CVCT

9th Global CardioVascular Clinical Trialists Forum

PARIS CVCT live 012

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

www.globalcvctforum.com

November 30th
& December 1st,
2012

Pullman
Montparnasse
PARIS, France

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AZIZI Michel, Paris, FRA
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BAKRIS George, Chicago, USA
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MEBAZAA Alexandre, Paris, FRA
MEHRAN Roxana, New York, USA
METRA Marco, Brescia, ITA
NARULA Jagat, New York, USA
O'CONNOR Christopher, Durham, USA
PAIS Prem, Bangalore, IND
PATHAK Atul, Toulouse, FRA
PEACOCK Frank, Cleveland, USA
PFEFFER Marc, Boston, USA
PIÑA Ileana, New York, USA
PITT Bertram, Ann Arbor, USA
POCOCK Stuart, London, GBR
RAY Kausik, London, GBR
REDBERG Rita, San Francisco, USA
ROSENSON Robert, New York, USA
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ROUSSEL Ronan, Paris, FRA
RUDD James, Cambridge, GBR
RUILOPE Luis, Madrid, ESP
SILVAIN Johanne, Paris, FRA
SIMON Tabassome, Paris, FRA
SIMOONS Maarten, Rotterdam, NED
SLEIGHT Peter, Oxford, GBR
SOBHY Mohamed, Alexandria, EGY
STAELS Bart, Lille, FRA
STROES Eric, Amsterdam, NED
SWYNGHEDAUW Bernard, Paris, FRA
TARDIF Jean-Claude, Montréal, CAN
TAVAZZI Luigi, Cotignola, ITA
TAWAKOL Ahmed, Boston, USA
TORP-PEDERSEN Christian, Copenhagen, DEN
TSCHOEPE Carsten, Berlin, GER
VERHEUGT Freek, Amsterdam, NED
VOORS Adrian, Groningen, NED
WACHTER Rolf, Göttingen, GER
WAHL Denis, Nancy, FRA
WARNOCK David, Birmingham, USA
WASSMANN Sven, Munich, GER
WHEELER David, London, GBR
WIERZBICKI Anthony, London, GBR
ZANNAD Faiez, Nancy, FRA

EMEA–FDA–NHLBI-PMDA-MHRA

ANDO Yuki, PMDA, JAP
ALONSO Angeles, EMEA, ESP
BONDS Denise, NHLBI, USA
COOK Nakela, NHLBI, USA
DE GRAEF Pieter, EMEA, NED
DUNDER Kristina, EMEA, SWE
FARB Andrew, FDA, USA
GELLER Nancy, NHLBI, USA
GORDON David, NHLBI, USA
HEMMINGS Robert, MHRA, GBR
MASCETTE Alice, NHLBI, USA
PRASAD Krishna, MHRA, GBR
ROSANO Giuseppe, EMEA, ITA
ROSENBERG Yves, NHLBI, USA
SHINAGAWA Kaori, PMDA, JAP

INDUSTRY

ADOURIAN Aram, BG Medicine, USA
AUDHYA Paul, Reata, USA
BERKOWITZ Scott, Bayer, USA
BUYSSE Jerry, Relypsa, USA
CARLSON Mark, St Jude Medical, USA
CODY Robert, J&J, USA
DELIARGYRIS Efthymios, The Medicines Company, USA
FRIEDMAN Jeffrey, Boehringer Ingelheim, USA
GAUDIN Christophe, Sanofi, FRA
GOBBI Giorgio, Medtronic, CHE
HASKEL Lloyd, J&J, USA
HOUDIJK Wim, Biomérieux, FRA
KHDER Yasser, Boehringer Ingelheim, FRA
KIEVAL Rob, CVRx, USA
KIM Jae, Amgen, USA
KOGLIN Joerg, Merck, USA
KUPFER Stuart, Takeda, USA
LASALVIA Luis, Siemens, USA
LAWRENCE John, BMS, USA
MENDELSOHN Michael, Merck, USA
MIX Chris, Amgen, USA
ROESSIG Lothar, Bayer, GER
SCOTT Robert, Amgen, USA
SEMJONOW Véronique, Philips, NED
SHIPMAN Tami, St Jude Medical, USA
SNIDER James, Critical Diagnostics, USA
STEIN Kenneth, Boston Scientific, USA
TAIEL-SARTRAL Magali, Lilly, FRA
TSOUDEROS Yannis, Servier, FRA
VINCENT Alphons, Medtronic, CHE
YADAV Jay, CardioMEMS, USA
YARED Nadim, CVRx, USA
WASSERMAN Scott, Amgen, USA
WOEHRLE Holger, ResMed, GER

GENERAL PRESENTATION

Organized in collaboration with the European Society of Cardiology Working Group on Cardiovascular Pharmacology and Drug Therapy, CVCT Forum is a meeting specifically and totally dedicated to the discussion of clinical trials in cardiovascular disease.

CVCT Forum is attended by experts principally engaged in cardiovascular clinical trials (hence it's name).
Participants are among the group of major international opinion leaders and come from various functions linked with primary care, pharmaceutical industry, pharmaceutical regulatory bodies, and publishing houses from around the world (US, Canada, Asia, Europe, and Japan).

An outstanding faculty members are committed to disseminating concise data from controlled clinical trials that contribute to better clinical care and to discussing and identifying issues and relevant information. Such as how to do better clinical trials, how to satisfy regulatory authorities, and most importantly, how to improve cardiovascular health care.

The CVCT meetings are 'grass root' meetings, attended by individuals who are eager to communicate with one another and to share experiences with primary care physicians and the people that create and analyze major trials. CVCT meetings are primarily oriented toward discussion among persons as opposed to lecturing to a broad audience. Thought process counts, communication (during the meeting, but more importantly informal discussions outside of the meeting) is the important agenda, as opposed to dictating doctrine.
The format of the meeting is set to fulfill these aims. Beyond plenary sessions the meeting is structured with a variety of small interactive brainstorming workshops, expert discussions and consensus building workshops.

The discussion takes place with a selected audience of opinion leaders, clinical trialists, pharmaceutical industry partners, regulators, investigators and cardiologists.

CVCT Forum aims to:

- Familiarize practitioners and young investigators with the science of clinical trials from trial protocol design to trial result interpretation
- Examine the background of knowledge which led to the design of major trials
- Identify and understand best evidence from clinical trials
- Examine the consequences of trial results on the updating of guidelines
- Consider the consequences and relative weight of Evidence based vs Mechanism based and Marketing based medicine
- Identify emerging important issues in cardiovascular medicine
- Examine opportunities and needs for new trials

We do hope that you will share with us the excitement of this unique learning experience and we are very happy to welcome you in Paris.

Pr. Faiez ZANNAD *Dr. Bertram PITT*

SUMMARY

FRIDAY NOVEMBER 30, 2012

PARIS / CET	08:00 am - 10:00 am	COFFEE BREAK	10:20 am - 12:30 am	LUNCHBOXES SERVED	12:45 am - 03:15 pm	COFFEE BREAK	03:30 pm - 05:00 pm	COFFEE BREAK	05:20 pm - 07:30 pm
MODIGLIANI	**WORKSHOP 1** THE THROMBOSIS TRIALISTS WORKSHOP		**WORKSHOP 1** THE THROMBOSIS TRIALISTS WORKSHOP		**LUNCH DEBATE SESSION 1** THE DEVICE THERAPY TRIALISTS WORKSHOP		**WORKSHOP 2** ATHEROSCLEROSIS IMAGING IN CLINICAL TRIALS		**WORKSHOP 2** ATHEROSCLEROSIS IMAGING IN CLINICAL TRIALS
SOUTINE / UTRILLO	**WORKSHOP 3** THE DIABETES TRIALISTS WORKSHOP		**WORKSHOP 3** THE DIABETES TRIALISTS WORKSHOP		**LUNCH DEBATE SESSION 2** NEW EVIDENCE, NEW GUIDELINES & FUTURE DEVELOPMENTS WITH IVABRADINE SATELLITE SYMPOSIUM		**WORKSHOP 4** CARDIOVASCULAR PREVENTION IN CHRONIC KIDNEY DISEASE		**WORKSHOP 4** CARDIOVASCULAR PREVENTION IN CHRONIC KIDNEY DISEASE

SATURDAY DECEMBER 1, 2012

PARIS / CET	08:00 am - 10:00 am	COFFEE BREAK	10:20 am - 12:30 am	LUNCHBOXES SERVED	12:45 am - 03:15 pm	COFFEE BREAk	03:30 pm - 05:00 pm	COFFEE BREAK	05:20 pm - 07:30 pm
MODIGLIANI	**WORKSHOP 5** THE ATHEROSCLEROSIS TRIALISTS FORUM		**WORKSHOP 5** THE ATHEROSCLEROSIS TRIALISTS FORUM		**LUNCH DEBATE SESSION 3** HEART FAILURE TRIALISTS WORKSHOP		**DEBATE SESSION 4** HEART FAILURE REMOTE MONITORING TRIALS		**DEBATE SESSION 5** NOVEL DIURETIC STRATEGIES IN HEART FAILURE
SOUTINE / UTRILLO	**WORKSHOP 6** ESC 2012 CHRONIC HEART FAILURE GUIDELINES		**WORKSHOP 6** ESC 2012 CHRONIC HEART FAILURE GUIDELINES		**LUNCH DEBATE SESSION 6** PERSONALIZED CARDIOVASCULAR MEDICINE AND DRUG DEVELOPMENT		**DEBATE SESSION 7** WHAT IS THE OPTIMAL DESIGN FOR BIOMARKER STUDIES?		**DEBATE SESSION 8** HYPERTENSION TRIALIST WORKSHOP: AUTONOMIC MODULATION THERAPY

FRIDAY NOVEMBER 30, 2012

08.00 am - 12.30 am MODIGLIANI — Workshop 1

THE THROMBOSIS TRIALISTS WORKSHOP
DOSE AND TARGET PATIENT POPULATIONS ISSUES

Chairpersons: Peter CLEMMENSEN, Copenhagen, DEN - George-Andrei DAN, Bucharest, ROM
Webcast: Johanne SILVAIN, Paris, FRA

The development of new antithrombotic agents is a challenging area of cardiovascular medicine.
These agents generally have a narrow therapeutic margin, and it is often difficult to find the optimal balance between efficacy (reduction of ischemic events) and safety (no excess of bleeding events).

- Phase II trials are designed to generate signals of safety and efficacy and to select the dose or doses for phase III pivotal trials. However, phase II data are limited by small numbers of events and short follow-up. Some recent phase III trials have produced results that were unanticipated from the phase II findings.
- Adaptive designs to explore safety (bleeding) risks have been proposed to overcome the current limitations of dose selection for phase III. Several concerns with these designs remain unresolved, such as appropriate methods to control Type I error for both safety and efficacy. Also, adaptive designs will only be useful if they are accepted by the regulatory agencies. The agencies have not announced a final position yet. Implementation of adaptive designs requires early and in-depth interaction between the agencies and study sponsors.
- With the newer anti-thrombotic agents progressively potentially replacing warfarin, we are moving from a target INR guided dosing to an indication/risk guided dosing. Different doses are being developed for different indications. There is an intense discussion on whether doses of anticoagulants should be similar or different for preventing DVT after orthopedic surgery, for treating DVT and pulmonary embolism, for AFib, for prevention after ACS and for prevention in artificial valves. Dose - effect relationships are difficult to establish. A balance should be found between the dose relationship with clinical benefit and the dose relationship with the risk of bleeding. An intense discussion is also ongoing on whether a range of doses rather than one single dose should be made available for the same disease.
- Exploring new indications for the newer anti-thrombotic agents might be one target of interest in patients with heart failure. In patients with coronary artery disease and HF, a majority of deaths (including sudden death) appear to be related to ischemia and worsening of heart failure. The presence of pulmonary embolism as a cause of worsening HF is underestimated and certain underlying pathophysiological mechanisms are common to both arterial and venous thrombi. It has been recognized since long that HF is associated with hypercoagulable state, and, at the cellular level, it has been reported that thrombin exerts multiple actions on cardiomyocytes which can favor the genesis of arrhythmias and myocyte injury. Antithrombotic strategies to reduce the risk of death, myocardial infarction (MI), or stroke have been tested in several randomized trials. These studies were underpowered and the recently published WARCEF trial is inconclusive. With the newest ant-thrombotic agents being probably safer, heart failure might be one of the next diseases where to expand the indications of new anti-thrombotics. Designing an anti-thrombotic trial in HF might also yield meaningful data regarding the potential role of thrombosis in patients with heart failure.

The aim of this session is to explore novel, scientifically rigorous methodologies through an open, cooperative dialogue among investigators, regulators, and sponsors.

Session program:

Dosing issues

- **How to secure the optimal dose(s) for phase III? Can adaptive design help?**
  Speaker: Nancy GELLER, NHLBI, USA
  Discussant: Michael GIBSON, Boston, USA
- **Different doses, different indications? DVT and pulmonary embolism, Atrial fibrillation, ACS, artificial valves**
  Speaker: Freek VERHEUGT, Amsterdam, NED
  Discussant ACS: Maarten SIMOONS, Rotterdam, NED

Industry viewpoint: Scott BERKOWITZ, Bayer, USA - Christophe GAUDIN, Sanofi, FRA - Lloyd HASKEL, J&J, USA - Yasser KHDER, Boehringer Ingelheim, FRA - Joerg KOGLIN, Merck, USA - John LAWRENCE, BMS, USA

Regulatory viewpoint: Angeles ALONSO, EMEA, ESP - Pieter DE GRAEF, EMEA, NED - Kaori SHINAGAWA, PMDA, JAP

New indications: Is heart failure a viable new potential indication for anti-thrombosis therapy
Speaker: Faiez ZANNAD, Nancy, FRA
Discussants: Efthymios DELIARGYRIS, MedCo, USA - Lloyd HASKEL, J&J, USA
Regulatory viewpoint: Krishna PRASAD, MHRA, GBR

Panellists:
ALONSO Angeles, EMEA, ESP - ANDO Yuki, PMDA, JAP - ANKER Stephan, Berlin, GER - BERKOWITZ Scott, Bayer, USA - BEYGUI Farzin, Paris, FRA - CALVO Gonzalo, Barcelona, ESP - CLEMMENSEN Peter, Copenhagen, DEN - CODY Robert, J&J, USA - DAN George-Andrei, Bucharest, ROM - DE FERRARI Gaetano, Pavia, ITA - DE GRAEF Pieter, EMEA, NED - DELIARGYRIS Efthymios, MedCo, USA - GAMRA Habib, Monastir, TUN - GAUDIN Christophe, Sanofi, FRA - GELLER Nancy, NHLBI, USA - GIBSON Michael, Boston, USA - HASKEL Lloyd, J&J, USA - KHDER Yasser, Boehringer Ingelheim, FRA - KOGLIN Joerg, Merck, USA - KUPFER Stuart, Takeda, USA - LAWRENCE John, BMS, USA - LEWIS Basil, Haïfa, ISR - MEHRAN Roxana, New York, USA - PRASAD Krishna, MHRA, GBR - ROSENBERG Yves, NHLBI, USA - SHINAGAWA Kaori, PMDA, JAP - SILVAIN Johanne, Paris, FRA - SIMON Tabassome, Paris, FRA - SIMOONS Maarten, Rotterdam, NED - TAIEL-SARTRAL Magali, Lilly, FRA - VERHEUGT Freek, Amsterdam, NED - WAHL Denis, Nancy, FRA - WASSMANN Sven, Munich, GER - ZANNAD Faiez, Nancy, FRA

08.00 am - 12.30 am SOUTINE / UTRILLO Workshop 3

THE DIABETES TRIALISTS FORUM
DIABETES CLINICAL TRIALS: HELPED OR HINDERED BY THE CURRENT SHIFT IN REGULATORY REQUIREMENTS?

Chairpersons: Marc PFEFFER, Boston, USA - Kausik RAY, London, GBR
Webcast: Daniela DOBRE, Nancy, FRA

Preamble: Glycaemic 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 (glycaemic 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 emphasize 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 as glycaemic control, serum creatinine, micro-albuminuria, or retinopathy are inadequate surrogates. 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 chronic 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.

Trials *(Interventions)*

- ADVANCE - VADT - ACCORD - PROACTIVE - TODAY *(Gliclazide, metformin, acarbose, glimepiride, TZDs (rosiglitazone, pioglitazone)* - FREEDOM
- DPP4 Inhibitors: EXAMINE - TECOS - SAVOR (TIMI-53) - CAROLINA *(Alogliptin, Sitagliptin, Saxagliptin, Linagliptin, Glimepiride)*
- GLP-1 Analogues: REWIND - ELIXA - EXSCEL - LEADER *(Dulaglutide, Lixisenatide, Exenatide, Liraglutide)*
- SGLT2 Inhibitors: BI 10773 - CANVAS *(BI 10773, Canagliflozin)*
- Glitazones/Glitazars: ALECARDIO *(Aleglitazar, PPARα and γ)*
- IFG/IGT/Insulin Resistance: ORIGIN62 - ACE - IRIS - EASIE *(Insulin glargine, Acarbose, Pioglitazone)*

Session program:

- **Target populations: How do we risk-stratify? Are additional biomarkers helpful?**
  Speaker: Wolfgang KOENIG, Ulm, GER
  Discussant: Adrian HERNANDEZ, Durham, USA
- **Globalization of Diabetes trials: Epidemiology of diabetes in the Middle East and Asian countries**
  Speaker: Prem PAIS, Bangalore, IND
  Speaker: Mohamed SOBHY, Alexandria, EGY
- **Study drug and background therapy**
  On top of or vs. Metformin? The issue of background therapy and comparator
  Speaker: Ronan ROUSSEL, Paris, FRA
- **Insulin in type 2 diabetes: bad guy or good guy?**
  Speaker: Michel MARRE, Paris, FRA
- **What else than glucose control? Lipids, BP, Weight, Kidney**
  Speaker: Denise BONDS, NHLBI, USA
- **Non-inferiority, superiority, or both? Operationalizing the FDA guidance**
  Speaker: Marc PFEFFER, Boston, USA
  Discussant: Stuart POCOCK, London, GBR
  Regulatory viewpoint: Kristina DUNDER, EMEA, SWE

Panellists:
BONDS Denise, NHLBI, USA - DREXEL Heinz, Feldkirch, AUS - DUNDER Kristina, EMEA, SWE - GOLDSMITH David, London, GBR - GORDON David, NHLBI, USA - HERNANDEZ Adrian, Durham, USA - KOENIG Wolfgang, Ulm, GER - MARRE Michel, Paris, FRA - PAIS Prem, Bangalore, IND - PFEFFER Marc, Boston, USA - POCOCK Stuart, London, GBR - RAY Kausik, London, GBR - ROUSSEL Ronan, Paris, FRA - SOBHY Mohamed, Alexandria, EGY - SWYNGHEDAUW Bernard, Paris, FRA - TORP-PEDERSEN Christian, Copenhagen, DEN

FRIDAY NOVEMBER 30, 2012

12.45 am - 03.15 pm MODIGLIANI — Lunch Debate Session 1

THE DEVICE THERAPY TRIALISTS WORKSHOP

Chairpersons: Gaetano DE FERRARI, Pavia, ITA - Ileana PIÑA, New York, USA
Webcast: Tariq AHMAD, Durham, USA

Device trial methodology, regulatory and implementation issues

Advances in interventional medical devices are increasingly affecting cardiovascular therapy, just as pharmacological innovation did the generation before. Yet, designing and conducting a device trial is challenging and drug trial designs may not necessarily be applied fully to device trials.

- Although there is increasing recognition that this development process substantially differs from that for drugs, how much device trial methodology may deviate from drug trial methodology is a matter of discussion.
- Regulation works differently for drugs, devices, and procedures, and there are wide international variations. Although progressively moving toward some alignment, currently, in Europe, industry needs only to fulfill the (light) criteria of "CE" mark before approval. General sale of devices may be permitted on the basis of proof of safety, rather than of efficacy or effectiveness. In any case, reimbursement claims may require collecting evidence in outcome cost-effectiveness trials. Regulators and commercial bodies should seek consensus.
- Innovation is led by device industry which is facing the economic challenge of bringing innovation to the market in a very competitive environment. Multi sponsored trials and the cooperation with public funders may be instrumental in improving knowledge production for a better device therapy.
- Interpretation of trial results, and consequently therapy adoption, is another challenge. The strength of evidence is not necessarily the main driver for adoption. Coronary angioplasty in stable CAD is widely adopted while, despite evidence for a beneficial effect of device therapy in heart failure, only a minority of eligible patients is currently offered these options.
- Beyond trials aimed at evaluating safety, effectiveness and approval, trials that establish the value of a therapy and hence support utilization in clinical practice are most needed.

The aim of this session is to contribute to identifying and promoting innovative, cooperative and practical solutions that may help filling the gaps between device and drug trials, between CE mark and FDA regulations and between generating evidence and practical implementations.

