CVCT

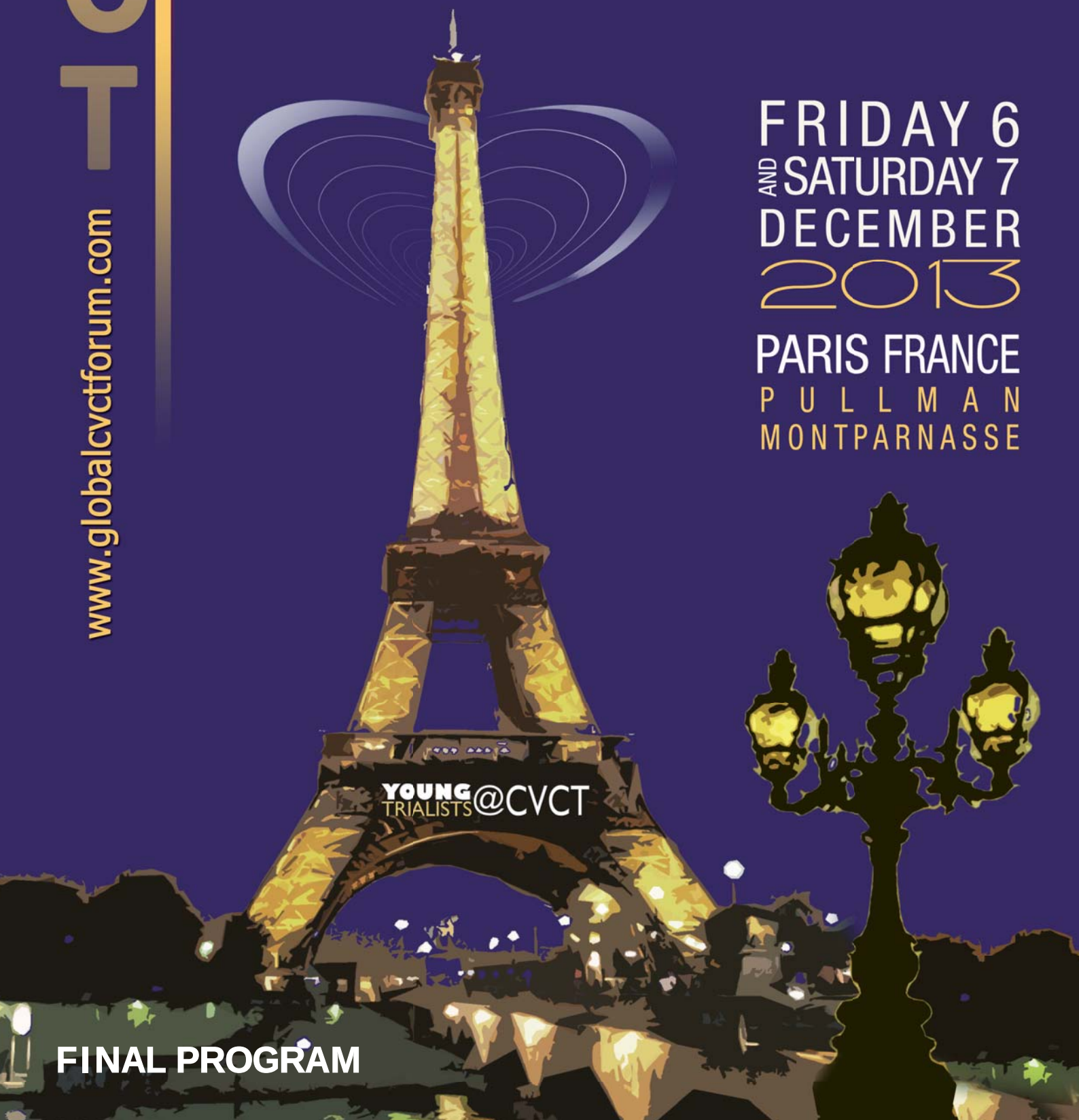
10th ANNIVERSARY

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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Gianpaolo Rossi (Padua, ITA)
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Christian Torp-Pedersen (Copenhagen, DEN)
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Adriaan Voors (Groningen, NED)
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Hans Wedel (Gothenburg, SWE)
William White (Farmington, USA)
Stephan Windecker (Bern, CHE)
Janet Wittes (Washington, USA)
Faiez Zannad (Nancy, FRA)

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)
David Rutledge (Abbott Vascular, USA)
Dan Schaber (Medtronic, USA)
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Danni Shi (Novartis, CHN)
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)

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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)