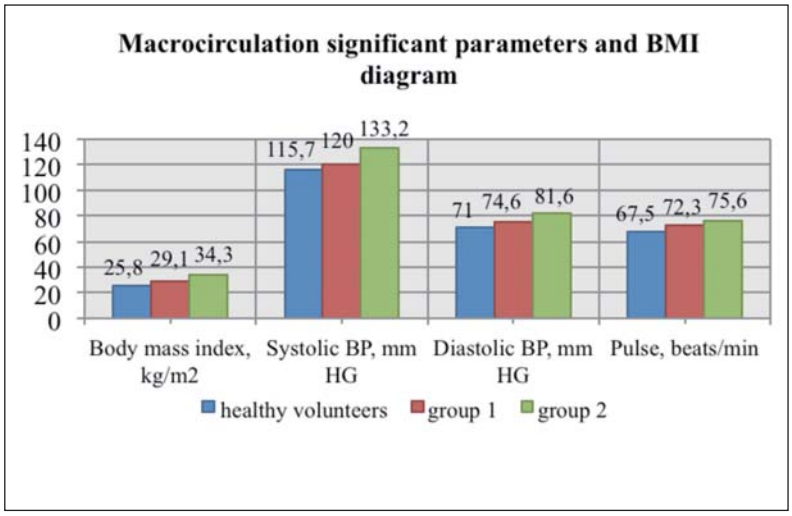
Method: In total it was surveyed 118 persons: control group (n=43) of nondiabetic normotensive individuals (50,1±9,9 years) and 72 diabetic patients (divided into 2 groups). Group 1 included 31 normal secretion of c-peptide patients (49,7±10,9 years and (697,2±284,4 pmoll), glycated hemoglobin (HbA1C)- 8,37±1,9%. Group 2 consisted of 41 hypersecretion c-peptidepatients (49,9± 9.1 years and 1317,3±502,9 pmoll), HbA1C 8,2±1,7%.In both groups there were the patients with arterial hypertension. We performed a non-invasive vital capillaroscopy (ZAO “Center for Analyses of Substances”) to evaluate the density of vascular network, degree of coiled capillaries, diameters of capillary parts, perivascular zone size, average capillary blood velocity (aCBV).

Results: Most important difference in microcirculation parameters was a significant expansion of the diameters of capillaries, especially of arterial one (p<0,05). We revealed decrease of the aCBV, which was significantly lower (p<0,03) in diabetic patients, than in the controls. Coiled capillaries quantity in both groups was significantly higher in comparison with the controls (p<0,05). In group with C-peptide hypersecretion high values of Body Mass Index and of blood pressure were revealed that confirmed the relationship of obesity and insulin resistance.

Conclusion: C-peptide hypersecretion resulted in microcirculation abnormalities, especially regarding expansion of the diameters of capillaries. We suppose the assessment of abnormal c-peptide secretion is possible according to the non-invasive capillaroscopy. Microcirculation parameters are already changed in the first weeks of drugs administration that affect hyperinsulinism.

Reference: Suchkova (Makeeva) O.V., “Assessment of correlation of microcirculation parameters and secretion of c-peptide in diabetic patients”, IUPS, Birmingham 2013.





Improving prognosis estimation in patient with reduced kidney function after acute coronary syndrome

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Background: The development of cardiorenal syndrome (CRS) proved worse prognosis in patients with acute coronary syndrome (ACS). The Growth differentiation factor 15 (GDF 15) is a new markers for diagnosis of CRS in combination with ACS.

Objective: To determine the significance of GDF 15 in the prediction of the development of CRS in patients with ACS.

Method: Examined 70 patients with ACS: 54 men and 16 women, mean age was 61, 8 ± 1, 3 years, 38 patients with Q-wave myocardial infarction (Q-wave MI), 14 - with non-Q-wave myocardial infarction (non-Q-wave MI), 18 - unstable angina (UA). The glomerular filtration rate (GFR) was estimated by Cockcroft-Gault formula. The level of GDF 15 was determined during the first day of hospitalization via ELISA (BioVendor, Czech Republic).

Results: After comparison of the levels of serum creatinine and GDF 15, the rank of correlation coefficient was identified (r=0,5; p=0,00001), that corresponds to the communication of medium strength. Correlation analysis of the studied parameters showed significant negative correlation between the GFR and GDF 15 (r=-0,44; p<0,05). The most expressed relationship between GFR and GDF 15 (r= -0,9; p= 0,01) was detected in patients with severely and moderately reduced kidney function. Discussion: the highest level of GDF 15 has been detected in patients with ACS and reduced kidney function, which is an additional marker of adverse outcomes.

Conclusion: The studies established the correlation between the GDF 15, serum creatinine and GFR, which makes it possible to use a new marker in the diagnosis of CRS.

GENERAL INFORMATION

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REGISTRATION FEE

On-site registration: 790 euros

Participant registration fee includes:
Access to all scientific sessions
Access to the Clinical Gathering Space
Congress materials
Lunches on 6 and 7 December 2013
Daily coffee breaks
Networking Reception on 6 December 2013
at Le Petit Journal Montparnasse
Upon invitation only. Please ask as the congress desk

Opening hours of the welcome desk
Thursday 5 December: 2:00 pm - 7:00 pm
Friday 6 December: 7:30 am - 7:30 pm
Saturday 7 December: 7:30 am - 6:30 pm

CLINICAL GATHERING SPACE

The Clinical Gathering Space will be located in the Foyer.
Morning coffee breaks will take place Foyer in front of the conference rooms.
Afternoon coffee breaks will take place in the Foyer
Lunch boxes will be served during the lunch sessions

OFFICIAL LANGUAGE

The official language of the meeting is English.


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