Session program:

How much one could deviate from "randomized - controlled" trials?

- **Non randomized and/or non-blinded trials: When can they be trusted, what can help them to be "acceptable"?**
  Speaker: Stuart POCOCK, London, GBR
- **Options of and alternatives to the "control group" in device trials**
  Speaker: William T. ABRAHAM, Columbus, USA
- **Industry perspective**
  Speakers: Rob KIEVAL, CVRx, USA - Holger WOEHRLE, ResMed, GER

Approvability issues: Pathway to a more global device approval process
Speaker: Ileana PIÑA, New York, USA

Post approval and registry studies. Advantages and limitations in complementing trial evidence base and improving therapy adoption
Speaker: Ileana PIÑA, New York, USA
Discussant: Roxana MEHRAN, New York, USA

Comparative effectiveness studies. How they may help decision makers and support utilization in clinical practice?
Speaker: Rita REDBERG, San Francisco, USA
Discussant: Kenneth STEIN, Boston Scientific, USA

Panellists:
ABRAHAM William T., Columbus, USA - ANKER Stephan, Berlin, GER - CARLSON Mark, St Jude Medical, USA - DE FERRARI Gaetano, Pavia, ITA - FARB Andrew, FDA, USA - GELLER Nancy, NHLBI, USA - JARCHO John, Boston, USA - KIEVAL Rob, CVRx, USA - LINDE Cecilia, Stockholm, SWE - MASCETTE Alice, NHLBI, USA - MEHRAN Roxana, New York, USA - PIÑA Ileana, New York, USA - POCOCK Stuart, London, GBR - REDBERG Rita, San Francisco, USA - STEIN Kenneth, Boston Scientific, USA - VINCENT Alphons, Medtronic, CHE - YADAV Jay, CardioMEMS, USA - WOEHRLE Holger, ResMed, GER

12.45 am - 03.15 pm SOUTINE / UTRILLO — Lunch Debate Session 2

SATELLITE SYMPOSIUM

NEW EVIDENCE, NEW GUIDELINES AND FUTURE DEVELOPMENTS WITH IVABRADINE

Chairpersons: Jean-Claude TARDIF, Montréal, CAN - Faiez ZANNAD, Nancy, FRA

Webcast: Nicolas GIRERD, Nancy, FRA

- The new set of guidelines of the ESC Heart Failure Association and of other major international societies has recently been published. They have integrated the newest evidence with the main pharmacological innovation Ivabradine.
- Beyond the main results of the BEAUTIfUL and SHIfT trials, a number of pre-specified analyses have yielded results that will help optimizing the implementation of the use of this new agent in ischemic heart diseases as well as in heart failure with LV systolic dysfunction.
- Ivabradine is a specific inhibitor of the If current in the sinoatrial node providing a pure HR reduction without modification of other cardiovascular parameters. Treatment with ivabradine therefore provides an opportunity to assess the effects of lowering HR without directly altering other aspects of cardiac function. Beta-blockers and digoxin are other heart rate slowing agents, but with additional pharmacological effects, some of which are beneficial and others are deleterious, thus limiting the safety and adherence to these agents.
- It is likely that the newest heart failure guidelines will extend the recommendation of using mineralocorticoid receptor antagonists (MRAs) to Class I, level of evidence A. While, ivabradine benefits were observed in SHIfT on top of beta-blockers, of digoxin and also of MRAs, the question of the right timing of initiating ivabradine, relative to the optimization of beta-blocker and digoxin therapy and the timing of initiating an MRA is to be debated.
- BEAUTIfUL and SHIfT have also led to a series of stimulating hypotheses that constitute the rationale for the currently SIGNIfY trial, which is enrolling patients with coronary artery disease and normal left ventricular systolic function with a resting HR of ≥70 bpm. The primary endpoint will take into consideration only coronary artery disease outcomes.
- Is heart failure with preserved ejection fraction the next frontier?

Session program:

CLARIfYing the CAD patient in our practice
Speaker: Jean-Claude TARDIF, Montréal, CAN

SHIfTing evidence in heart failure management
Speaker: Jeffrey BORER, New York, USA

Save life and save cost with ivabradine
Speaker: Martin COWIE, London, GBR

Debate: When to initiate ivabradine therapy in clinical practice?

Panellists:
BORER Jeffrey, New York, USA - COHEN-SOLAL Alain, Paris, FRA - COWIE Martin, London, GBR - DAN George-Andrei, Bucharest, ROM - GHEORGHIADE Mihai, Chicago, USA - MAGGIONI Aldo, Florence, ITA - METRA Marco, Brescia, ITA - ROSANO Giuseppe, EMEA, ITA - TARDIF Jean-Claude, Montréal, CAN - TAVAZZI Luigi, Cotignola, ITA - TSOUDEROS Yannis, Servier, FRA - ZANNAD Faiez, Nancy, FRA

FRIDAY NOVEMBER 30, 2012

03.30 pm - 07.30 pm MODIGLIANI Workshop 2

ATHEROSCLEROSIS IMAGING IN CLINICAL TRIALS FACILITATING THE DISCOVERY OF EFFECTIVE THERAPIES

Chairpersons: Jagat NARULA, New York, USA - Ahmed TAWAKOL, Boston, USA
Webcast: Bart STAELS, Lille, FRA

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).

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 the rapid development and implementation of these imaging approaches, it is important to delineate the opportunities and limitations associated with these tools. In particular, it is essential to identify imaging biomarkers that might accurately predict eventual clinical success based on the observed changes in the atherosclerotic imaging measurements. With such 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.

Session program:

Overview: Why are imaging endpoints needed in CV clinical trials
Speaker: Jagat NARULA, New York, USA

Well Established Methods for Imaging Approaches: IVUS and IMT
Speaker: Jean-Claude TARDIF, Montréal, CAN
Discussant: Wolfgang KOENIG, Ulm, GER

Coronary CTA in clinical trials
Speaker: Udo HOFFMANN, Boston, USA

MRI imaging in clinical trials
Speaker: Zahi FAYAD, New York, USA
Discussant: Robin CHOUDHURY, Oxford, GBR

PET-CT imaging in clinical trials
Speaker: Ahmed TAWAKOL, Boston, USA
Discussant: James RUDD, Cambridge, GBR

Panellists:
AGEWALL Stefan, Oslo, NOR - BONDS Denise, NHLBI, USA - CHOUDHURY Robin, Oxford, GBR - FAYAD Zahi, New York, USA - GAMRA Habib, Monastir, TUN - GAUDIN Christophe, Sanofi, FRA - HOFFMANN Udo, Boston, USA - KOENIG Wolfgang, Ulm, GER - MENDELSOHN Michael, Merck, USA - NARULA Jagat, New York, USA - REDBERG Rita, San Francisco, USA - ROSANO Giuseppe, EMEA, ITA - ROSENBERG Yves, NHLBI, USA - RUDD James, Cambridge, GBR - SCOTT Robert, Amgen, USA - STAELS Bart, Lille, FRA - TARDIF Jean-Claude, Montréal, CAN - TAWAKOL Ahmed, Boston, USA - WASSERMAN Scott, Amgen, USA

03.30 pm - 07.30 pm SOUTINE / UTRILLO — Workshop 4

CARDIOVASCULAR PREVENTION IN CHRONIC KIDNEY DISEASE
NEW THERAPEUTIC OPTIONS AND FUTURE OPPORTUNITIES

Chairpersons: David GOLDSMITH, London, GBR - Luis RUILOPE, Madrid, ESP
Webcast: Nicolas GIRERD, Nancy, FRA

- Cardiovascular events are 10 to 20 fold higher in CKD patients. Heart failure is the main cardiovascular complication that occurs in renal patients. Nearly all CV prevention and heart failure trials excluded patients with moderate to severe CKD. Therefore, the general approach and recommendations for CV prevention in the general population may not be equally effective and completely safe in renal patients.
- Renal failure is associated with increased vascular inflammation and oxidative stress linked to development of cardiovascular disease. Nrf-2 (NF-E2-related factor 2) is a regulator of anti-oxidant, anti-inflammatory and detoxification pathways. Intervention trials of the synthetic nrf2/nfκb modulator, bardoloxone methyl, in patients with advanced kidney disease associated with type 2 diabetes, demonstrated improvement of renal function (BEAM trial), suggesting that such agents may have therapeutic benefit in chronic renal failure.
- The ongoing BEACON trial assesses the efficacy of bardoxolone methyl relative to placebo in delaying progression to end-stage renal disease and cardiovascular deaths in patients with Stage 4 CKD and type 2 diabetes.
- More specifically in chronic hemodialysis patients, results from the very few clinical trials undertaken thus far, including trials on lipid reduction, normalization of hematocrit, and increased dialysis dosage, have been unsuccessful.
- New CV prevention opportunities are being investigated in specific trials in CKD and hemodialysis patients.

The aim of this workshop is to discuss innovative designs and execution plans of CV prevention trials in CKD as well as the interpretation and implementation of the results of such trials and the approvability - regitrsbaility of potentially new CV prevention in CKD indications.

Standard of care and novel opportunities for CV prevention and the treatment of heart failure in patients with moderate to severe CKD?
Speaker: Hermann HALLER, Hannover, GER

Lipid lowering agents. Now, we have an option! (SHARP, 4D, AURORA)
Speaker: Colin BAIGENT, Oxford, GBR

Erythropoiesis stimulating agents and iron treatment optimization in CKD patients (CREATE, CHOIR, TREAT)
Speaker: Marc PFEFFER, Boston, USA

EVOLVE: A major cardiovascular outcomes trial in hemodialysis patients
Speakers: Chris MIX, Amgen, USA - David WHEELER, London, GBR
Discussant: Ziad MASSY, Boulogne-Billancourt, FRA

Antioxidant inflammation modulation with bardoxolone? (BEACON)
Speaker: David WARNOCK, Birmingham, USA

RAAS inhibitors and Mineralocorticoid receptor antagonists (FOSIDIAL, ALCHEMIST)
Speaker: Patrick ROSSIGNOL, Nancy, FRA

Heart failure and other CV endpoints in CKD trials. Definition and adjudication issues.
Speaker: Stefan ANKER, Berlin, GER

Interpretation and approvability issues
Industry viewpoint: Paul AUDHYA, Reata, USA
Regulatory viewpoint: Pieter DE GRAEF, EMEA, NED

Panellists:
ANKER Stefan, Berlin, GER - AUDHYA Paul, Reata, USA - BAIGENT Colin, Oxford, GBR - BUYSSE Jerry, Relypsa, USA - CALVO Gonzalo, Barcelona, ESP - DE FERRARI Gaetano, Pavia, ITA - DE GRAEF Pieter, EMEA, NED - GOLDSMITH David, London, GBR - GORDON David, NHLBI, USA - HALLER Hermann, Hannover, GER - KJELDSEN Keld, Copenhagen, DEN - MASSY Ziad, Boulogne-Billancourt, FRA - MIX Chris, Amgen, USA - PFEFFER Marc, Boston, USA - ROSANO Giuseppe, EMEA, ITA - ROSSIGNOL Patrick, Nancy, FRA - RUILOPE Luis, Madrid, ESP - WACHTER Rolf, Göttingen, GER - WARNOCK David, Birmingham, USA - WHEELER David, London, GBR

SATURDAY DECEMBER 1st, 2012

08.00 am - 12.30 am MODIGLIANI — Workshop 5

THE ATHEROSCLEROSIS TRIALISTS FORUM

Chairpersons: Wolfgang KOENIG, Ulm, GER - Anthony WIERZBICKI, London, GBR
Webcast: Tabassome SIMON, Paris, FRA

Will new compounds be able to reduce the residual risk in high risk patients when treatment targets based on new ESC guidelines have been achieved (e.g. LDL-C < 70mg/dl)?

Despite widespread early intervention in acute coronary syndromes and complete revascularization of stenotic lesions complemented by aggressive polypharmacotherapy, 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 clinical research programme is delivering an important number of new potential therapeutic targets that may be ready for trial testing.
  - Can OMICS technology help us out here in terms of new specific biomarkers taking advantage of the proteome, metabolome or the transcriptome?
  - What is the relevance of Mendelian Randomisation studies to investigate the potential causal role of biomarkers in the pathophysiology of disease and to identify and select new drug biotargets.
- One major question relates to the value of biomarker-guided and/or risk guided therapy and how to design appropriate trials to test these therapeutic strategies. Should therapy be targeted to patients with specific biomarkers profiles? e.g. low HDL, high inflammatory burden (elevated CRP), high Lp-PLA2 activity etc.?
- 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 randomised controlled clinical trials looking for important cardiovascular endpoints. In all of these trials the standard of care is much better than seen in the real world situation. Thus, the question arises, whether these additional compounds will lead to a clinically significant reduction in cardiovascular events on top of optimal standard care.

Trials *(Interventions)*

- CETP inhibitors: dalcetrapib, anacetrapib, evacetrapib (DAL-Outcomes I, DAL-Outcomes II, DEFINE, REVEAL, evacetrapib, ApoA1 mimetics, ApoA1 Milano, AIM-HIGH, HPS-Thrive)
- Directly augmenting apo A-I: Intravenous apo A-I therapy, Recombinant apo A-I Milano/phospholipids (ETC-216), Purified native apo A-I/phospholipids (CSL-111/112)
- Oral upregulators of endogenous apo A-I production RVX-208: ASSURE, SUSTAIN
- Phospholipase inhibitors: VISTA-16, SOLID, STABILITY
- Anti-inflammatory therapy: CANTOS (IL-1β antibody), CIRT (MTX), Anakinra (IL1 RA), IL-6 RA (Taxilicumab)
- New LDL-lowering compounds: PCSK9 inhibitors, apoB antisense, ISIS

Session program:

Will we be able to answer the question of HDL as a therapeutic target after the CETP inhibitor trials?
Speaker: Eric STROES, Amsterdam, NED
Discussant: Robert ROSENSON, New York, USA

Identifying new targets: The value of omics and mendelian randomization studies
Speaker: Juan Pablo CASAS, London, GBR

Identifying new targets: Monoclonal Antibody Inhibitor of PCSK9
Speakers: Wolfgang KOENIG, Ulm, GER - Robert SCOTT, Amgen, USA

Panellists:
AGEWALL Stefan, Oslo, NOR - BONDS Denise, NHLBI, USA - CASAS Juan Pablo, London, GBR - CHOUDHURY Robin, Oxford, GBR - DAN George-Andrei, Bucharest, ROM - DREXEL Heinz, Feldkirch, AUS - FAYAD Zahi, New York, USA - GAUDIN Christophe, Sanofi, FRA - GORDON David, NHLBI, USA - HOFFMANN Udo, Boston, USA - KOENIG Wolfgang, Ulm, GER - MENDELSOHN Michael, Merck, USA - POCOCK Stuart, London, GBR - RAY Kausik, London, GBR - REDBERG Rita, San Francisco, USA - ROSENBERG Yves, NHLBI, USA - ROSENSON Robert, New York, USA - RUDD James, Cambridge, GBR - SCOTT Robert, Amgen, USA - SIMON Tabassome, Paris, FRA - STAELS Bart, Lille, FRA - STROES Eric, Amsterdam, NED - TARDIF Jean-Claude, Montréal, CAN - TAWAKOL Ahmed, Boston, USA - TORP-PEDERSEN Christian, Copenhagen, DEN - WASSERMAN Scott, Amgen, USA - WIERZBICKI Anthony, London, GBR

MULTIDISCIPLINARY EXPERT WORKSHOP: ACHIEVEMENTS, CHALLENGES AND BARRIERS TO IMPLEMENTATIONS OF THE ESC 2012 CHRONIC HEART FAILURE GUIDELINES

Chairpersons: Alain COHEN-SOLAL, Paris, FRA - Adrian VOORS, Groningen, NED
Webcast: Nicolas GIRERD, Nancy, FRA

Background: The ESC-HFA chronic and acute heart failure guidelines have recently been published. However, the challenge for guidelines does not cease with a consensus document. Practical implementation is the critical step in establishing higher standards of care for individual patients. Improved guideline uptake is not only an index of better standards but a validation of the process of guideline production.

Improving consensus between guidelines is also important, differences in recommendations may act as a barrier to guideline. The NICE CHF guidance was updated in 2010, and it is not likely to be revised in short term.

Practice differs from the guideline recommendations. Registries suggest differences in guideline interpretation and treatment/management of CHF between different stakeholders. Similarities and differences exist between GPs and hospital physicians' approaches to management of CHF.

One important issue that is not covered by the current guidelines is the class effect issue. Canadian and Australian CHF guideline and 2010 NICE guideline name eplerenone as preferred drug in heart failure, ESC mentions only mineralocorticoid receptor antagonists (MRAs.) as a class.

How to interpret compound vs. class effects while following guideline recommendations is an important issue.

Cost-effectiveness is a key not only to the content of guidelines but also in the assessment of implementation. Limits on healthcare resources mandate that resource-allocation decisions be guided by considerations of cost in relation to expected benefits. In cost-effectiveness analysis, the ratio of net healthcare costs to net health benefits provides an index by which priorities may be set.

Aims: This multidisciplinary consensus workshop aims at discussing CHF guideline implementation issues and the consequences on defining the place of MRA/eplerenone in management of CHF.

Session program:

Impact of major clinical trials on ESC Chronic Heart Failure 2012 guidelines. Game changer trials: EMPHASIS-HF, SHIFT, Devices…
Speaker: Faiez ZANNAD, Nancy, FR
Discussant: John CLELAND, Hull, GBR

Expected implications on heart failure epidemiology
Speaker: Justin EZEKOWITZ, Edmonton, CAN

National guideline implementation and national registries

- **NICE**
  Speaker: Suzanna HARDMAN, London, GBR
- **German CHF registry: REFLECT –HF**
  Speaker: Carsten TSCHOEPE, Berlin, GER
- **Eurobservational, the ESC Heart failure Registry**
  Speaker: Aldo MAGGIONI, Florence, ITA

Compound *vs.* class effect. Drug class recommendations in guidelines

- **ESC-HFA guidelines**
  Speaker: Luigi TAVAZZI, Cotignola, ITA
- **Canadian, Australian CHF guideline and 2010 NICE guideline**
  Speaker: Justin EZEKOWITZ, Edmonton, CAN

Is it always safe to believe in class effect: Spironolactone vs. eplerenone differences and clinical relevance?
Speaker: Bertram PITT, Ann Arbor, USA

EMPHASIS-HF Cost effectiveness Model and Guideline implementation from the payer's perspectives
Speaker: Ron AKEHURST, Sheffield, GBR

Panellists:
AKEHURST Ron, Sheffield, GBR - ANKER Stephan, Berlin, GER - AZIZI Michel, Paris, FRA - BRUTSAERT Dirk L, Antwerp, BEL - BUYSSE Jerry, Relypsa, USA - CLELAND John, Hull, GBR - CODY Robert, J&J, USA - COHEN-SOLAL Alain, Paris, FRA - EZEKOWITZ Justin, Edmonton, CAN - FIUZAT Mona, Durham, USA - HARDMAN Suzanna, London, GBR - KJELDSEN Keld, Copenhagen, DEN - MAGGIONI Aldo, Florence, ITA - METRA Marco, Brescia, ITA - PFEFFER Marc, Boston, USA - PIÑA Ileana, New York, USA - PITT Bertram, Ann Arbor, USA - ROSANO Giuseppe, EMEA, ITA - SWYNGHEDAUW Bernard, Paris, FRA - TAVAZZI Luigi, Cotignola, ITA - TSCHOEPE Carsten, Berlin, GER - VOORS Adrian, Groningen, NED - WACHTER Rolf, Göttingen, GER - ZANNAD Faiez, Nancy, FRA

SATURDAY DECEMBER 1st, 2012

12.45 am - 03.15 pm MODIGLIANI — Lunch Debate Session 3

HEART FAILURE TRIALISTS WORKSHOP
LEARNING FROM RECENT TRIALS AND SHAPING THE FUTURE OF HEART FAILURE TRIALS

Chairpersons: Alexandre MEBAZAA, Paris, FRA - Christopher O'CONNOR, Durham, USA
Webcast: Daniela DOBRE, Nancy, FRA

Decreasing the very high mortality and rate of re-hospitalization associated with acute worsening HF is one of the most important unmet needs in cardiovascular medicine. Despite positive signals in Phase II studies, no drug has proven to reduce the appallingly high mortality or readmission rates. The reasons for these 'failed' trials are multiple, including the adequacy of candidate drugs, dosing, patient selection and disease characterization, and trial conduct. The phenotypes and pathophysiology of the syndrome are poorly understood. The syndrome is heterogeneous and the taxonomy is complex and remains without a consensus. Hospitalization for acute worsening HF is understood by some as the result of progressive worsening of chronic HF and by others as an entity which acuteness has been compared to what is acute coronary syndrome to chronic coronary artery disease. Some believe that hospitalizations for HF do not represent a distinct pathophysiology than chronic HF and could be better managed by the optimization of chronic HF neurohumoral therapy. On the other hand although there are no data to support that short-term in-patient therapeutic approach improves post-discharge clinical outcomes, some speculate that protecting the injured heart during the acute process might have long term benefit. Alleviating dyspnea is still considered by regulatory agents as an endpoint valid in itself, as far as there is no excess of deaths. However most patients improve with standard therapy and the magnitude of additional dyspnea relief by the investigational drug might be marginal and therefore hardly statistically detectable. Alternative ways to test for and/or quantify dyspnea have been investigated with the aim to define a dyspnea measure that is more sensitive to change.

RELAX-HF and ASTRONAUT are two trials whose results have just been announced. Both exemplify the issues highlighted here above. RELAX-HF is a phase II/III trial design trial of 48 hour IV infusion of relaxin for the treatment of signs and symptoms in patients hospitalized for acute decompensated HF (no EF criteria). ASTRONAUT evaluates the 6 months efficacy and safety of aliskiren therapy on top of standard therapy, on morbidity and mortality when initiated early after hospitalization for acute decompensated HF and low EF. Results of PRONTO are now available. PRONTO is a randomized trial comparing the potent and rapid acting calcium channel blocker Clevidipine vs. SOC for the ability to rapidly control blood pressure and provide dyspnea relief in acute heart failure patients. PRONTO examplifies yet another trial model: intervening within the first 2 hours after admission. Lessons learnt from RELAX-HF and PRONTO within the context of other recent trials in acute heart failure will be the main topic of brainstorming at this workshop, examining the potential change in paradigm in this area.

The aim of this workshop is to learn from the PRONTO, RELAX-HF and ASTRONAUT experiences within the context of the other acute HF trials, understand the consequences of the results on the design of future trials, revision of regulatory guidlenes and on possible regulatory labeling on clinical practice.

The various drug intervention options

RELAX-HF, Omecamtiv mecarbil and other drug still on trial
Speaker: Michael FELKER, Durham, USA

ASTRONAUT
Speaker: Aldo MAGGIONI, Florence, ITA

Execution issues. Where best to screen and enroll patients? Overcoming variations in health care systems and globalization issues
Speaker: Mihai GHEORGHIADE, Chicago, USA

PRONTO: The merit and consequences of a very early intervention with an arterial vasodilator
Speaker: Frank PEACOCK, Cleveland, USA

Endpoint related issues. The value of dyspnea as an endpoint in acute HF, upon admission trials
Speaker: Alexandre MEBAZAA, Paris, FRA

The value of repeat events in post discharge hospitalized HF trials
Speaker: Stuart POCOCK, London, GBR

Regulatory viewpoint: Yuki ANDO, PMDA, JAP - Robert HEMMINGS, MHRA, GBR

Panellists:
ANDO Yuki, PMDA, JAP - ANKER Stephan, Berlin, GER - BAKRIS George, Chicago, USA - BRUTSAERT Dirk L, Antwerp, BEL - BUYSSE Jerry, Relypsa, USA - CLELAND John, Hull, GBR - CODY Robert, J&J, USA - COHEN-SOLAL Alain, Paris, FRA - DUNDER Kristina, EMEA, SWE - DUNLAP Stephanie, Chicago, USA - FELKER Michael, Durham, USA - FIUZAT Mona, Durham, USA - GHEORGHIADE Mihai, Chicago, USA - GORDON David, NHLBI, USA - HEMMINGS Robert, MHRA, GBR - KIM Jae, Amgen, USA - MAGGIONI Aldo, Florence, ITA - MARTINEZ Felipe, Cordoba, ARG - MEBAZAA Alexandre, Paris, FRA - METRA Marco, Brescia, ITA - O'CONNOR Christopher, Durham, USA - PEACOCK Frank, Cleveland, USA - PFEFFER Marc, Boston, USA - PIÑA Ileana, New York, USA - POCOCK Stuart, London, GBR - ROESSIG Lothar, Bayer, GER - ROSANO Giuseppe, EMEA, ITA - SHINAGAWA Kaori, PMDA, JAP - SWYNGHEDAUW Bernard, Paris, FRA - VOORS Adrian, Groningen NED - ZANNAD Faiez, Nancy, FRA

SATURDAY DECEMBER 1st, 2012

12.45 am - 03.15 pm SOUTINE / UTRILLO — Lunch Debate Session 6

ESC Working group on cardiovascular pharmacology and drug therapy
International Society of Cardiovascular Pharmacotherapy (ISCP)
CardioVascular Clinical Trialists (CVCT)
Joint session

PERSONALIZED CARDIOVASCULAR MEDICINE AND DRUG DEVELOPMENT: TIME FOR A NEW TRIAL PARADIGM

Chairpersons: Juan Carlos KASKI, London, GBR - Bertram PITT, Ann Arbor, USA - Luis RUILOPE, Madrid, ESP

Webcast: Patrick ROSSIGNOL, Nancy, FRA

- *"Drugs, in general, act not on single targets operating in a vacuum, but perturb a complex network of interacting proteins or metabolites to modify the dynamic output of a system that can extend well beyond the pathway in which the original target is operative. Therefore, to develop drugs in this century, one needs to move beyond the reductionist biomedical science of Occam, Descartes, Osler, and Ehrlich, and consider the complex biological system within which a drug acts holistically, in its tractable entirety. One needs to apply the principles of systems biology to pharmacology, and thereby establish the new discipline of systems pharmacology."*
  Dr Joseph Loscalzo, Lewis A. Conner Lecture, Circulation 2012.
- *"We need to develop a robust, viable business model through which the pharmaceutical industry can move from drug development strategies that are population-based to strategies that focus on increasingly individualized therapies. There needs to be an alignment of incentives that move the industry from conventional blockbuster drugs developed in large populations with single drug targets within which one size fits all toward smaller, better defined systems pharmacology-based molecular pathophenotypes that benefit from these well conceived therapies with minimal risk."*
  Dr Joseph Loscalzo, Lewis A. Conner Lecture, Circulation 2012.
- *"Heart Failure is not a disease and we should no longer approve drugs for a heterogeneous broad population, but for a well defined sub-population where we can demonstrate a marked benefit"*
  Dr. Stephen Grant, Deputy Director, Division of Cardiovascular Renal Products, CDER
- *"Regulatory bodies like the FDA and the EMA will most likely require new trials to scrutinize events (i.e. AMI) very strictly. Well conducted registries will be important in this context so clinicians can report their findings in real life patients. Academic institutions and independent pharmacological and pharmacotherapy associations such as ISCP should provide mechanistic data as to the possible reasons for the detected increased prevalence of MI in some patient groups receiving treatment with direct thrombin inhibitors. Lessons learned with other new pharmacological agents in the past will necessarily require that the medical and pharmacological communities together with industry and regulatory agencies take up the challenge and work synergistically and in synchrony to clarify the side effects and excess MI risk – albeit minimal according to current studies - associated with the newer anticoagulants.*
  We are all now at the start of a long and winding road that should hopefully take us to better understand the mechanism of action, the therapeutic efficacy and the adverse effects associated with the use of the new anticoagulants. Together we should prevent unnecessary complications that might derive from the use of these important agents in the wrong patient groups."
  Juan Carlos Kaski, Cardiovasc Drugs Ther, 2012

Omics research and system biology. Keys for future personalized medicine

How future trials may help optimizing benefit-to-risk ratio. The role of specialist scientific organizations.

ISCP:
Speaker: Felipe MARTINEZ, Cordoba, ARG

CVCT:
Speaker: Faiez ZANNAD, Nancy, FRA

ESC Working group in Pharmacology and Drug Therapy
Speaker: Christian TORP-PEDERSEN, Copenhagen, DEN

The role of biomarkers
Speaker: Stefan BLANKENBERG, Hamburg, GER

Industry viewpoints
Speaker: Michael MENDELSOHN, Merck, USA

Journal editor's viewpoints
Speaker: Joseph LOSCALZO, Boston, USA, *Circulation*
Discussant: Rita REDBERG, San Francisco, USA, *Arch Intern Med*

Regulatory Viewpoints
Speaker: Gonzalo CALVO, Barcelona, ESP

Panellists:
ADAMS Kirkwood, Chapel Hill, USA - ADOURIAN Aram, BG Medicine, USA - BLANKENBERG Stefan, Hamburg, GER - CALVO Gonzalo, Barcelona, ESP - CLEMMENSEN Peter, Copenhagen, DEN - COOK Nakela, NHLBI, USA - GELLER Nancy, NHLBI, USA - GOLDSMITH David, London, GBR – HOUDIJK Wim, Biomérieux, FRA - JANUZZI Jim, Boston, USA - JARCHO John, Boston, USA - KASKI Juan Carlos, London, GBR - LOSCALZO Joseph, Boston, USA - MARTINEZ Felipe, Cordoba, ARG - MENDELSOHN Michael, Merck, USA - PITT Bertram, Ann Arbor, USA - REDBERG Rita, San Francisco, USA - ROSENBERG Yves, NHLBI, USA - RUILOPE Luis, Madrid, ESP - SNIDER James, Critical Diagnostics, USA - TORP-PEDERSEN Christian, Copenhagen, DEN

SATURDAY DECEMBER 1st, 2012

03.30 pm - 05.00 pm MODIGLIANI — Debate Session 4

HEART FAILURE REMOTE MONITORING TRIALS

Chairpersons: Stefan ANKER, Berlin, GER - Ileana PIÑA, New York, USA
Webcast: Daniela DOBRE, Nancy, FRA

Case studies and ultimate methodology for future trials

Remote monitoring remains an appealing option for following patients after a heart-failure hospitalization. Trials employing common strategies (simple phone calls with a nurse and Telemonitoring of vital signs) have in general not demonstrated improvement in survival and or reduction in risk of readmission; meta-analysis of telemonitoring trials using these common strategies, however, have shown improvements in survival and hospitalization rates. Recently, trials of more complex implanted remote monitoring devices that provide physiologic information have reported mixed results.

The 2 most recently published device remote monitoring trials are excellent case-studies that may serve for methodologically refining future trials:

- The CHAMPION trial was the first trial of a technology based (pulmonary artery pressure) telemonitoring (CardioMEMS), published in a major scientific journal (The Lancet) without standing positive results. The FDA advisory panel found the device to be safe (9-1 vote) but did not vote in favor of efficacy (4-6 vote) because of inability to distinguish the effect of the device from the support provided by the Sponsor to the investigators during the trial. The panel and the FDA were also concerned that this level of Sponsor support may not be practical in the commercial setting. The PIs and the Sponsor, however, pointed out that the device provides information only and to adequately test the trial hypothesis (management of pulmonary artery pressure in addition to routine HF care would reduce HF hospitalizations), there had to be a protocol compliance mechanism to ensure that physicians reviewed and responded to pulmonary artery pressures per the protocol mandated guidelines. This trial poses interesting methodological questions regarding the evaluation of diagnostic devices; how do we design trials with therapeutic endpoints for purely diagnostic devices?
- The DOT-HF trial reported that Telemonitoring based on thoracic impedance was unexpectedly associated with more frequent hospital admissions in the Telemonitoring group. Then the question arises whether this trial failed because the technology - i.e. impedance - failed to deliver the right alerts at the right time or whether the strategy of care using the technology (beep alerts to the patient, no decision support to the health care providers who managed patients according to a standardized intervention algorithm, on the basis of the available data and the clinical evaluation) was inadequate/ insufficient.

The aim of this workshop is by analyzing lessons from these 2 case-studies, to hopefully reach agreement on the ultimate methodology of future trials of remote monitoring.

Session program:

How to minimize bias? Trial design, control group, blinding and other methodological issues
Speaker: Stefan ANKER, Berlin, GER

Treatment optimization: Letting investigators decide vs. applying protocol defined algorithms (predefined, monitored, decision support systems)
Speaker: William T. ABRAHAM, Columbus, USA

What endpoint for securing approval (FDA, and in EU, beyond CE mark) and reimbursement
Debate led by regulatory agencies: Andrew FARB, FDA, USA - Ileana PIÑA, New York, USA

Panellists:
ABRAHAM William T., Columbus, USA - ANKER Stefan, Berlin, GER - BORER Jeffrey, New York, USA - BRUTSAERT Dirk L, Antwerp, BEL - CODY Robert, J&J, USA - DE FERRARI Gaetano, Pavia, ITA - FARB Andrew, FDA, USA - LINDE Cecilia, Stockholm, SWE - MEHRAN Roxana, New York, USA - SHIPMAN Tami, St Jude Medical, USA - STEIN Kenneth, Boston Scientific, USA - SWYNGHEDAUW Bernard, Paris, FRA - VINCENT Alphons, Medtronic, CHE - YADAV Jay, CardioMEMS, USA

03.30 pm - 05.00 pm SOUTINE / UTRILLO — Debate Session 7

WHAT IS THE OPTIMAL DESIGN FOR BIOMARKER STUDIES?

Chairpersons: Jim JANUZZI, Boston, USA - Faiez ZANNAD, Nancy, FRA
Webcast: Alain COHEN-SOLAL, Paris, FRA

How should diagnostic/prognostic markers be studied?
Speaker: Jim JANUZZI, Boston, USA
Discussant: James SNIDER, Critical Diagnostics, USA

Best statistical methods for evaluating the merits of a novel marker
Speaker: Stefan BLANKENBERG, Hamburg, GER
Discussant: Nancy GELLER, Bethesda, USA

Biomarker guided-therapy: Are there other endpoints besides mortality that matter? Selecting the best outcome measures
Speaker: Michael FELKER, Durham, USA

Targeting biomarker defined mechanistic phenotypes. Challenges and opportunities of a new paradigm
Speaker: Faiez ZANNAD, Nancy, FRA
Discussant: Kirkwood ADAMS, Chapel Hill, USA

Debate led by Journal Editors: There are too many studies and the quality is variable.
Should there be a position statement establishing rules for biomarker studies?
John JARCHO, Boston, USA, *NEJM*
Rita REDBERG, San Francisco, USA, *Arch Intern Med*
Joseph LOSCALZO, Boston, USA, *Circulation*
Jagat NARULA, New York, USA, *JACC imaging*
Mona FIUZAT, Durham, USA, *JACC-HF*
John CLELAND, Hull, GBR, *Former Eur J Heart Failure*

Panellists:
ADAMS Kirkwood, Chapel Hill, USA - BLANKENBERG Stefan, Hamburg, GER - CLELAND John, Hull, GBR - COHEN-SOLAL Alain, Paris, FRA - COOK Nakela, NHLBI, USA - DUNLAP Stephanie, Chicago, USA - FELKER Michael, Durham, USA - FIUZAT Mona, Durham, USA - GELLER Nancy, NHLBI, USA - HOUDIJK Wim, Biomérieux, FRA - JANUZZI Jim, Boston, USA - JARCHO John, Boston, USA - KIM Jae, Amgen, USA - LASALVIA Luis, Siemens, USA - LOSCALZO Joseph, Boston, USA - MASCETTE Alice, NHLBI, USA - MEBAZAA Alexandre, Paris, FRA - NARULA Jagat, New York, USA - O'CONNOR Christopher, Durham, USA - PATHAK Atul, Toulouse, FRA - POCOCK Stuart, London, GBR - REDBERG Rita, San Francisco, USA - SEMJONOW Véronique, Philips, NED - SNIDER James, Critical Diagnostics, USA - VOORS Adrian, Groningen, NED - ZANNAD Faiez, Nancy, FRA

SATURDAY DECEMBER 1st, 2012

05.20 pm - 07.30 pm MODIGLIANI — Debate Session 5

NOVEL DIURETIC STRATEGIES IN HEART FAILURE

Chairpersons: Keld KJELDSEN, Copenhagen, DEN - Gian Paolo ROSSI, Padua, ITA
Webcast: Patrick ROSSIGNOL, Nancy, FRA

- Clinical congestion due to volume overload is the main cause of hospitalization for patients with HF and is an important therapeutic target. Failure to achieve effective and rapid correction of this condition in many patients hospitalized for HF results in prolongation of hospital stay and unfavorable after-discharge outcome.
- Loop diuretics, though often effective for treating congestion, have significant limitations. Discovering ways to optimize exposure to loop diuretics, achieving effective decongestion while protecting renal function, is an important goal of current clinical research in HF.
- Vasopressin antagonists are effective in removing large amounts of water, but not salt, in HF. The EVEREST trial in unselected acute systolic heart failure did not show benefit on CV outcomes and only a modest benefit on dyspnea. Whether vaptans in HF are still a viable option is an important question. Better targeting specific vasopressin receptors with highly selective agents, better profiling of patients more likely to benefit, combination with mineralocorticoid receptor antagonists are options that are worth exploring.
- Aquapharesis (Ultrafiltration: UF) has been shown to be a safe and effective therapeutic modality for correction of volume overload in hospitalized patients with HF, not responding to intravenous diuretics and vasoactive medications. Should UF replace intravenous diuretics as a first-line therapy for patients with hypervolemia admitted for HF? The validity of such a concept is being examined in the NHLBI larger CARRESS study.

Session program:

Insights from DOSE and gaps in evidence with diuretic therapy
Speaker: Alice MASCETTE, NHLBI, USA

The Vaptans story post-EVEREST.
What is next? ACTIVATE, TACTICS and BALANCE trials
Speaker: Michael FELKER, Durham, USA
Discussant: William T. ABRAHAM, Colombus, USA

Ultrafiltration for acute cardiorenal syndrome in heart failure. UNLOAD and AVOID-HF and CARRESS trial
Speaker: Gian Paolo ROSSI, Padua, ITA

Debate: New diuretic modalities: Remaining gaps in evidence or ready for clinical use?

Panellists:
ABRAHAM William T., Colombus, USA - ANKER Stefan, Berlin, GER - CLELAND John, Hull, GBR - CODY Robert, J&J, USA - FELKER Michael, Durham, USA - FIUZAT Mona, Durham, USA - GHEORGHIADE Mihai, Chicago, USA - GOLDSMITH David, London, GBR - HEMMINGS Robert, MHRA, GBR - KIM Jae, Amgen, USA - KJELDSEN Keld, Copenhagen, DEN - MASCETTE Alice, NHLBI, USA - MEBAZAA Alexandre, Paris, FRA - PITT Bertram, Ann Arbor, USA - ROSSI Gian Paolo, Padua, ITA - VOORS Adrian, Groningen, NED

HYPERTENSION TRIALIST WORKSHOP: AUTONOMIC MODULATION THERAPY

Chairpersons: George BAKRIS, Chicago, USA - Sverre E. KJELDSEN, Oslo, NOR
Webcast: Michel AZIZI, Paris, FRA

Resistant hypertension is usually defined as uncontrolled hypertension despite the intake of at least 3 antihypertensive drugs in full doses including a diuretic. Most investigators would also claim that this also implies 24-hours systolic blood pressure remaining above 135 (or 140) mmHg. Over the years some evidence has accumulated that raised sympathetic nervous system activity is involved in the pathogenesis of hypertension and particularly so in more severe hypertension.

- Ablation of the renal nerves located in the adventitia of renal arteries has emerged as a novel treatment modality and a catheter manufactured by Adrian/Medtronic has been CE approved in Europe based on one RCT (SYMPLICITY -2). A much larger trial is ongoing (SIMPICITY 3). Several other producers have applied for approval.
- CVRx have developed Barostim based on carotid baroreceptors stimulation and have gathered some early experience with encouraging results that led to CE mark.
- These techniques have rapidly been taken up in several countries including in a large number of centers in Germany.
- Beyond resistant hypertension, various devices providing autonomic modulation therapy are entering the clinical development stages also in heart failure, CKD and diabetes.
- Vagal stimulation developed by Medtronic (Biocontrol) and Boston Scientific are being tested in the INOVATE-HF and NECTAR-HF respectively in systolic heart failure.
- Spinal Cord stimulation is considered by many in small proof of concept trials (St Jude SCS HEART) (Medtronic DEFEAT-HF)
- Understanding the differences in the clinical and regulatory environments in the United States and Europe helps explain why much early device testing takes place outside of the United States, and why the introduction of new devices into clinical practice is usually significantly delayed in the United States when compared with Europe.
- Both phenomena are direct results of inherent differences in the criteria for approval and the process required to obtain approval. In particular, the European CE Mark process requires demonstration of safety only (and not efficacy) and relies heavily on non-governmental notified bodies to regulate the approval and post-approval process. In contrast, the approval of a new high-risk device in the United States requires demonstration of both safety and efficacy and is more highly regulated by a central governmental agency (CDRH/FDA).

The aim of this workshop is to assemble primary investigators of a number of important ongoing trials and discuss preliminary results, strengths and limitations of the current trials, efficacy and safety endpoint related issues, as well as issues related to optimal trial design, approvability and implementation into daily clinical practice.

Device companies: CVRx, Medtronic, St. Jude, Marquette, Boston Scientific, Vessix Vascular, ReCor Medical, Adrian, Biosense, Maya Medical.

Trials: ARSENAL – DERENEDIAB - DENERV-HTN – DEPART – DREAMS – DIASTOLE - the Dutch trial – ENCOReD – INSPiRED - Oslo RDN Trial - PRAGUE-15 - REDUCE-HTN – ReSET – REVISE - Symplicity HTN 1-2-3 - the GBR trial - INNOVATE-HF - NECTAR-HF - SCS HEART - DEFEAT-HF - SCS Heart

Session program:

Resistant hypertension trials: Can renal denervation therapy lower blood pressure?
Speaker: Felix MAHFOUD, Homburg, GER
Discussant: Michel AZIZI, Paris, FRA

Barostim: Experience so far and future developments
Speaker: Hermann HALLER, Hannover, GER
Discussant: Yared NADIM, CVRx, USA

Autonomic modulation therapy for heart failure: Preclinical data and ongoing trials
Speaker: Faiez ZANNAD, Nancy, FRA
Discussant: Gaetano DE FERRARI, Pavia, ITA

Debate : What relevant endpoints in autonomic nerve modulation therapy trials?
What kind/level of evidence? Targets to meet for approval (FDA, and in EU, beyond CE mark) and reimbursement
Investigator viewpoint: George BAKRIS, Chicago, USA - Ileana PIÑA, New York, USA
Regulatory viewpoint: Andrew FARB, FDA, USA
Industry viewpoint: Rob KIEVAL, CVRx, USA - Kenneth STEIN, Boston Scientific, USA

Panellists:
AZIZI Michel, Paris, FRA - BAKRIS George, Chicago, USA - DE FERRARI Gaetano, Pavia, ITA - FARB Andrew, FDA, USA - GOBBI Giorgio, Medtronic, CHE - HALLER Hermann, Hannover, GER - KIEVAL Rob, CVRx, USA - KJELDSEN Sverre E., Oslo, NOR - LINDE Cecilia, Stockholm, SWE - MAHFOUD Felix, Homburg, GER - PATHAK Atul, Toulouse, FRA - PIÑA Ileana, New York, USA - SLEIGHT Peter, Oxford, GBR - STEIN Kenneth, Boston Scientific, USA - WACHTER Rolf, Göttingen, GER - YARED Nadim, CVRx, USA - ZANNAD Faiez, Nancy, FRA

CVCTlive
LIVE SESSIONS: HOW TO BE IN TWO PLACES AT ONCE!

CVCT Forum 2012 will be featuring live Webcast Sessions through which cardiologists from all over the world will be able to interact and share their ideas and research among peers while the CVCT forum takes place in Paris. This is a great way to engage in discussions and meet other colleagues with the advantage of technology.

As time is of the essence, this provides the perfect opportunity to exchange with some of the leading Key Opinion Leaders and Principal Investigators from all over the world!

FRIDAY NOVEMBER 30, 2012

PARIS / CET	08:00 am - 10:00 am	COFFEE BREAK	10:20 am - 12:30 am	LUNCHBOXES SERVED	12:45 am - 03:15 pm	COFFEE BREAK	03:30 pm - 05:00 pm	COFFEE BREAK	05:20 pm - 07:30 pm
MODIGLIANI	**WORKSHOP 1** THE THROMBOSIS TRIALISTS WORKSHOP		**WORKSHOP 1** THE THROMBOSIS TRIALISTS WORKSHOP		**LUNCH DEBATE SESSION 1** THE DEVICE THERAPY TRIALISTS WORKSHOP		**WORKSHOP 2** ATHEROSCLEROSIS IMAGING IN CLINICAL TRIALS		**WORKSHOP 2** ATHEROSCLEROSIS IMAGING IN CLINICAL TRIALS
	CVCTlive Russia		CVCTlive Russia		CVCTlive Brasil		CVCTlive Brasil		CVCTlive Brasil
	CVCTlive Ukraine		CVCTlive Ukraine		CVCTlive Hungary		CVCTlive Argentina		CVCTlive Argentina
	CVCTlive China		CVCTlive China						
SOUTINE / UTRILLO	**WORKSHOP 3** THE DIABETES TRIALISTS WORKSHOP		**WORKSHOP 3** THE DIABETES TRIALISTS WORKSHOP		**LUNCH DEBATE SESSION 2** NEW EVIDENCE, NEW GUIDELINES & FUTURE DEVELOPMENTS WITH IVABRADINE SATELLITE SYMPOSIUM		**WORKSHOP 4** CARDIOVASCULAR PREVENTION IN CHRONIC KIDNEY DISEASE		**WORKSHOP 4** CARDIOVASCULAR PREVENTION IN CHRONIC KIDNEY DISEASE
	CVCTlive Russia		CVCTlive Russia						
	CVCTlive Netherlands		CVCTlive Netherlands						

SATURDAY DECEMBER 1, 2012

PARIS / CET	08:00 am - 10:00 am	COFFEE BREAK	10:20 am - 12:30 am	LUNCHBOXES SERVED	12:45 am - 03:15 pm	COFFEE BREAk	03:30 pm - 05:00 pm	COFFEE BREAK	05:20 pm - 07:30 pm
MODIGLIANI	**WORKSHOP 5** THE ATHEROSCLEROSIS TRIALISTS FORUM		**WORKSHOP 5** THE ATHEROSCLEROSIS TRIALISTS FORUM		**LUNCH DEBATE SESSION 3** HEART FAILURE TRIALISTS WORKSHOP		**DEBATE SESSION 4** HEART FAILURE REMOTE MONITORING TRIALS		**DEBATE SESSION 5** NOVEL DIURETIC STRATEGIES IN HEART FAILURE
					CVCTlive Brasil		CVCTlive Brasil		CVCTlive Brasil
SOUTINE / UTRILLO	**WORKSHOP 6** ESC 2012 CHRONIC HEART FAILURE GUIDELINES		**WORKSHOP 6** ESC 2012 CHRONIC HEART FAILURE GUIDELINES		**LUNCH DEBATE SESSION 6** PERSONALIZED CARDIOVASCULAR MEDICINE AND DRUG DEVELOPMENT		**DEBATE SESSION 7** WHAT IS THE OPTIMAL DESIGN FOR BIOMARKER STUDIES?		**DEBATE SESSION 8** HYPERTENSION TRIALIST WORKSHOP: AUTONOMIC MODULATION THERAPY
					CVCTlive Japan				CVCTlive Dom. Rep.

CVCTlive FACULTY (Local Moderators)

CVCTlive with Sao Paolo, Brasil
Dr. Marcelo KATZ, Brazilian Clinical Research Institute (BCRI)
Renato D. LOPES, MD, PhD, MHS, Duke University Medical Center

CVCTlive with Cordoba, Argentina
Alberto LORENZATTI, MD, International Society of Cardiovascular Pharmacology (ISCP)
Javier COURTIS, MD, Argentine Federation of Cardiology (FAC)

CVCTlive with Budapest, Hungary
Gabor SZEPLAKI, MD, PHD, Consultant Cardiologist
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Dr. Vladimir POPOV, Research Medical Center JSC Russian Railways
Dr. Emma VOYCHIK, Research Medical Center JSC Russian Railways
Dr. Julia ISAKOVA, Research Medical Center JSC Russian Railways

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Dr. Vladimir POPOV, Research Medical Center JSC Russian Railways
Dr. Katherina ZAKHARCHENKO, QA and training manager ESMAR

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Dr. Arnaud OLIVIER, Institut Lorrain du Cœur et des Vaisseaux, CHU de Nancy

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Prof. Dr. Gerard A. RONGEN, Radboud University Nijmegen Medical Centre

CVCTlive with Sendai, Japan
Pr. Koji HASEGAWA, Kyoto Medical Center, NHO

CVCTlive with Beijing, China
Dr. Yong HUO, Peking University First Hospital

CVCTlive with Santo Domingo, Dominican Republic
Dr. Roberto FERNANDEZ-DE-CASTRO, International Society of Cardiovascular Pharmacology (ISCP)

In collaboration with ISCP, EACPT, Duke Heart Center, ESC cardiologists of tomorrow

CVCTlive
LIVE SESSIONS: HOW TO BE IN TWO PLACES AT ONCE!

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 2012 in Paris as well as hotel accommodation and a 200 EUR travel grant.

This **Young Investigators Grant** scheme is possible through 2 mechanisms:

1. **Grant applications that may be filled out on the CVCT website : www.globalcvctforum.com**
2. **Nomination by CVCT Faculty members:** CVCT Meetings are supported by unrestricted educational grants with no allocation for speaker's fees. Rather, and in recognition of the valued contribution of faculty members and aiming at attracting Young Fellows to the CV clinical trial science, CVCT invites Faculty members to recommend one fellow who will be invited to attend the CVCT Forum, waiving registration fees and providing accommodation and a travel grant of up to 200 EUR.

CVCT RESSOURCE CENTER

We are very pleased to offer a complete record of the very successful recent CVCT Forum 2011 and 2012 as all sessions are being webcasted.

The resource center includes webcasts of selected sessions and slide sets from most of the presentations, but also the latest CVCT publications.

Every year, position papers from the CVCT Forum sessions are published with the endeavor of advancing the science of CV clinical trials. CVCT Forum & CVCT Workshop published more than 12 papers so far. Please monitor the progress of CVCT publications on www.globalcvctforum.com

This year, many more are in the pipeline

The topics are: Thrombosis in ACS, HF anti-thrombotic trials, RAAS trials, geographical differences, consensus paper on mineralocorticoid recpetor antagonists, personalized medicine trials, Serum potassium in cardio-renal trials, Heart rate: a biomarker and a bio-target in cardiovascular disease trials/ Focus on Co-morbidities: Diabetes and HF

The science discussed in the CVCT Forum is of paramount importance to investigators, industry R&D and regulators involved in trials in the cardiovascular area, diabetes, thrombosis & atherosclerosis.

EUROPEAN BOARD FOR ACCREDITATION IN CARDIOLOGY

EBAC

The CVCT Forum is accredited by the European Board for Accreditation in Cardiology (EBAC) for 12 hours of External CME credits. Each participant should claim only those hours of credit that have actually been spent in the educational activity. EBAC works according to the quality standards of the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS).

CVCT FORUM IS ENDORSED BY

Cardiovascular Pharmacology and Drug Therapy
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

It is with great pleasure that the nucleus of the WG of Cardiovascular Pharmacology and Drug Therapy invites all those attending the CVCT meeting to become members of our WG.

The WG is devoted to activities very similar to those you will attend in this meeting in the wide field of Cardiovascular Pharmacology in particular trials design.

www.escardio.org/communities/Working-Groups/pharmacology

European Drug Development Hub

EDDH, European Drug Development Hub is an academic clinical research organisation, under the aegis of the Transplantation Foundation, a public-interest Foundation.

EDDH was founded in 2007, from a partnership between the Clinical Investigation Center of the University Hospital of Nancy and the transplantation Foundation.

EDDH provides full-service clinical project management. This enables investigtors and promoters to concentrate on their core tasks, while still being actively involved in clinical research.

Our clinical project management services cover the planning, coordination and implementation of all types of clinical studies, in France and Europe.

EDDH works with a range of partners. These include clinical investigators (institutional clinical trials), pharmaceutical and medical device developers (commercial clinical trials) and EU Framework Programs.

www.fondationtransplantation.org/index.php?page=eddh

Inserm

Nancy-Université
Université Henri Poincaré

CHU NANCY

Nancy Inserm 9501 Clinical Plurithematic Investigation Centre (CIC) is supported by both INSERM (National Institution for Health Care and Medical Research), Nancy University hospital, and Nancy University and is headed by Pr Faiez Zannad.

With its staff specifically dedicated to clinical research, it acts as an interface between basic research and completed medical research, and its purpose is to produce new scientific and medical knowledge in compliance with ethical and legal standards. The CIC objectives are :

- to provide logistical and technical support for the design and implementation of research projects.
- to develop clinical research especially in Cardiovascular diseases, Aging and Metabolism, within the community of University Hospitals and research laboratories, and in particular within INSERM, as well as with general hospitals and health care facilities and private practice investigators
- to train physicians, pharmacists and paramedics in clinical research, the use of good clinical practices and quality control. The CIC provides support throughout each entire project, from the preparatory stage to termination and follow-up.

www.chu-nancy.fr/cic/

Duke Heart Center
DUKE UNIVERSITY HEALTH SYSTEM

CVCT Publications

CVCT meetings aim at disseminating expert opinions discussed during the meetings. CVCT publications are posted at **www.globalcvctforum.com**

A Publications Committee has been developed and is producing a number of manuscripts following the CVCT forum. Co-Chairs are Pr. Zannad and Dr. Pitt. Operational Director is Dr. Fiuzat.

For anyone interested in participation in a writing group, please contact Dr. Fiuzat at **Mona.Fiuzat@Duke.edu**

EACPT

European Association of Clinical Pharmacology and Therapeutics
The aims of the Association are to develop clinical pharmacology and therapeutics in Europe.

www.eacpt.org

ISCP
International Society of Cardiovascular Pharmacotherapy

The mission of the ISCP is to promote and facilitate strategies to improve cardiovascular health through cooperation among cardiac physicians and surgeons, pharmacologists, pharmacists, scientists, and medical practitioners worldwide.

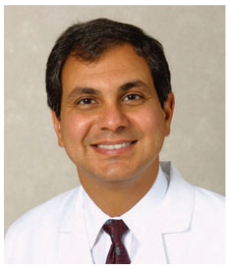
www.iscpcardio.org

2012 Biannual International Forum
Frontiers in Drug Discovery

Friday November 30, 2012, 9:00 for 9:30 am - 3:30 pm
Maastricht School of Management
Endepolsdomein 150, 6229 EP Maastricht

9th Global CardioVascular Clinical Trialists Forum

SPEAKERS BIOGRAPHIES & ABSTRACTS



ABRAHAM William T., Columbus, USA

William T. Abraham, M.D., is Professor of Internal Medicine and Chief of the Division of Cardiovascular Medicine at The Ohio State University, Columbus, Ohio. He earned his medical degree from Harvard University and completed post-graduate training at the University of Colorado. Dr. Abraham's clinical activities and research interests focus on heart failure. He has received grants from the National Institutes of Health and participated in more than 100 multicenter clinical drug and device trials. In addition to authoring more than 600 original works, Dr. Abraham has co-edited a leading textbook, Heart Failure: A Practical Approach to Treatment.

ADAMS Kirkwood, Chapel Hill, USA

Kirkwood F. Adams Jr., M.D., 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 also served on the data and safety monitoring boards of the DEFINITE, EMOTE, IMPACT and SADHART-CHF trials and on national advisory boards for several pharmaceutical companies. He has served on the Steering Committees for the ESCAPE, ACQUAINT-HF, ACTIV in CHF, RITZ 4, OPTIME CHF, REVERT, and HF-ACTION, ASCEND, RELAX trials and the ADHERE and STAMINA-HFP registries. 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. Dr. Adams has a major interest in developing practice guidelines for congestive heart failure. He also served as chair of the Guidelines/Clinical Positions Committee of the Heart Failure Society of America from 1996 to 2006 and is a past member of the Executive Council of this society. He led the development of the original guideline devoted to pharmacological therapy and the first comprehensive guideline for heart failure developed by this society. In addition to heart failure drug development, his current research interests are heavily focused on personalized medicine with ongoing projects related to novel biomarkers for heart failure, pharmacogenomics of heart failure therapeutics, and biomarker guided therapy for improving outcomes in CHF. He is very actively involved on the Executive Committee for the NHLBI sponsoredtrial of NT-proBNP guided therapy know as GUIDE-IT.

AKEHURST Ron, Sheffield, GBR

Ron Akehurst is a Professor of Health Economics at The University of Sheffield and the Strategic Director or BresMed, a HTA consulting company. Ron holds his Chair in ScHARR, one of the worlds leading centres for Health Services Research with in excess of 200 staff. Professor Akehurst stepped down as Dean of ScHARR in 2010, having founded and run the School for 17 years. His academic interests are primarily in Health Technology Assessment (HTA) and he has published widely in that area, contributing to the development of methods of HTA. In addition he has carried out research and conducted HTAs in many different therapeutic areas. He has had some involvement in developing HTA processes in other countries, including Hungary and Korea.

Ron was a founding member of the National Institute for Clinical Excellence (NICE) Appraisal Committee, serving on it for 7 years; served on the NICE Topic Selection Committee; the NICE Public Health Interventions Advisory Committee and is currently a member of the NICE Diagnostics Advisory Committee. He is also a member of the Advisory Group on National Specialised Services (AGNSS) which advises the Secretary of State for Health on organisation of services for people with very rare conditions. Past activities include a 2 year period as an Economic Advisor in the Department

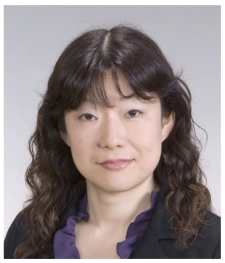
of Health, a five year period as economic advisor to North Western Regional Health Authority, seven years as founding Director of the York Health Economics Consortium and three years as a Specialist Advisor to the House of Commons Health Select Committee. Ron spent 3 years as a Non-Executive Director of Rotherham Health Authority, responsible for commissioning Health Services.

Ron has been providing consulting services to many pharmaceutical and devices companies since 1984. This has involved supporting early stage decisions on whether to kill products; developing strategies for evidence development as well as preparing cost effectiveness cases. He has been involved in preparing HTA submissions to many bodies, including NICE, SMC, TLV, PBAC and CADTH. He has also advised companies on developing their in house HEOR capabilities.

ALONSO Angeles, EMEA, ESP

Senior Consultant. Cardiology Dpt. Hospital Universitario Puerta de Hierro, Madrid, Spain.

Honorary Professor. School of Medicine, Universidad Autónoma, Madrid, Spain.
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).



ANDO Yuki, PMDA, JAP

Ms. Yuki Ando is a senior scientist for biostatistics of the Pharmaceuticals and Medical Devices Agency (PMDA), Japan.

She received a master's degree in engineering from Tokyo Science University. Then she joined the Pharmaceuticals and Medical Devices Evaluation Center, which was subsequently transformed into the current PMDA.

Currently she is the leader of Biostatistics Group and is responsible for the statistical review and consultation in the new drug review offices in the PMDA. She is also the leader of "Innovative Statistical Strategies for New Drug Development" project team which is one of the projects across multi-offices in PMDA, and is involved in the research of design and evaluation of multi-regional clinical trials.

ANKER Stefan, Berlin, GER

Stefan D. Anker is Professor of Cardiology and Cachexia Research (W2, tenured) at the Department of Cardiology in the Charité, Campus Virchow-Klinikum in Berlin, Germany (since 2002).

Dr. Anker studied medicine and obtained his M.D. from Charité Medical School in Berlin, Germany (1987–1993). He went on to earn a Ph.D. (1998) at the National Heart & Lung Institute, Imperial College London, UK. Dr. Anker started his clinical training in Germany and completed it in the UK.

Dr. Anker has authored more than 475 original papers, reviews, and editorials (total citations: 19,500; h-index: 77; Scopus November 2012).

For his work Dr. Anker has won several prizes and has obtained a number of fellowships and grants, including 2 NIH grants (Warcef-Study) and 2 EU-FP7 grants. Dr. Anker is the overall co-ordinator for the EU-FP7-project "SICA-HF".

Dr. Anker serves on the editorial boards of 8 scientific journals (including European Heart Journal, European Journal of Heart Failure, International Journal of Cardiology & Nutrition). Dr. Anker is founding Editor-in-Chief of the Journal of Cachexia, Sarcopenia and Muscle (JCSM, see www.jcsm.info).

Dr. Anker was and is member of more than 10 international steering committees (chairing or co-chairing 4), several DSMB's (chairing 2) as well as several end-point committees of clinical trials in heart failure.

Dr. Anker serves in the board of the Heart Failure Association (HFA) of the European Society of Cardiology (since 2006) and now is President of the HFA (2012-2014).

Since 2008, Dr. Anker is the founding president of the International Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD) – see also www.cachexia.org.

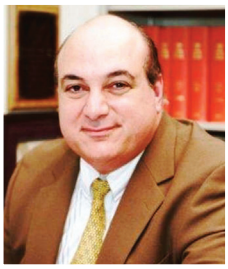
AZIZI Michel, Paris, FRA

Michel Azizi, Hypertension Unit, Hôpital Européen Georges Pompidou, Paris-Descartes University, F-75015 Paris, France.

ABSTRACT

Renal Denervation: Caution is still required

Despite the availability of multiple classes of orally active antihypertensive treatments, resistant hypertension remains an important public health issue in 2012. The failure of purely pharmacological approaches to treat resistant hypertension has stimulated interest in invasive device-based treatments. A new catheter system using radiofrequency energy has been developed, allowing a percutaneous endovascular approach to renal denervation and providing patients with resistant hypertension with a new therapeutic option. To date, this technique has been evaluated only in open-label trials including small numbers of highly selected uncontrolled hypertensive patients with suitable renal artery anatomy. The available evidence suggests a favorable blood pressure (BP)-lowering effect in the short-term and a low incidence of immediate local and endovascular complications. This follow-up period is, however, too short for the detection of rare or late-onset adverse events. Published studies are subjected to several limitations inherent to their open-label design subject to expectation, performance and evaluation biases, potentially jeopardizing their internal validity and decreasing the degree of BP reduction we can expect to be achieved. Furthermore, the evaluation of the BP effect of renal denervation was mainly based on office BP measurement, a primary outcome that is subjected to observer bias. As expected, the BP-lowering effects of renal denervation, as assessed by ambulatory BP monitoring in few patients were smaller than those evaluated by office BP measurement. Finally, the external validity of the studies is also limited because they included a small sample of highly selected patients (mainly obese, Caucasian patients with resistant hypertension despite treatment with ≈5 antihypertensive drugs, a glomerular filtration rate >45 ml/min and a suitable renal artery anatomy) making it difficult to extrapolate the results to the general population of patients with resistant hypertension. In this context, there are strong arguments against the widespread and uncontrolled use of this procedure in routine practice: an unknown benefit/risk ratio, inconsistency and unpredictability of the BP response, absence of markers of primary success of the procedure, absence of cost-effectiveness evaluation, higher risk when renal denervation is performed by interventionalists less skilled at patient selection and performance of the procedure. The best way to ensure the rigorous follow-up of patients after renal denervation would therefore be to include them in clinical trials or international registries.



BAKRIS George, Chicago, USA

George L. Bakris, MD, Hon. D, F.A.S.H, F.A.S.N.,F.A.H.A.

Professor of Medicine.

Director, ASH Comprehensive Hypertension Center.

The University of Chicago Medicine, Chicago, IL.

Dr. Bakris received his medical degree from the Chicago Medical School and completed residency in Internal Medicine *at the Mayo Graduate School of Medicine where he also completed a research fellowship in* Physiology and Biophysics*. He then completed fellowships in* Nephrology *and* Clinical Pharmacology *at the University of Chicago. From 1988 to 1991, he served as Director of Renal Research at the Ochsner Clinic and on the faculty in the Departments of Medicine and Physiology Tulane University School of Medicine. He later was Professor and Vice Chairman of Preventive Medicine and Director of the Rush University Hypertension Center in Chicago from 1993 until 2006.* ***Currently****, he is a* Professor of Medicine *and* Director of the ASH Comprehensive Hypertension Center *in the Department of Medicine at the University of Chicago Medicine.*

Dr. Bakris has published over 600 articles and book chapters in the areas of diabetic kidney disease, hypertension and progression of nephropathy. He is the Editor or Co-Editor of 14 books, in the areas of Kidney Disease Progression and Diabetes and three on Kidney Function and Heart Failure. These include The Kidney and Hypertension, Hypertension: a Clinician's Guide to Diagnosis and Treatment, Hypertension: Principles and Practice, Handbook of Hypertension, The Kidney in Cardiovascular Disease, Therapeutic Strategies in Hypertension, Chronic Kidney Disease (CKD) and Hypertension Essentials, Managing Diabetic Nephropathy in the Hypertensive Patient and others. Additionally, he is the Associate Editor of the International Textbook of Cardiology and Current Diagnosis & Treatment in Nephrology. He also served as an expert-member on the Cardio-renal Advisory Board of the FDA (1993-2003) and is currently a special consultant to the FDA. He was a co-principal investigator on the NIH Clinical Research training grant for clinical research (K30) (1999-2004). He chaired the first *National Kidney Foundation Consensus report on blood pressure and impact on kidney disease progression (2000). He has served on many national guideline committees including: the Joint National Committee Writing Groups VI & 7 writing committees (1997, 2003), the JNC 7 executive committee (2003), the American Diabetes Association Clinical Practice Guideline Committee (2002-2004), the National Kidney Foundation (K-DOQI) Blood Pressure Guideline committee (2002-2004) and (K-DOQI) Diabetes Guideline committee (2003-2005). Dr. Bakris is also the past-President of the* ***American College of Clinical Pharmacology*** *(2000-2002) and the* ***American Society of Hypertension (ASH)***

*(2010-2012). 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 **Nephrology, Dialysis & Transplant.** He serves on more than 20 different editorial boards including Kidney International, Hypertension, J Hypertension, J American Soc. Hypertension and J Clin Hypertens.*

ABSTRACT

What are relevant endpoints in autonomic nerve modulation therapy trials? What kind/level of evidence? Targets to meet for approval and reimbursement

What kind of evidence is needed and the level is somewhat clear. Obviously, data from prospective randomized trials such as SYMPLICITY HTN-1, 2 and 3 is level 1 evidence. Additionally, there are two domains of answers: **a).** adequate response relative to a clinical endpoint of interest, and **b).** adequate relative to mechanism of either efferent and/or afferent neurologic activity reduction. Ideally, both should be demonstrated, as the demonstration of either one of these does not assume the other has been proven. Obviously, *efferent nerve measures,* the "gold standard" being reduction of renal noradrenaline (NA) spillover or less accepted alternative would be alterations of renal vein renin production or angiotensin II. Direct measurements of renal sympathetic nerve activity are also possible. Afferent nerve measures are more complicated as reductions of MSNA and total body NA spillover can each be a consequence of reduced afferent nerve conduction and/or reduced ANGII influence on hypothalamic efferent activity. To meet approval clear evidence of blood pressure reduction of at least 10-15 mmHg needs to be achieved and sustained for at least six months. Follow-up of up to three years shows persistence of effect. Frankly, if the procedure provides a high likelihood of achieving a blood pressure target of <140/90 mmHg with minimal to no adverse effects it should be approved and reimbursed as the cost saving from reduced CV and renal events will be markedly reduced.

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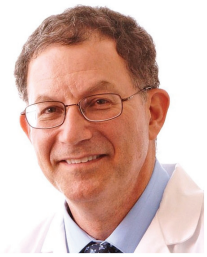

BERKOWITZ Scott, Bayer, USA

Scott D. Berkowitz, MD, FACP, FACC is currently Vice President and Head, Thrombosis and Hemostasis Group, Cardiovascular and Coagulation Therapeutic Area, Global Clinical Development at Bayer Healthcare Pharmaceuticals. He oversees the clinical development of the oral direct Factor Xa inhibitor rivaroxaban, the antithrombotic known as Xarelto®. Prior to this he worked at AstraZeneca LP on the clinical development of the first oral direct thrombin inhibitor, ximelagatran. His pharmaceutical clinical trial experience includes protocol development, trial medical oversight, data interpretation, synthesis, and presentation, IND and NDA/CTD authoring, health regulatory authority interactions with the FDA, EMA, and those of many other countries, and preparations for and representation to four FDA Advisory Committee meetings. Dr. Berkowitz has over 12 years of pharmaceutical industry experience and has been involved in clinical studies of coagulation medications for 22 years. Prior to joining industry, from 1993 – 2000 Dr. Berkowitz was Associate Professor of Medicine and Pathology at Duke University Medical Center, where he held dual appointments in Hematology and Cardiology of the Department of Medicine, and at the Duke Clinical Research Institute, where he provided coagulation and hematologic expertise to the Cardiology clinical trials group.

BORER Jeffrey, New York, USA

Jeffrey S. Borer, M.D., is Professor of Medicine, Cell Biology, Radiology and Surgery at the State University of New York Downstate Medical Center. He is Chairman, Department of Medicine and Chief, Division of Cardiovascular Medicine, and Director of two research institutes at Downstate. Dr. Borer received his BA from Harvard, his M.D. from Cornell, trained at the Massachusetts General Hospital, spent 7 years in the Cardiology Branch of the NHLBI and a year at Guy's Hospital in London as a Senior Fullbright Hays Scholar and Glorney-Raisbeck Fellow in the Medical Sciences, where he completed the first clinical demonstration nitroglycerin's utility in acute myocardial infarction. Upon returning to the NIH, he developed stress radionuclide cineangiography, enabling non-invasive assessment of cardiac function with exercise. He returned to Cornell for 30 years as Gladys and Roland Harriman Professor of Cardiovascular Medicine and Chief of the Division of Cardiovascular Pathophysiology. At Cornell and now at SUNY Downstate, in addition to teaching and clinical service, his research primarily has involved developing prognosticators for regurgitant valve diseases.

exploring the cellular/molecular myocardial biology of valve diseases, and assessing the effects of heart rate modification on clinical outcomes, with trials in coronary artery disease and heart failure. He has been an Advisor to the USFDA for 34 years, was a life sciences Advisor to NASA for 24 years, has served as officer or board member of several national professional societies, has published more than 400 scientific papers and 4 books, is editor-in-chief of the journal, Cardiology, and has received several awards/recognitions for his work.

ABSTRACT

SHIFTing Evidence in Heart Failure Management

SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) involved 6505 patients with moderate to severe heart failure (HF), heart rate ≥70bpm in sinus rhythm, at least one HF hospitalization during the year prior to study, and LVEF ≤35% who were receiving guidelines-based HF therapy including maximized beta blockade, who were randomized to add either placebo or ivabradine (pure HR slowing drug) during a median 22.9 months follow-up. The results of SHIFT unambiguously demonstrated the benefits of HR slowing (placebo-subtracted ivabradine-mediated HR reduction averaged approximately 10 bpm at 1 month and 1 year of therapy) in mitigating adversities of HF: 18% reduction in the primary composite SHIFT endpoint of cardiovascular death or HF hospitalization, 26% reduction in HF hospitalization (importantly reducing health care costs) and 26% reduction in HF death, significant and clinically meaningful >5 unit increase in quality of life (HQoL) by Kansas City Cardiomyopathy Questionnaire and, among patients admitted to study with HR ≥75bpm, significant reduction in mortality alone. The combination of improvement in natural history (survival, reduction in hospitalization) and improvement in HQoL is unusual with HF therapies and, specifically, is not a feature of beta blockade. Importantly, despite proven benefits of beta blockade, ivabradine-mediated HF benefits were independent of beta blocker dose and were solely attributable to HR slowing; in addition, ivabradine is devoid of many adverse effects of beta blockers unrelated to HR slowing. The plausibility of SHIFT results was supported by improved LV function and reduced LV volumes with ivabradine (vs placebo) in an echocardiographic substudy of SHIFT. The results of SHIFT support a new clinical perspective for management of HF, i.e., pure HR slowing, currently possible pharmacologically only with ivabradine, provides profound natural history and QoL benefits for patients with moderate and severe systolic HF when undertaken on a background of standard HF therapy including beta blockade.

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BUYSSE Jerry, Relypsa, USA

Dr. Jerry Buysse is Chief Scientific Officer and Co-founder of Relypsa, Inc., which was formed in October, 2007. Previously, Dr. Buysse was Vice President of Preclinical Research and Development at Ilypsa, responsible for chemistry, lead discovery, preclinical development and pharmacology. Dr. Buysse joined Ilypsa in May, 2003 following seven years at Microcide Pharmaceuticals (1996-2003) where he was Vice President of Discovery Biology, responsible for screening and lead discovery in Microcide's antibacterial and antifungal programs. Dr. Buysse was a Senior Research Scientist at Pharmacia & Upjohn (1992-1996) and contributed to preclinical and early clinical development of Linezolid (Zyvox). He was a National Research Council Fellow and Senior Research Microbiologist at the Walter Reed Army Institute of Research (1984-1992), working on vaccines for enteric bacterial infections. Dr. Buysse received his BS in Microbiology at The University of Michigan, Ph.D. in Immunology and Microbiology from Wayne State University School of Medicine and completed postdoctoral studies at Tufts University School of Medicine.

CALVO Gonzalo, Barcelona, ESP

Gonzalo Calvo is consultant in Clinical Pharmacology at Hospital Clinic of Barcelona, and Associate Professor of Pharmacology at the University of Barcelona (UB). He represented the Spanish Agency on Medicines and Healthcare Products (AEMPS) in the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) from 2002 to 2011. He was chair of the Cardiovascular Working Party and the Respiratory Drafting Group. He was elected President of the European Association of Clinical Pharmacology and Therapeutics in 2011.

CHOUDHURY Robin, Oxford, GBR

Professor Robin Choudhury is a Wellcome Trust Senior Research Fellow in Clinical Science and Professor of Cardiovascular Medicine at the University of Oxford; Consultant Cardiologist at the Oxford Heart Centre and Clinical Director of the Oxford Acute Vascular Imaging Centre. He is past President of the Royal Society of Medicine Section on Lipids, Metabolism and Vascular Risk and serves on the Editorial Board of the American Heart Association Journal, ATVB.

Prof. Choudhury chairs the British Cardiovascular Society Clinical Research Studies Steering Group, which promotes interactions between UK clinicians, scientists; industry and government in furthering cardiovascular research. His research interests focus on the development and application of imaging techniques for the characterization of atherosclerosis, thrombosis and vascular inflammation and on interventions that regress atherosclerosis. His group in Oxford has led a number of clinical studies using multi-modal vascular MRI at 1.5T and 3T. His laboratory is supported by the Wellcome Trust, the British Heart Foundation and the National Institute for Health Research, Oxford Comprehensive Biomedical Research Centre. He is a Fellow of the American College of Cardiology, the European Society of Cardiology and the Royal College of Physicians, London.

CLELAND John, Hull, GBR

Professor of Cardiology, University of Hull. 1999 Senior lecturer (BHF Funded), Clinical Research Initiative in Heart Failure, Glasgow. 1994-98. Senior Lecturer in Cardiology, Hammersmith Hospital, London.1989 – 1994. Past chairman of the Working Group on Heart Failure of the ESC Founding Editor of the European Journal of Heart Failure (an official journal of the ESC). Member of the data standards committee on heart failure for the AHA/ACC Task Force Past-chairman of the British Society for Heart Failure.

CLEMMENSEN Peter, Copenhagen, DEN

Professor Peter Clemmensen completed his medical training at he University of Copenhagen, and currently holds the positions of Professor of Invasive and Diagnostic Cardiology, University of Copenhagen and function as Chief physician – CAD services, the Heart Centre, Department of Cardiology, Rigshospitalet, Denmark. President of ACCA – Acute Cardiovascular Care Asssociation under the ESC. Past President of the Danish Heart Foundation. Previous board member of ISCE and ISCP.

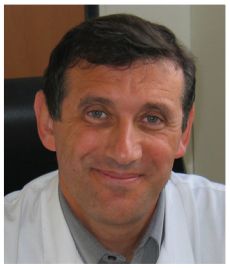
Professor Clemmensen has published over 200 scientific papers and chapters in international texbooks. The research has mainly been on assessment of reperfusion therapies in patients with ST segment elevation myocardial infarction, including non-invasive methods to estimate the effects of thrombolytic therapy, primary and rescue PTCA on infarct size. A recent focus of the research has been risk stratification in patients with non-ST elevation acute coronary syndromes, inclunding cardiac markers and electrocardiology. Professor Clemmensen has also acted as a mentor on 10 completed and ongoing dissertations in Cardiology at he University of Copenhagen, University of Southern Denmark, and the University of Oslo, Norway. Professor Clemmensen has participated in a large number of clinical trials and registries ranging from investigator to Steering Committee functions : FRISC II; DANAMI1-3; PLATO; EUROMAX; TRILOGY; MULTIPRAC.

He has served on several national and international end-points committees and working groups including the Joint ESC/ACC/AHA/WHO Committee for redefinition of myocardial infarction 2000, and its 2004-2012 GLOBAL MI Task Force. He is also a referee for 10 international journals.

CODY Robert, J&J, USA

Dr. Cody is Vice-President, and Heart Failure Disease Area Leader in the Cardiovascular and Metabolism franchise of Janssen Pharmaceuticals.LLC, of Johnson and Johnson. He previously was Executive Director, Merck & Co., and Global Director for Scientific Affairs-Cardiovascular. Prior to Merck, Dr. Cody was Vice-President for Medical Affairs and Chief Medical Officer of CVRx, Inc., a medical device company in Minneapolis, MN, (while on leave from the University of Michigan). At the University of Michigan Health System, Dr. Cody was a Professor of Internal Medicine and Associate Chief of the Division of Cardiovascular Disease. He was also Director of the Heart Failure & Transplant Management Program, and co-chair of the Institutional Review Board.

Dr. Cody has previously held faculty/clinical positions at the Ohio State University Medical Center and Weill Cornell Medical School, New York-Presbyterian Hospitals. Dr. Cody has led the design and execution of international clinical trials in heart failure, and served as Chair of numerous Data and Safety Monitoring Boards for cardiovascular trials. Dr. Cody received his M.B.A. degree from the University of Michigan, and his M.D. degree from Penn State University. Dr. Cody completed a Residency in Internal Medicine at the Cleveland Clinic Foundation, and his Cardiovascular Fellowship at Massachusetts General Hospital and Harvard Medical School.



COHEN-SOLAL Alain, Paris, FRA

Alain Cohen-Solal, MD, PhD, is Professor of Cardiology at the Faculty of Medicine (Paris 7) and Head of the Department of Heart Failure, Echocardiography and Cardiac Rehabilitation at the Hospital Lariboisière, in Paris.

Pr A. Cohen-Solal is a member of several professional organizations, including the French Society of Cardiology, the French Society of Hypertension, the European Society of Cardiology. He is member of the Working Group on Heart Failure of the ESC and Secretary of the European Association of Cardiac Prevention and Rehabilitation of the ESC.

He has been President of the Groupe de Reflexion sur la Recherche Cardiovasculaire, a working group of the French Society of Cardiology, in charge of cardiological research.

He acted as the principal investigator in France on several trials in Heart Failure, including recently REACH 1, CHARM, SENIORS, SURVIVE, RED-HF, EFFECT-HF, ATOMIC-HF, as well as IMPROVEMENT and SHAPE, two initiatives of the Study Group on Diagnosis of the WG on Heart Failure of the ESC, as well as other European and French Registries. He has been participating at various Steering Committees of Studies on Heart Failure.

He also heads since 2009 a Universitary Research Unit U942 "Biomarkers in Heart Failure" dedicated at finding, validating and developing new biomarkers in HF. This team develop translational research in HF both in humans and in animals and has launched an International Network on this topic, GREAT.

Currently, his activity is mainly oriented towards the care of patients with acute and chronic heart failure. A multidisciplinary ambulatory program of care of patients with CHF is ongoing as well as a programme of cardiac rehabilitation for patients with HF or after heart transplantation. He has focused his research on several aspects of HF, mainly: the abnormalities of the cardiac and peripheral responses to exercise in CHF; the evaluation of CHF by cardiopulmonary exercise testing; the diagnostic and prognostic role of neurohormones (BNP); the pathophysiology of diastolic heart failure.

Pr A. Cohen-Solal is author or co-author of several articles published in peer-reviewed medical journals, including Circulation, the Journal of the American College of Cardiology, the American Journal of Cardiology, Heart, the European Heart Journal, the Journal of Hypertension. He is also member of the editorial board of the European Journal of Cardiac Prevention and Rehabilitation.

COWIE Martin, London, GBR

Professor Martin Cowie is Professor of Cardiology at the National Heart & Lung Institute, Imperial College, London, UK and Honorary Consultant Cardiologist at the Royal Brompton Hospital, London. A founding member and past-chairman of the British Society for Heart Failure, Professor Cowie has also been a Board member (and Chair of the Education Committee) of the Heart Failure Association of the European Society of Cardiology (ESC). He advises the National Institute for Health and Clinical Excellence (NICE) on the management of heart failure. He sits on the Cardiovascular Round Table and the EU Affairs Committee of the European Society of Cardiology.

Professor Cowie's studies and reviews have been featured in a variety of peer-reviewed journals, including The Lancet Circulation, European Heart Journal, British Medical Journal, Heart, European Journal of Heart Failure, J American College of Cardiology *and* Journal of Cardiac Failure. *He is a member of the editorial board of* Heart, The British Journal of Diabetes and Vascular Diseases, *and* Cardiovascular Diabetology. *He has contributed chapters to many books, 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.*

ABSTRACT

Save life and save costs with ivabradine

Clinical evidence suggests that an elevated resting heart rate is a risk factor for mortality and morbidity in heart failure (HF) patients. SHIfT examined the effect of adding ivabradine, a heart rate lowering therapy, to optimised standard therapy in HF patients with a heart rate ≥70bpm, in sinus rhythm and with left ventricular systolic dysfunction.[1] Ivabradine plus standard therapy significantly reduced the risk of a primary composite event (CV death and hospitalisation for worsening HF) versus standard therapy (hazard ratio 0.82, 95% CI: 0.75-0.90 p<0.0001), exhibiting greater efficacy with increasing baseline heart rate. The European Medicines Agency has authorised ivabradine in HF patients with a heart rate ≥ 75bpm.[2] This presentation will report the results of a UK cost-effectiveness analysis based on SHIfT for two populations (heart rate ≥75bpm and ≥70bpm).

A Markov cohort model was used to simulate lifetime costs and outcomes for HF patients. Two health states were modelled, alive and dead; all-cause hospitalisations were additionally captured for resource use and quality of life implications. The incremental cost per additional Quality Adjusted Life Year (QALY) for ivabradine plus standard care versus standard care was estimated at £8,498, for heart rate ≥75bpm (approximately €10,500), and £13,764, for heart rate ≥70bpm (€17,100). Ivabradine has over a 95% chance of being cost-effective in the European licensed population using the NICE cost-effectiveness threshold [£20,000 (€24,800) per QALY]. This result was robust to sensitivity analyses.

Conclusion

Ivabradine plus standard care has a high probability of being cost-effective in patients with HF from a UK national health service perspective.

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DAN George-Andrei, Bucharest, ROM

Professor of Internal Medicine Department of the University of Medicine and Pharmacy "Carol Davila" in Bucharest. VP/ President Elect, International Society of Cardiovascular Pharmacotherapy (affiliated to World Heart Federation), Head of the Cardiology Department and Diagnostic Cardiovascular Procedures and Arrhythmology Unit - University Hospital Colentina, Head of Internal Medicine Clinic, Colentina University Hospital, Executive President of the Internal Medicine Scientific Foundation "N. Gh. Lupu" , Editor in Chief of "The Romanian Journal of Internal Medicine".

Leading Research Investigator of the Romanian Academy of Medical Sciences.

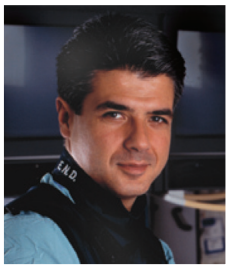
Member of board of certification - European Heart Rhythm Association of the ESC (EHRA).

Main areas of interest: sudden cardiac death, ventricular arrhythmias, atrial fibrillation and antiarrhythmic drugs, Heart Failure, atherosclerosis.

Published and communicated more than 150 original scientific papers and research, chair and member of the Faculty in more than 400 national and international medical conferences.

DE GRAEF Pieter, EMEA, NED

He was born in 1950 and finished medical training at the University of Groningen in 1975. Following a training in internal medicine at the department op Internal Medicine of the UMCG he was registered as an internist in January 1983. Subsequently, he became a clinical advisor for the MEB, maintaining a position as associate professor at the depts. of Internal Medicine and Pharmacology/Clinical Pharmacology. In 1989 he finished his thesis (PhD), In 1994 he was co-registered as a clinical pharmacologist. In 1996 he became professor in pharmacotherapeutics, responsible for implementing rational pharmacotherapy. In 2003 he was elected as "teacher of the year". He maintained a part-time position as senior clinical adviser of the MEB as head of the regulatory cardiovascular subdivision. In 2007 he became member of the CHMP and in 2012 of the Dutch MEB. He has fulfilled a number of positions at various organisations, among which the cardiovascular subgroup WP of the EMA (since 1999 member, since 2011 chairman), the hospital Medical Ethics Committee, the hospital Pharmacotherapy Committee, and the Board of the Dutch Society Clinical Pharmacology & Biopharmaceutics (chairman 1996-2000). He (co-)authored more than 100 publications in peer-reviewed journals. He was involved in writing a number of regulatory cardiovascular guidelines, including those on antihypertensive, lipid-lowering and anti-arrhythmic agents.



DELIARGYRIS Efthymios, The Medicines Company, USA

Dr. Deliargyris completed his medical studies at the Kapodistrian University of Athens School of Medicine and subsequently completed his post-doctoral studies in the United States where he obtained triple board certification in Internal Medicine, Cardiovascular Medicine & Interventional Cardiology. He was subsequently Assistant Professor of Medicine/Cardiology at Wake Forest University, NC, USA where he also served as Director of the Intravascular Ultrasound Laboratory. In 2004 he returned to Athens, GREECE and served as Chief of Cardiology at Athens Medical Center. In 2010 Dr. Deliargyris joined The Medicines Company where he now serves as the Global Medical Director at of Munich, GERMANY. Dr. Deliargyris has been the recipient of multiple research awards including the 1997 Merck Young Lipid Investigator Award, the 1999 Society of Cardiac Angiography and Interventions Research Competition - 1st Prize, the 2001 David A. Hack Excellence in Cardiovascular Research Competition - 1st Prize and the 2003 Vascular Biology Working Group Research Award. His primary research interests are in thrombosis and antithrombotic agents, including the pathophysiology of anti-PF4/heparin complex antibodies and their significance, also in imaging and treatments of vulnerable atherosclerotic plaques, and in novel risk factors for cardiovascular events with extensive prior research in the link between periodontal disease and atherosclerosis.

DUNDER Kristina, 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 currently the Swedish delegate in the CHMP (Committee of Human Medical Products) at the EMA (European Medicine Agency) in London, UK and a member of the cardiovascular working party at the EMA.

Dr Dunder was one of the Rapporteurs for the update of the EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus which has recently been adopted.

ABSTRACT

THE DIABETES TRIALISTS FORUM, DIABETES CLINICAL TRIALS: HELPED OR HINDERED BY THE CURRENT SHIFT IN REGULATORY REQUIREMENTS? A REGULATORY VIEWPOINT

The evaluation of cardiovascular safety of rosiglitazone (2006-2010) had implications on regulatory guidance for glucose lowering drugs both in the EU and in the US and both the FDA and the CHMP guidelines for development of glucose lowering drugs have been updated including new requirements for assessment of cardiovascular safety.

While the FDA Guidance is very precise specifying that the upper bound of the 95% confidence interval for the estimated risk should be below 1.8 at the time of marketing application, the CHMP guidance focuses more on the totality of data as a base for assessing the cardiovascular risk.

The presentation will focus on the interpretation of the requirements in the CHMP guideline (type of studies, study population, outcome measures, evaluation of the results) as well as experience from recent applications for marketing authorization for glucose lowering drugs, e.g. the usefulness of MACE meta analyses and the need for CV outcome studies for all new drugs.

Suggested Reading

Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, CHMP/EWP/1080/00 Rev. 1 (EMA website)

Guidance for Industry ; Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (FDA website)

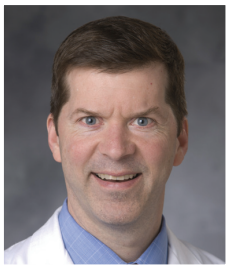
EZEKOWITZ Justin, Edmonton, CAN

Dr. Justin Ezekowitz obtained his undergraduate medical training at the Royal College of Surgeons in Ireland, achieving an honors degree. He completed his internal medicine residency at the University of Texas Southwestern Medical Centre in Dallas, Texas. He then returned to Canada to do a heart failure fellowship and research training, completed a Masters of Science in Clinical Epidemiology at the University of Alberta Public Health Sciences and Cardiology Fellowship at the University of Alberta. He is currently on faculty as Assistant Professor of Medicine in the Division of Cardiology.

He is the Director of the Heart Function Clinic at the University of Alberta Hospital and Mazankowski Alberta Heart Institute. He is a Population Health Investigator of AHFMR and an Investigator with the CIHR.

His research focus is on heart failure. He is involved in numerous clinical trials as a local investigator, national coordinator as well as multicenter international trials. Primary interests include clinical research into heart failure with a preserved systolic function, and novel processes or treatments of care for acute heart failure.

Ezekowitz is involved with the Canadian Cardiovascular Society (on the Heart Failure Guidelines committee), the Heart and Stroke Foundation of Alberta, the Canadian Institutes of Health Research and on the guidelines for the Heart Failure Society of America.



FELKER Michael, Durham, USA

G. Michael Felker, MD, MHS, is an Associate Professor in the Division of Cardiology at Duke University Medical Center and the Director of Heart Failure Research at the Duke Clinical Research Institute. He did his medical training at Duke University School of Medicine, his internal medicine training at Johns Hopkins Hospital where he was chief resident, and his cardiology training at Duke. Dr. Felker has published over 120 peer reviewed articles and book chapters in the field of heart failure. He has served on the Steering Committee for multiple national and international clinical trials in heart failure. He Directs the Advanced Heart Failure Fellowship Training Program at the Duke University School of Medicine. Dr Felker is an editorial board member or peer reviewer for multiple high impact medical journals, including the New England Journal of Medicine, JAMA, Lancet, Circulation, and JACC. He is the Associate Editor of JACC: Heart Failure *and co-editor of* Heart Failure: A Companion to Braunwald's Heart Disease *textbook. His research focus in on clinical trials (including clinical trials methodology) in acute and chronic heart failure, and the use of biomarkers as diagnostics, prognostic, and therapeutic tools in heart failure.*

FIUZAT Mona, Durham, USA

Dr. Fiuzat is a Senior Research Associate in the Heart Failure Research Program at Duke University and Assistant Professor of Medicine in the Division of Clinical Pharmacology. She is also the Managing Deputy Editor of the new JACC-Heart Failure Journal.

Dr. Fiuzat has worked at Solvay Pharmaceuticals and SmithKline Beecham Pharmaceuticals and was the Director of Clinical Operations and Development at ARCA biopharma, Inc. Her prior work experience included filing an NDA for the first proposed pharmacogenetically targeted heart failure drug and writing protocol and study development for Phase I, II and III studies, in both adults and pediatrics.

Dr. Fiuzat's clinical research experience has been in cardiovascular trials, with a focus on pharmacogenetics in heart failure. She is the Operational Leader of the PROTECT Publications Committee and a liaison for industry sponsors of clinical trials. Additionally, she has participated in the preparation for Cardio-renal Advisory Committee presentations to the FDA on behalf of drug sponsors.

Dr. Fiuzat completed undergraduate training at Clemson University and received her PharmD at Mercer University School of Pharmacy.

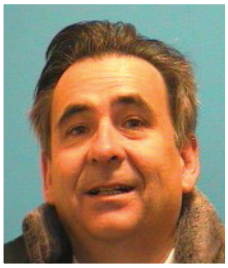
FRIEDMAN Jeffrey, Boehringer Ingelheim, USA

Physician with U. S. board certification in paediatrics and paediatric nephrology following training at Cornell University Medical College-The New York Hospital, with an additional research fellowship in paediatric nephrology at Harvard University.

Prior academic appointment at Cornell University Medical College.

Thirty years experience in the clinical development of cardiovascular products for the following indications: hypertension, cardiovascular outcomes (MACE) prevention, heart failure, acute stroke outcomes improvement and chronic stroke prevention, prevention of cardiovascular outcomes associated with cardiac and non-cardiac surgery, diabetic nephropathy, acute coronary syndromes.

Major Accomplishments include management of all clinical development of Pradaxa (dabigatran etexilate) from Phase II through registration in multiple indications.



GAUDIN Christophe, Sanofi, FRA

After a 3-year post-doctoral training in US as a fellow from Harvard Medical School, then Columbia University in a research program of transgenic mice overexpressing the Gsalpha protein in the cardiomyocytes, Christophe Gaudin first joined the pharmaceutical industry in France as a Clinical Pharmacologist and was then appointed by Sanofi in 1997. As a Clinical Research Director, he was responsible for the clinical development of clopidogrel in acute coronary syndrome, and then extended his responsibilities as Vice President Head of Cardiovascular and Thrombosis Clinical Investigations to lead the clinical development of a large portfolio of phase 2 and phase 3 projects. Over 15 years in Sanofi, he led successful registration programs including the worldwide extension of clopidogrel indications and the dronedarone program. Studies conducted under his responsibility at Sanofi included among others the

CURE, CLARITY, CHARISMA, ACTIVE, STRADIVARIUS, CRESCENDO and ATHENA trials. His current role is focused in the phase 3 development of a new intravenous anticoagulant for patients with an acute coronary syndrome.

ABSTRACT

The Thrombosis Trialists Workshop. Dose and target patient population issues

Discussant – industry viewpoint

The identification of a proper dose to maximize the efficacy with an acceptable bleeding risk is critical for the successful development of an anti-thrombotic drug. The optimal dose may differ among indications and among subpopulations for a given indication. Consequently, despite substantial phase II programs aimed at identifying dose(s) with a favorable benefit-risk profile, many recent antithrombotic drugs underwent extensive phase III trials investigating more than one dose for each indication.

For indications such as prevention of stroke in patients with atrial fibrillation or prevention of myocardial infarction in patients with an acute coronary syndrome, which require the recruitment of many thousands of patients to guarantee a sufficient power to demonstrate efficacy, the investigation of one additional dose can lead to even larger trials: typically, one additional dose means a 50% increase in sample size for a pivotal trial.

In order to allow the investigation of two doses of an anti-thrombotic agent in a phase 3 trial with an acceptable sample size, one original approach is the use of an adaptive design. This approach will be presented, integrating both strategic aspects to comply with expectations for registration and operational aspects to prevent bias.

Suggested readings: package insert and summary of product characteristics of the most recently approved anti-thrombotic drugs.

GELLER Nancy, NHLBI, USA

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, COAG (Clarification of Optimal Anticoagulation through Genetics) and the Ranolazine ICD trial (RAID). She has published nearly 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.

GHEORGHIADE Mihai, Chicago, USA

Mihai Gheorghiade, MD, FACC

Dr. Gheorghiade currently serves as Professor of Medicine and Surgery, Director of Experimental Therapeutics at the Center for Cardiovascular Innovation, Division of Cardiology, at Northwestern University's Feinberg School of Medicine and Northwestern Memorial Hospital. He was recently appointed Adjunct Professor of Medicine and Co-Director of the new Cardiovascular Center for Drug Development 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. He then moved to Virginia, where he was Chief of Cardiology at the Salem VA Medical Center and Associate Professor of Medicine at the University of Virginia. In 1985, Dr. Gheorghiade became Chief of the Cardiac Care Unit at the Henry Ford Hospital in Detroit and Associate Professor of Clinical Medicine at the University of Michigan. During his tenures in Virginia and Michigan, he received numerous teaching awards from both medical students and residents. In 1992, he joined Northwestern University as Associate Chief of the Division of Cardiology, Chief of the Cardiology Clinical Service, and Director of the Telemetry Unit at Northwestern University Feinberg School of Medicine until 2010.

Dr. Gheorghiade has served as a visiting professor in the United States and abroad. He has chaired or co-chaired more than 200 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, *and is an associated editor of the* Journal of Cardiovascular Medicine. *He has also served as guest editor on several occasions for* The American Journal of Cardiology, The American Heart Journal, *and* The American Journal of Medicine. *He has chaired many international trials in heart failure including OPTIME-HF, ACTIV-HF, IMPACT, PRESERVD, HORIZON and COMPOSE 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 currently serves as Chair of the international ASTRONAUT, RENO-DEFEND, and IMPROVE-HF Bridge.*

Dr. Gheorghiade has authored more than 500 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.

In 2004, Dr. Gheorghiade founded the Acute Heart Failure Syndromes International Group, comprised of physicians, scientists, clinicians, and regulatory and governmental agencies from North America and Europe to advance the knowledge and care of patients with acute heart failure syndromes through clinical research. This group has met annually, producing several consensus documents published in Circulation, Journal of the American College of Cardiology, and European Heart Journal.

In 2011, Dr. Gheorghiade assembled The Academic Research Team in Heart Failure(ART –HF) a group of expert clinicians and researchers with complimentary expertise to guide the development of heart failure therapeutics spanning the spectrum ranging from pre-clinical, phase I-III, and post marketing studies; to regulatory and guideline process *and remains actively involved in animal and human research for the development of novel compounds for acute heart failure syndromes. He dedicates significant time and energy to the mentorship of medical students, residents and junior faculty as attested by their primary authorship of more than 100 peer-reviewed publications in recent years. Improving outcomes of hospitalized patients with heart failure through research and education remains his top priorities.*

GOLDSMITH David, London, GBR

Dr Goldsmith is a Consultant Nephrologist and Reader (Associate Professor) in Renal Medicine at Guy's King's St Thomas' Medical School in London, UK, Clinical Director for London South NIHR Comprehensive Local Research Network Biomedical Research Centre and Associate Professor of Nephrology at the G.T. Popa University of Medicine and Pharmacy, Iasi, Romania. He is a Fellow both of the American Society of Nephrology (2010) and also of the European Renal Association (2011).

Dr Goldsmith is a current member of the Royal Society of Medicine, the London Hypertension Society, the Medical Society of London, the UK Renal Association, the European Renal Association, and the International Society of Nephrology. He was Executive Member (2002-2008) and Honorary Secretary (2004-2008) of the UK Renal Association, Council Member of the European Renal Association (2004-2007), Chairman of the Paper Selection Committee of ERA-EDTA (2005-2007), Founder Board member of ERA-EDTA Working Group EURECA-m (2008 – present). He is on the Hypertension Advisory Group for the ASN (2011 – present). He also led the European Best Practice Group response to KDIGO CKD-MBD guidelines (2010), and is on the ERBP work-group on diabetes and CKD (2011 – present). He was Co-Editor of the Journal of Nephrology (2006-2009), and currently is Associate Editor of CJASN (2010 – present), and on the Editorial Boards of Nephrology, Dialysis and Transplantation and International Urology and Nephrology (2006-present).

Dr Goldsmith has authored over 330 scientific articles published in peer-reviewed journals, presented over 220 research abstracts, given over 100 National and International Lectures, and written 3 books, including ABC of Renal Disease *(Eds 2007, 2012) and the forthcoming 4th Edition of the* Oxford Textbook of Clinical Nephrology *(Senior Commissioning Editor, OUP, 2013).*

Dr Goldsmith's main clinical and research interests are hypertension, cardiovascular disease, inflammation, Vitamin D and calcification syndromes in renal patients.

GORDON David, NHLBI, USA

Dr. Gordon is a cardiovascular clinical trialist and epidemiologist, who has served since 2002 as Special Assistant for Clinical Studies in the NHLBI's Division of Cardiovascular Sciences. He is a graduate of the University of Chicago undergraduate (1967) and MD/PhD (1973) programs and also received an MPH in epidemiology from the University of North Carolina in 1981. He first joined NHLBI as a post-doc in Ed Korn's Laboratory of Cell Biology in 1974, where he developed a procedure to isolate and purify actin from non-muscle cells. In 1977, he moved to the NHLBI extramural Lipid Metabolism Branch as a medical officer for the Lipid Research Clinics (LRC) program. He has worked with numerous NHLBI clinical trials since then, including WAVE, ALLHAT, BARI 2D, and the Cardiovascular Cell Therapy Network, and has published papers on the epidemiology of HDL, meta-analysis of cholesterol trials, seasonal variation of cholesterol, the correlates and predictive value of exercise testing, and on data and safety monitoring in clinical trials. He has also participated in all four National Cholesterol Education Program Adult Cholesterol Treatment panels.

HALLER Hermann, Hannover, GER

Prof. Hermann Haller is presently Director of the Department of Nephrology at Hannover Medical School and Dean of Medical Education. He graduated the Free University of Berlin in 1983. From 1983 until 1992 he trained at the Free University at Berlin. He spent three years as a post-doctoral fellow in the Division of Endocrinology at the Yale Medical School. In 1992 he became Professor of Medicine at the Franz-Volhard-Clinic at the Max-Delbrück-Centre of Molecular Medicine in Berlin. Prof. Haller's scientific interest is in hypertension, diabetic nephropathy and transplantation.

He is especially interested in vascular complications and endothelial cell function in these areas. Prof. Haller is post-president of the German Hypertension Society. He has published more than 500 peer-reviewed articles. Prof. Haller has received the Folkow Award of the European Society of Hypertension, the Franz Volhard Prize of the German Hypertension Society and the Jan Brod Award, Czech Society of Hypertension. He is also a principal investigator in international multicenter studies.

Furthermore in 2011 he was awarded the Honorary Professor of Huazhong University of Science and Technology in Wuhan, China201 and became Director of Sino-German Clinical Trial Centre of Tongji Hospital.

ABSTRACT

Cardiovascular prevention in patients with chronic kidney disease

Patients with chronic kidney disease are both at risk developing chronic vascular disease as well as progression of the renal disease. These risks are especially important for patients with metabolic disease such as diabetes and hypercholesterolemia. Several approaches have been used to prevent cardiovascular disease in these patients: The contribution of existing antihypertensive therapy to prevent the mechanisms of inflammation, oxidative stress and fibrosis has been tested in several recent trials. Unfortunately, the inhibition of the renin-angiotensin system by combination therapy has proven to be non-effective in these patients. It seems, that especially in patients with advance kidney disease may be even an unfortunate effect on the progression of renal disease. With regard to antihypertensives only calcium antagonists seem to have a beneficial effect. However, these compounds have not been tested in larger trials. The problem with larger prevention trials in this area is the assessment of long-term effects. As can be deduced from the STENO trials long-term treatment over more than seven years seem to be necessary to demonstrate an effect in patients.

Recently novel compounds have appeared in clinical trials. Based on promising basic and animal research Bardoxolon, an agent which reduces oxidative stress, has been successfully tested. However, recently because of safety concerns this drug has been stopped. Novel treatment strategies are also inhibition of aldosterone. The risk of hypercholesterolemia seems to be less in novel agents such as aldosterone synthase inhibitors. Other novel approaches are anti-inflammatory drugs such as MCP-1 inhibitors. These novel drugs will be discussed.

Other approaches with especially facts on the progression of kidney disease such as vitamin D treatment or treatment with heparin analogues will also be discussed.

A major issue in the progression of kidney failure and/or cardiovascular disease is the role of surrogate endpoints. One major question is a. besides proteinuria, other endpoints are feasible to draw a conclusion about the efficacy of treatment.

Baro-stimulation

Experience so far and future developments.

The treatment of patients with resistant hypertension is a major problem. Besides the renal degeneration a second intervention or method has become available. The stimulation of the baroreflex is a potent method to reduce blood pressure in patients. However, the method is more invasive as compared to renal denervation. We will discuss in this session the experience with baro-stimulation so far and discuss possibilities for future trials. An important question is which patients will benefit and which patients will need a stable reduction in blood pressure. Patient groups are obviously patients with late stage renal disease and heart failure. However, other patients with an increased risk for stroke etc. can be considered. An interesting issue will also be the technological development of the devices and what we can see in the future.

HASKEL Lloyd, J&J, USA

Lloyd Haskell, MD is currently Senior Director in the CV/ Metabolism group at Janssen Pharmaceutical Research. Dr. Haskell was faculty at the Albert Einstein College of Medicine Bronx, NY and New York Medical College, NY, NY and was Chief of the division of Nephrology at Texas Tech Medical School, prior to joining the pharmaceutical industry. A graduate of New York Medical College, he did his post graduate training at Beth Israel Medical Center and NYU Medical Center in New York City. He is Board Certified in Internal Medicine, Nephrology and Critical Care Medicine and is a certified specialist in Clinical Hypertension.

ABSTRACT

Heart failure is a well recognized pro thrombotic condition.

There are many factors that contribute to this hypercoagulable state in HF including platelet and coagulation cascade activation, endothelial dysfunction ,low cardiac output and stasis. Actual thromboembolic events are difficult to diagnose in a CHF patient, but autopsy studies have documented the increased occurrence in these patients. It is further recognized that these events may increase the incidence of death and hospitalization in this patient population. Randomized controlled trials with Vitamin K antagonists in CHF such as WASH, WATCH and WARCEF have suggested there may be some benefit to HF patients with this therapy but results have not been conclusive and excess bleeding is also of concern. Over the last few years newer oral anticoagulants are being developed which may offer advantages over the Vitamin K antagonists. These agents , which are more specific within the coagulation cascade, typically act on factor Xa or thrombin. They have been developed in multiple clinical conditions such as stroke prevention in non valvular atrial fibrillation, ACS and treatment of DVT and PE. Although no specific trials have been conducted to date in CHF, analysis of patients with CHF in trials for other indications have suggested that benefit extends to the population with HF. For example in the SPORTIF study with ximelagatran, a direct thrombin antagonist, patients with HF treated with the drug, had a reduction in hospitalization for worsening HF compared to the HF population treated with warfarin. In this talk we will discuss other evidence that has accumulated that may suggest these newer oral agents may benefit patients with HF and we will discuss potential mechanisms and clinical conditions that may be affected by these agents. Rationale and need for conducting a randomized controlled clinical study in HF patients will also be discussed. Lloyd Haskell, MD.

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HEMMINGS Robert, MHRA, GBR

Rob is a professionally qualified medical statistician. He has been with the MHRA for 12 years and heads the group of medical statisticians. Much of Rob's time is spent educating medical colleagues in the importance and artistry of clinical trial statistics; their use in proof and in obfuscation. Rob holds the following positions within the European drug regulatory system:

- *CHMP member: CHMP is the body responsible for preparing the opinions of the European Medicines Agency on questions concerning medicinal products for human use.*
- *Chair of the CHMP's Scientific Advice Working Party with responsibility for preparing advice to the pharmaceutical industry on the appropriate tests and trials to conduct in the development of a medicine for marketing authorisation.*
- *Rob is also a member of CHMP's Biostatistics Working Party with responsibility for giving advice on matters relating to clinical trial methodology across the EU regulatory network.*

Rob regularly speaks at national and international scientific meetings on a broad range of topics relating to medical statistics and drug licensing.

HOFFMANN Udo, Boston, USA

Dr. Hoffmann received his medical degree and doctorate from the University of Leipzig, Germany in 1995. After an internship in the Division of Cardiology at the General Hospital and University of Vienna, Austria he completed radiology residency at the General Hospital and University of Vienna (Chair, Prof. Christian Herold). In 2001, Dr. Hoffmann joined the MGH Department of Radiology for a fellowship in cardiovascular imaging. In 2003 Dr. Hoffmann defended his habilitation thesis at the University of Vienna entitled "Cardiovascular crosssectiona imaging - Experimental and Clinical studies using Magnetic Resonance Tomography and Computed Tomography". He also attended the Harvard School of Public Health (HSPH) and graduated as a Master of Public Health in 2006. The specific focus of Dr. Hoffmann's research over the past 20 years has been the feasibility, accuracy, and efficiency and effectiveness of cardiac CT technology in a bench to bedside approach.His research has resulted in >250 peer reviewed publications, Dr. Hoffmann became a clinical staff member of the Department of Radiology and the MGPO and was appointed Instructor in Radiology at Harvard Medical School in 2003. He subsequently was promoted to Assistant Professor in 2004 and to Associate Professor in 2007 and is an associate radiologist in the Department of Radiology. In addition to these appointments, Dr. Hoffmann has also served as a fellow of the Framingham Heart Study and as a faculty of the HSPH. He is the Division Chief of Cardiac Imaging at MGH, the Director of the Cardiac MR PET CT Program and the MGH Imaging Trial Center.

ABSTRACT

Coronary CTA in Clinical Trials

Cardiac computed tomography angiography (CTA) is a state-of-the-art technology that has emerged as an accurate non-invasive modality to assess for coronary artery disease. With its high spatial resolution, contrast-enhanced CTA enables the evaluation for presence and extent of coronary plaque based on its composition. There have been good correlations between CTA and intravascular ultrasound (IVUS) for the assessment of non-calcified atherosclerotic plaque.[1-3]

Serial quantification of noncalcified atherosclerotic plaque—In a study of 50 patients, the mean annualized plaque volume change in non-calcified lesions in the left main (LM) or proximal left anterior descending (LAD) artery was relative increase of 22% (95% confidence interval 14.7% to 29.7%) per year observed over a mean 17-month interval (range 12 to 25 months), with 28% of patients on a statin [4] The exclusion of the left circumflex and right coronary arteries in this study was explained by lower interobserver variability, likely due to motion-prone artifact.[5] In a two-year serial 64-slice CTA study of 69 patients using a semi-quantitative score based on cross-sectional segments of the LM coronary artery and proximal 40 mm segments of the other coronary vessels (Figure 1), there was significant relative increase in any plaque (12.7%, p=0.01) and non-calcified plaque cross-sectional segments (41.9%, p=0.04) between baseline and twoyea repeat CTA scan, but not for calcified plaque (p=0.2).[6] In histological study, noncalcified plaque is believed to be part of the earlier process of the atherosclerosis process, while calcified plaque is part of the later advanced stages of atherosclerosis, which is less prone to change.[7]

Furthermore, in a small study where 27 patients underwent serial CTA after 1 year treatment with low dose atorvastatin 20 mg, there was a relative 24% reduction in noncalcified mean plaque volume whereas calcium scoring or total plaque burden were unchanged.[8] This, in combination with the constraints of calcified plaque evaluation (i.e. blooming artifact and beam hardening artifact) by CTA, makes noncalcified plaque the ideal plaque morphology to assess for progression or regression of disease, which can be used as a surrogate-endpoint in clinical trials to test the efficacy of novel anti-atherosclerotic therapy. Automated

volumetric methods to quantify non-calcified plaque burden are now available and will enable quick, accurate, and highly reproducible assessment using CTA in large size studies.[9]

CTA features of the vulnerable plaque—Certain CTA features of atherosclerotic plaque (Figure 2) have been described as "vulnerable" with high risk for ACS.[10-13] These features include positive vascular remodeling, spotty calcification, and low attenuation plaques. A remodeling index (lesion diameter/reference diameter) is used to define the presence of positive remodeling, which is when the lesion diameter is >10% larger than reference segment. Low attenuation plaque is a noncalcified plaque with <30 Hounsfield Unit (HU). Spotty calcification is defined as <3mm in size and occupying only one side of the lumen. In an observational study of 1059 patients with suspected coronary artery disease and low annual event rate of 15 ACS (0.8%), the presence of both positive remodeling and low attenuation plaque (n=45) concurred a 23-fold increase in hazard for ACS as compared to those without either features.[13]

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JANUZZI Jim, Boston, USA

Dr. James Januzzi is currently the Roman W. DeSanctis Endowed Distinguished Clinical Scholar in Medicine and Director of the Cardiac ICU at the Massachusetts General Hospital, and an Associate Professor of Medicine at Harvard Medical School. Dr. Januzzi has contributed greatly to the understanding of cardiac biomarker testing in patients with heart disease, where his work with the natriuretic peptides has set international standards for their use in diagnosis, prognosis, and management of patients suffering from heart failure. Additionally, Dr. Januzzi's research group has actively studied many novel biomarkers such as ST2, galectin-3, GDF-15, and highly sensitive troponin in several populations including heart failure, acute coronary syndromes as well as apparently well patients. He has published more than 300 works, has edited two text books on cardiac biomarker testing, and is on the editorial board of numerous scientific journals, including serving as an Associate Editor for JACC: 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 ACC/AHA Clinical Practice Guidelines for Heart Failure.

ABSTRACT

How should Diagnostic and Prognostic Markers Be Studied?

The measurement of biomarkers for diagnosis and prognosis in heart disease has changed the fundamental way that patients are evaluated, and has led to a literal explosion of studies exploring both novel applications of established biomarkers as well as the discovery of newer biological markers.

With the rise in interest in novel biomarkers has come a clear heterogeneity in the approach with which these potentially important tests have been studied, partially due to a lack of guidance as to nominal expectations for the approach for their evaluation. To this point, there is no consensus yet articulated with respect to the minimum expectations for which a new diagnostic or prognostic biomarker should be held to in order to clarify or reject their potential value.

We recently proposed several standards to which novel biomarkers in heart failure should be held during their evaluation (**Table**) (1); these "rules" do not specifically apply to heart failure *per se,* and could thus theoretically serve as a starting point for determining the basic framework upon which the evaluation of novel applications of prior markers or the description of a frankly new biomarker.

1. The method by which a novel biomarker is judged (including and especially when compared to or in combination with other biomarkers) should be thorough: novel tests should be evaluated across a wide range of patients typical of the diagnosis for which it will be applied, and the statistical methods used to evaluate the biomarker (relative to clinical variables as well as other biomarkers) should be contemporary, rigorous, standardized and fair.
2. Measurement of a novel HF biomarker (e.g. in blood, urine or any easy obtainable tissue) should be easily achieved within a short period of time, provide acceptable accuracy and assays for its measurement should have defined biological variation and low analytical imprecision.
3. The biomarker should primarily reflect important (patho) physiological process(es) involved in HF presence and progression; use of biomarkers reflective of disease but originating outside the myocardium is acceptable as long as such a biomarker provides independently useful information involved in the diagnosis, prognosis, progression or therapy of HF syndromes.
4. The biomarker must provide clinically useful information for caregivers (physician, nurses, patient and others) to more swiftly and reliably establish/reject a diagnosis, to more accurately estimate prognosis, or to inform more successful therapeutic strategies. The information from such a biomarker should not recapitulate clinical information already available at the bedside, and must be additional to other biomarkers.

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JARCHO John, Boston, USA, NEJM

John Jarcho is a deputy editor at the New England Journal of Medicine and a cardiologist on the staff of the Brigham and Women's Hospital in Boston, Massachusetts, USA. He attended medical school at the University of Utah and received his training in medicine and cardiology at Brigham and Women's Hospital. His area of clinical interest is heart failure, ventricular assist, and cardiac transplantation.

ABSTRACT

Biomarker studies have proliferated widely, but the actual impact of most such studies on the practice of medicine is modest. One major underlying problem is a lack of clarity (on the part of both investigators and readers) about what biomarker data can be expected to contribute. In many cases, studies merely demonstrate a statistical association between a putative biomarker and a clinical correlate, but the implications of this association are not made explicit. In some cases, there is an expectation that a new biomarker, if found to correlate with disease, will reveal previously unsuspected or unproven aspects of disease pathogenesis; but scientific discovery is achieved by an association study alone. Novel biomarkers may occasionally improve diagnosis, as with high-sensitivity troponin assays, or guide patient management, as has been suggested for assays for natriuretic peptides. By far the most common type of biomarker study in cardiovascular medicine, however, seeks to associate novel markers with cardiovascular risk. The incremental value of novel biomarkers in this setting has typically been quite limited, and it is important when considering the relationship of a novel biomarker to cardiovascular risk to be clear about how large (or small) the increment actually is. Newer statistical methods such as the integrated discrimination index and net reclassification improvement are helpful in discerning the actual prognostic value of a novel biomarker. Even given a substantial increment in predictive value, however, the question remains whether the improvement in prediction thus attained will justify a change in patient management.

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KASKI Juan Carlos, London, GBR

ISCP President, Professor of Cardiovascular Science, Department of Cardiological Sciences, St George's, University of London, United Kingdom.

KHDER Yasser, Boehringer Ingelheim, FRA

Dr Yasser KHDER obtained his medical degree and his speciality in internal medicine from Damascus University, in 1987; subsequently he was graduated as specialist in cardiovascular pathology from Nancy Medical School, France in 1992. Between 1992 and 1996 Yasser worked partial-time as clinical cardiologist. Meanwhile, he also had a partial-time academic research assignment in the National Institute of Health and Medical Research (INSERM). During this period Yasser was successfully graduated as a BSc in clinical pharmacology, an MSc in clinical epidemiology, methods in clinical research and a DSc in human biology from the Nancy University and accomplished several scientific works in the vascular biology arena.

Yasser is working as a Scientific Director Cardiology in Boehringer-Ingelheim, Paris, France since June 2008. Beforehand, Yasser worked 7 years in Novartis Pharma AG, Basel as a Global Phase IV Leader for valsartan, Clinical Team Leader for Aliskeren, Protocol Review Committee Cardiovascular Scientific Director and Global Program Leader for a LCZ696 in hypertension/heart failure.

Before joining Novartis, he worked 5 years in Merck KGaA, where he led several development programs such as bisoprolol in silent myocardial ischemia, nicorandil in cardiac surgery and PCI as well as Na+/H+ exchanger inhibitor at the acute phase of myocardial infarction.

ABSTRACT

Different cardiovascular diseases requiring chronic use of oral anticoagulants (OAC) confer various degrees of predisposition for thrombotic events (hypercoagulability, blood flow abnormalities, presence of an artificial surface or endothelial/vessel wall injury), as well as risk for bleeding. Medical history and concomitant therapy could also influence thrombosis risk, bleeding tendency and risk/benefit ratio of OAC in the target population. Recent clinical trials with new OAC in patients with acute coronary syndromes, atrial fibrillation, venous thromboembolism and patients with artificial heart valve enhanced our understanding with respect to the critical role of the dosing algorithm and dose-selection for the success of Phase 3 trials and success in market place. Ideally, dose-selection of OAC relies on an accumulated body of evidence throughout clinical development (PK in target population, PK/PD relationship, and efficacy and safety data in other populations), as well as, data from well-designed, appropriately powered, dose-finding study in the target population. However, due to a low incidence of thromboembolic and bleeding events, dose finding studies with OAC are scarcely powered to answer all questions related to dose-selection and to provide robust dosing recommendation for Phase 3. Adaptive seamless Phase 2/3 designs enable a clinical trial to be conducted in consecutive stages; based on the data observed in the first stage the most promising dose(s) of the experimental treatment are selected to continue along with the control treatment to the subsequent stages. Traditionally, the same endpoint is used throughout the study and the final analysis incorporates the endpoints which occurred in the same dose-groups in all periods. The main methodological challenge in such a design is maintaining the study integrity and ensuring control of the type I error. Likewise, regulatory bodies' consultation with the aim to get backing of dose-selection is often unworkable in an ongoing study. Moreover, adaptive seamless designs always confer major operational challenges such as frontloading of clinical trial preparations, huge upfront investment in time and resources, anticipation of drug supply needs for different scenarios, regulatory challenges and inability for full consideration of demographic, ethnic and geographic confounding factors which could hardly be appreciated before the start of Phase 2 studies. Clinical indication could also influence the usefulness of adaptive seamless designs; for instance, when endpoints occur after a long observation period in trials comprising long follow up, early decision-making regarding dose-adaptation becomes impractical. Therefore, although conceptually attractive the suitability of adaptive seamless designs for pivotal trials with OAC is debatable in the current regulatory environment; however this approach could be viewed as a useful methodological tool for combining Phase 2 and 3 when surrogate endpoints are used and/or when biomarkers could be trusted for early decision making in Phase 2.

In conclusion: dose-selection is a major development milestone which could determine the future success of OAC in Phase 3. Efforts to shorten drug development by using alternative methodological approaches to conventional drug development carry significant risks and should be considered cautiously on case-by-case basis with full awareness of the related challenges and the fundamental limitations.

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KIEVAL Rob, CVRx, USA

Robert Kieval is the Founder of CVRx, Inc., a company in Minneapolis, MN, USA that has developed proprietary implantable medical technology for the treatment of hypertension and heart failure. Dr. Kieval served as the company's CEO from 2001 to 2006, and has been serving as Chief Technology Officer since that time. In 2006, Dr. Kieval was named an 'Innovator of the Year' by the Minnesota-based journal, Twin Cities Finance & Commerce.

Dr. Kieval has over 20 years of medical device industry experience. His previous positions include Business Development Director at ProtoStar, Inc., and divisional Medical Director at Medtronic, Inc, both in Minneapolis. He received doctorate degrees in Veterinary Medicine and in Physiology from The University of Pennsylvania. He currently holds over 50 U.S. and international patents.

Dr. Kieval serves on the Boards of Directors of CVRx, the Medical Device Manufacturers Association in Washington DC, LifeScience Alley in Minneapolis, Minnesota, and The Center for Large Landscape Conservation in Bozeman, Montana.

ABSTRACT

Therapies that can modulate the Autonomic Nervous System (ANS) hold promise in treating disease conditions such as heart failure, hypertension and others in which autonomic imbalances or inappropriate neurohormonal activation are prominent pathologic features. This is especially true of interventions that can address both sympathetic as well as parasympathetic components of the ANS. The proposed benefits of ANS modulation include sparing of and/or improvements in tissue and target organ function that are expected to translate into functional benefits for patients and ultimately into improvements in patient outcomes.

Mechanistically, the effectiveness of such interventions can be demonstrated by measuring corresponding physiological parameters. These may include indices of sympathetic nervous system activation, such as microneurography recordings of muscle sympathetic nerve activity, and regional or whole-body Norepinephrine spillover. Additionally, and where applicable, these may also include indices of parasympathetic nervous system activity such as heart rate, components of heart rate variability and other measures. Relevant functional and outcomes metrics will depend on the specific disease state being evaluated.

In approaching human clinical investigation of such novel therapies, consideration should be given to the existing standard of care of therapy for the disease under study. Conditions with few or no evidence-based effective therapies may warrant initial clinical evaluation of a new therapy once a reasonable level of safety of the proposed therapy has been demonstrated. In such cases, thresholds for expanding clinical evaluation might be based on continued acceptable safety and demonstration of predicted changes in the relevant physiological parameters. With regard to regulatory approval, outcomes improvements are often the gold standard for new therapies in diseases conditions with therapies that have already been demonstrated to positively impact patient outcomes. However, in conditions with few or no effective therapies, such as heart failure with preserved ejection fraction (HFpEF), consideration should be given to basing initial product approvals on demonstration of functional improvements in patients. Such improvements can have meaningful impacts not only on patient physical and emotional well-being but also on healthcare economics (patients maintaining greater independence, returning to work, etc). Once so established, post-market clinical research with these products can be continued in larger trials focused on outcomes measures.

Most innovations in medical devices happen in smaller companies, often created around just one product. A small company with a single novel therapy and no revenue streams from other products invariably has limited resources with which to complete product development and clinical research. A threshold for new product approval of a novel therapy that is set too high may fatally inhibit investment into a company and could ultimately deprive society of a therapy that might otherwise prove to be highly effective in treating patients. While ideally such economic considerations should not be an influencing factor in evaluation and approval of new products, in reality they play a significant role in determining whether or not a potentially effective new therapy could ever become available to patients.

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KIM Jae, Amgen, USA

Dr. Kim is a Clinical Research Medical Director in Global Development at Amgen where he is the Global Development Leader in the Cardiovascular Therapeutic Area for the AMG 423 (omecamtiv mecarbil) program. He has worked at Amgen for the last 3 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.

KJELDSEN Keld, Copenhagen, DEN

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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.

Supervisor of doctoral thesis and Ph.D.s etc.

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.

Teaching interests: Cardiology, cardiovascular pharmacology, research methodology.

More than 2800 teaching hours for students and doctors.

Officially appointed national examiner for medical students.

Extensive experience as chairman and organizer of educational courses.

No conflicts of interest declared.

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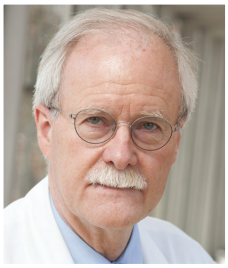
Sverre E. Kjeldsen is Professor and Senior Consultant at the Department of Cardiology, Ullevaal University Hospital, Oslo, Norway and Adjunct Professor of Medicine at the Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA. His main research interest is the pathophysiology, epidemiology and treatment of human hypertension with about 300 full peer-reviewed original articles published. He has served as executive or steering committee member of several large clinical outcome trials in hypertension (HOT, NORDIL, INSIGHT, LIFE, VALUE, ASCOT, ACCOMPLISH, SCAST). Dr. Kjeldsen has been President of the European Society of Hypertension 2005-2007, he is a fellow the American Heart Association - the Council for High Blood Pressure Research, and he is a member of the ESH-ESC 2003, 2007 and 2013 Hypertension Guidelines Committees. Dr. Kjeldsen received his medical degree from University of Oslo in 1979, his PhD degree from University of Oslo, 1984, and he was a medical resident and fellow in Cardiology at Ullevaal University Hospital and Assistant Professor at University of Michigan 1987-89. He organized the 20th Scientific Meeting of the European Society of Hypertension in Oslo, Norway, June 18-21, 2010.



KOENIG Wolfgang, 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 500 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.

ABSTRACT

Identifying new targets: monoclonal antibody inhibitor of PCSK9

LDL cholesterol (LDL-C) is causally involved in the atherosclerotic process and presents the major lipid variable for risk assessment, and statin therapy is guided by different levels of target LDL-C according to the absolute risk of the patient. Statins have revolutionized the treatment of hypercholesterolemia in patients without but also with manifest atherosclerosis and numerous trials since 4S have consistently documented a decrease in cardiovascular

risk associated with decreases in LDL-C. Thus, based on meta-analyses a decrease of LDL-C by 40 mg/dl or approx. 1 mmol/L is associated with a 22% decrease in vascular endpoints. Overtime, lower targets for LDL-C have been defined based on the results of randomized clinical trials but also on evidence from IVUS studies. A most recent large IVUS study comparing the two most potent statins atorvastatin 40 mg and atorvastatin 80 mg showed regression of atherosclerosis in almost 2/3 of the subjects who had achieved LDL-C levels between 60 and 70 mg/dl. A meta-analysis of all available IVUS trials has shown that regression of atherosclerosis seems feasible once the LDL-C target is below 80 mg/dl. However, even the most potent statins in the highest dose (atorvastatin 80 mg or rosuvastatin 40 mg) can reduce LDL-C by a maximum of 55%. Thus, in particular subjects with high baseline levels of LDL-C above 160 mg/dl will not achieve target which, based on most recent guidelines, is 70 mg/dl. The addition of other treatment modalities has several problems, either the yet unproven clinical efficacy of ezetimibe or a number of side effects with other compounds that prevent patients from taking this medication long-term like with bile acid sequestrants or nicotinic acid. Thus, there is still the need for further drugs to more potently lower LDL-C and get patients to target. In 2003, Abifadel et al. have described two families with autosomal dominant hypercholesterolemia which was associated with gain-of-function mutations in proprotein convertase subtilisin/kexin 9 (PCSK9). This initial human experience was shortly followed by animal studies that identified a role for PCSK9 in the posttranslational regulation of the LDL receptor activity. PCSK9 is mainly synthesized in the liver. In the plasma where it binds to LDL receptors it reduces recycling, effectively down-regulating LDL receptor activity and results in increased plasma LDL-C levels. It is known that humans with gain-of-function mutations have higher plasma LDL-C and increased coronary heart disease risk while those with loss-of-function mutations have lower plasma LDL-C and reduced coronary artery disease risk. Thus, PCSK 9 may truly represent an exciting new target for treatment of hypercholesterolemia. Meanwhile several inhibitors of PCSK9 have been developed, either as fully humanized monoclonal antibodies, or using antisense technology or considering small molecules. Initial dose-finding studies have yielded promising results with maximum reduction of LDL-C on top of statin treatment in the order of 60-70%. So far, there are no major safety concerns but still a number of issues related to the long-term efficacy and also potential side-effects that need to be addressed in large phase III clinical trials. Once the efficacy in terms of a further reduction of cardiovascular events has been proven, these compounds will provide an additional therapeutic opportunity primarily in patients with homozygous and heterozygous familial hypercholesterolemia, but also for those with proven statin intolerance. Based on the resulting cost issues, further high-risk subgroups that would greatly benefit from this new therapy have to be carefully defined.

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Stein EA, Mellis S, Yangcopoulus GD et al. Effect of a monoclonal antibody to PCSK 9 on LDL cholesterol. N Engl J Med 2012; 366:1108-18.

Well-established methods for imaging approaches: IVUS and IMT

Vascular imaging enables imaging of atherosclerosis in the arterial wall of blood vessels. It can be employed as surrogate markers of the status and progression of atherosclerosis prior to the occurrence of clinical events and finally enables assessment of treatment effects in controlled clinical trials. A number of imaging methods are available. In the context of clinical trials the two most frequently used methods are intravascular ultrasound (IVUS) as well as measurement of the intima media thickness (IMT) by high-resolution transcutaneous ultrasound. IVUS is an invasive method to detect atherosclerosis even in earlier stages. IVUS has been used in many clinical trials to assess the effects of statins on regression/progression of atherosclerosis but it has also been used for various other treatment modalities. One IVUS derived methodology is virtual histology (VH) which enables not only determination of the plaque volume but gives also a clue concerning the composition of the plaque. This has already been used in clinical trials like the IBIS-2 trial with darapladib, an Lp-PLA_2 inhibitor. Thus, IVUS allows accurate and reproducible assessment of plaque burden in situ. However, it is an invasive technique and, although IVUS is arguable the most direct way of assessing the effect of anti-atherosclerotic therapies on plaque burden, its predictive value for future cardiovascular events has yet to be firmly established.

Carotid IMT (cIMT) can be directly measured by high resolution transcutaneous ultrasound. The carotid artery offers the opportunity as an easily accessible window to gain insight into the systemic process of atherosclerosis. However, the correlation between atherosclerotic changes in the cerebral vascular bed and the coronary as well as peripheral vascular bed are modest. A number of studies over the last 20 years have shown that increased cIMT (>0.9 mm) or changes over time are associated with various cardiovascular outcomes like coronary artery disease and stroke. However, insufficient control for potential confounders has been a point of criticism in many studies. Yet, based on the large number of prospective studies, the 2010 ACCF/ AHA guidelines for measurement of cardiovascular risk in asymptomatic adults has given this measurement a class 2a level of evidence B recommendation for asymptomatic subjects at intermediate risk. In addition, cIMT measurements have also been used in many trials, in particular statin trials, where in almost all of them aggressive therapy was associated with a halt of progression or even regression of atherosclerosis. Other treatment modalities that have been tested in the context of cIMT measurements are nicotinic acid, CETP inhibitors, PPAR agonists and others. In a recent meta-analysis including 41 randomized trials with more than 18,000 participants, regression or slowed progression of cIMT induced by cardiovascular drug therapies did not reflect reduction in cardiovascular events. Finally, the largest meta-analysis to date, covering 16 studies and almost 37,000 participants with a mean follow-up of 7 years, concluded that the association between cIMT progression and cardiovascular risk in the general population remains unproven and that thus no conclusion can be derived for the use of cIMT progression as a surrogate in clinical trials.

In summary, cIMT measurement is a non-invasive procedure, it allows observation of the arterial wall from birth to old age as a continuous variable in both unaffected and affected patients. However, there are several disadvantages namely the ultrasound method is gain-independent, hence plaque morphology is difficult to assess and as seen in meta-analyses the association with atherosclerosis progression and clinical endpoints is still unproven.

Suggested reading:

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KOGLIN Joerg, Merck, USA

Joerg 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 and atrial fibrillation compounds and supporting the development of novel biomarker platforms to further enhance clinical development of cardiovascular drugs.

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

KUPFER Stuart, Takeda, USA

Stuart Kupfer serves as Global Therapeutic Area Head of Cardiovascular Medicine at Takeda Pharmaceuticals International and is based in Deerfield, IL, USA. His areas of research include heart failure, hypertension, thrombosis, diabetes, 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.

LAWRENCE John, BMS, USA

John H. Lawrence, M.D. is Vice President, Cardiovascular Global Clinical Research (GCR) in Research and Development at Bristol-Myers Squibb Company. As Development Lead for the apixaban (Factor Xa inhibitor) Full Development Team (FDT) and co-lead of the Collaboration FDT with Pfizer, he is leading efforts to complete an ambitious set of large Phase 3 trials across several indications. Dr. Lawrence is also a co-lead for the Cardiovascular Disease Strategy Team that is responsible for setting an overarching vision and the strategic objectives for the CV disease area to align internal and external activities worldwide. Prior to joining Bristol-Myers Squibb in 1999, Dr. Lawrence served as an Associate Professor in the School of Medicine and Cardiology Division at the Johns Hopkins University. He attended on the Electrophysiology Service and in the Electrophysiology Laboratory and directed a basic science laboratory investigating properties of cardiac ion channels.

ABSTRACT

Session: Dosing issues
Industry viewpoint
Issues:
1. How to secure the optimal dose (s) for phase III?
2. Different doses, different indications?

My perspective derives from my experience as the Development Lead for the apixaban program at Bristol-Myers Squibb and my comments relate to considerations and decisions made in support of a program involving 9 large Phase 3 trials across 5 potential indications.

Our intention was to select a dose or doses to be studied in Phase 3 with the greatest probability of balancing benefit vs risk for the target population in the trial. This of course depends on how benefit and risk are defined and weighted. We were especially sensitive to bleeding risk considering that physicians and patients have a healthy respect for bleeding and that bleeding is among the most common reasons that an anticoagulant is not used or continued for individual patients.

Phase 3 dosing decisions were informed by 3 Phase 2 dose-ranging trials. However we did not perform a Phase 2 trial in our stroke prevention AF indication as we did not believe that a modest size trial would be sufficiently informative or discriminating on endpoints occurring at an annual frequency of 2% or less.

An important decision made for our first Phase 3 trial and continued throughout our program related to dosing frequency. Since apixaban has a half-life of ~12 hrs, it had the potential to be a once-daily or twice-daily medicine. Our preference for twice-daily dosing was influenced by: (1) an 8-arm Phase 2 trial in VTE prevention where at each of 3 total daily doses, the BID dose had fewer efficacy events than did the QD dose; and (2) our recognition that the gold standard antithrombotic agents all had long pharmacodynamic half-lives and low peak-trough pharmacodynamic effects over a dosing interval. Once we had decided on a dosing frequency of twice-daily, the dosing magnitude was tailored to the target population (eg, a lower dose after orthopedic surgery attempting to avoid excess bleeding relative to enoxaparin; and a higher dose in AF patients considering the efficacy of warfarin and the morbidity of stroke). In our Phase 3 ACS trial, we also considered that the absolute treatment effect was as or more important that the relative treatment effect. Our dose selection efforts were also supported by modeling and population PK analyses.

We considered adaptive designs more than once but each time concluded that by the time an interim assessment was complete including full adjudication of key outcome events, the study would be almost over anyway. Therefore we have not included adaptive designs in our program ... yet. In several trials, we included provisions for early stopping due to very strong efficacy signals and Data Monitoring Committees were empowered to recommend early stopping for excess bleeding.

MAGGIONI Aldo, Florence, ITA

ABSTRACT

Multidisciplinary expert workshop: achievements, challenges and barriers to implementations of the ESC 2012 chronic heart failure

Eurobservational Research Program, the ESC Heart Failure Long Term Registry

Chronic Heart Failure (HF) is associated with a high burden of mortality and morbidity, reduced quality of life and increasing healthcare costs in both US and Europe. Evidence-based medicine represents the most effective means of ensuring that patients receive high-quality care and appropriate pharmacological/non-pharmacological management. With the increased prevalence of chronic HF, there is a concomitant increase in the number of related hospitalizations and, as chronic HF progresses, the risk of acute exacerbation increases. Acute HF is a complex, heterogeneous, clinical syndrome characterized by a rapid onset of signs and symptoms secondary to abnormal cardiac function, and it is often life threatening, requiring urgent therapy. In the United States, a primary diagnosis of acute HF accounts for more than one million hospitalizations each year, with similar numbers suggested for Europe. Despite significant advances in diagnosis and therapy obtained over the past 20 years, patients with HF, specifically those with acute HF, continue to have a poor long-term prognosis. Clinical destabilizations leading to hospitalization are associated with hemodynamic and neuro-hormonal alterations, which can contribute to progressive ventricular dysfunction and dilation, mitral regurgitation, increased wall stress, and progressive myocyte loss as a result of apoptosis and necrosis. Registries and surveys have been conducted in patients with either chronic HF or acute HF but a description of the whole clinical history of patients with HF, including the acute episodes and the consequent changes in clinical conditions and in the management strategies are not available. A registry able to capture all the relevant clinical information of patients with HF, including their acute episodes of decompensation, will enable us to improve our knowledge on epidemiology and outcomes of real world patients with this clinical condition. Further, specific questions of high clinical relevance could be answered using the information collected in the Registry.

The ESC-HF Long-term Registry is a prospective, multicentre, observational study of patients presenting to Cardiology Centres in European countries. Site selection in each participating country will target a sample of hospitals of different levels of complexity from which patients will be recruited, focusing on capturing a broad spectrum of cardiology and HF specialty units regularly following outpatients with HF and admitting patients with acute, pre-existing or new onset HF in order to build-up a network of centres representative of European reality. Up to the end of October 2012, more than 12,500 patients have been enrolled by 27 ESC countries.

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Heart failure trialists workshop. learning from recent trials and shaping the future of heart failure trials.

ASTRONAUT

Hospitalizations for acute heart failure syndromes (AHFS) are associated with high post-discharge mortality and readmission rates in spite of available therapies. Renin–angiotensin–aldosterone system (RAAS) antagonists improve the outcomes in outpatients with heart failure (HF)

and reduced ejection fraction, however these therapies have not been tested in AHFS. Aliskiren is a direct renin inhibitor (DRI) that is known to enhance RAAS inhibition, which may result in improved clinical outcomes in AHFS.

The aim of the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) study is to evaluate the effect of aliskiren on cardiovascular death and HF hospitalizations in AHFS patients. ASTRONAUT is an event-driven trial with an enrolment of 1639 patients hospitalized with worsening chronic HF, a left ventricular ejection fraction ≤40%, and an estimated glomerular filtration rate ≥40 mL/min/ 1.73 m2.

Patients have been randomized in a double-blind fashion to receive aliskiren or placebo, in addition to standard HF therapy. The primary endpoint is the composite of either cardiovascular death or first occurrence of re-hospitalization due to HF.

Given the neurohormonal abnormalities that are present during and after hospitalization for AHFS, it is hypothesized that adding aliskiren to standard therapy will reduce post-discharge mortality and re-hospitalization. The results of the trial will be likely available in the first quarter of year 2013.

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MARTINEZ Felipe, Cordoba, ARG

Professor of Medicine. Cordoba National University (since 1994). Director, Instituto Damic and Fundacion Rusculleda. (since 1993). Former President: Argentinean Federation of Cardiology (2002-2003). Co Chairman: Scientific Program World Congress of Cardiology (2008). Board Member: World Heart Failure Society. Board Member: Intern. Society of CV Pharmacotherapy. Fellow: American College of Cardiology. Member of 23 Steering Com. of International Trials.

129 publications. Invited Speaker in more than 200 International Meetings, in 21 Countries.

ABSTRACT

How future trials may help optimizing benefit to risk ratio: the role of specialist scientific organizations.

Clinical trials are key tools for testing pharmacological agents and devices that could improve human health. Well designed trials have, over the past 50 years, resulted in clear benefits in different areas of Medicine, in particular pharmacological treatments. Researchers, Trialist organisations, National societies (i.e. AHA and ACC), Regulatory Agencies, IRBs and other monitoring bodies have played an important role in improving the design and the implementation of large clinical trials.

In the future all the above may help optimizing benefits and reducing risk in trials.

The benefit-risk ratio analysis establishes whether the possible benefits of a given therapeutic procedure- if successful- outweighs the risks associated with the procedure. Trial design is of paramount importance to provide a clear and accurate answer to this important question.

How can Specialist Scientific Organisations i.e. WHF, ACC, AHA, ISCP and others contribute to this endeavour?

The focus of this presentation is on the possible role that The International Society of Cardiovascular Pharmacotherapy (ISCP) , can play in this context. ISCP is a non-for –profit scientific organisation whose mission is to promote and facilitate strategies to improve cardiovascular health through cooperation among different groups involved in cardiovascular therapy worldwide. ISCP, which has representatives from over 40 countries Worldwide runs educational programs and promotes evidence-based clinical management in all areas of cardiovascular pharmacotherapy with the ultimate goal of improving treatment, clinical outcomes and patient wellbeing.

ISCP has among its ranks world experts in different áreas of cardiovascular knowledge, including trial design and statistics. ISCP has also the potential to run multi-national trials offering a good representation regarding ethnic groups and socio-economic backgrounds Worldwide.

It can also offer logistic support for trial management and training in specific áreas of CV pharmacotherapy.

Future trials in cardiometabolic fields will surely encourage the participation of Scientific Societies to optimize the benefit-risk ratio.

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MASCETTE Alice, NHLBI, USA

Alice M. Mascette, M.D., is a board-certified cardiologist with more than 20 years of clinical experience spanning interventional and outpatient cardiology and medical education. She joined the National Heart, Lung, and Blood Institute (NHLBI) in 2003. While there, Dr. Mascette has served as Senior Clinical Science Adviser and as Chief of the Heart Failure & Arrhythmias Branch in the Division of Cardiovascular Sciences and as the Director of the Clinical and Molecular Medicine Program in the former Division of Heart and Vascular Disease. She has served as Project Officer for the Occluded Artery Trial, the Heart Failure Clinical Research Network, and the CABANA trial, and has overseen the initiation and/or management of two other large clinical trials networks, including the Resuscitation Outcomes Consortium. She has recently been named the Acting Deputy Director of the newly formed NIH Office of Emergency Care Research. She is a fellow in the American College of Cardiology, American College of Physicians, and the American Heart Association. She participates in clinical training at Walter Reed Army Medical Center and holds an adjunct appointment at the U.S. Uniformed Services University of the Health Sciences in Bethesda, MD.

ABSTRACT

"Insights from DOSE and Gaps in Evidence with Diuretic Therapy"

The presentation will highlight recent and future randomized clinical trials of the Heart Failure Clinical Trials Network, funded by the National Heart, Lung, and Blood Institute (U.S.), that examine diuretic administration and volume management in acute heart failure, as well as newer experimental therapies undergoing testing in Europe.

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MASSY Ziad, Boulogne-Billancourt, FRA

Ziad A. Massy MD, PhD, FERA is : Professor of Nephrology and Head of the Division of Nephrology at the Paris Ouset University (UVSQ)- Ambroise Paré Hopsital, Paris, and Director of Research Unit INSERM U-1088 at the UPJV, Amiens, France.

Professor Massy is a current Ordinary Council Member of ERA-EDTA and Chair of the ERA-EDTA International Committee, and is a current member and former co-chairman of the European Uremic Toxins group, Core-member of the EURECAM Working Group Advisory Board–ERA-EDTA, Core-member of the CKD-MBD Working Group Advisory Board–ERA-EDTA, as well as Board member of the Council of EVBO (European Vascular Biology Organisation). In September 2010, he was presented with the Fondation du Rein Award. He is on the editorial boards of Kidney International, NDT, Journal of Renal Nutrition, Journal of Nephrology and Néphrologie et Thérapeutique (where he served as Editor in Chief from 2007 to 2010, and is currently Emeritus Editor). His research areas of special interest include cardiovascular disease, vascular calcifications, hyperlipidemia, uremic toxins, oxidative stress, and chronic renal failure. He has published many original articles, reviews and chapters of books in his domain of interest.

ABSTRACT

The extracellular calcium-sensing receptor (CaR) was first described in the parathyroid gland. Recent studies have shown that the CaR is also expressed in cardiomyocytes, peri-vascular nerves of the adventitia, vascular smooth muscle cells, and endothelial cells, but our understanding of its physiological functions in the cardiovascular system remains incomplete. A variety of studies point to a possible role of CaR activity modulation in the control of cardiovascular functions. A decrease in CaSR expression in cardiac and vascular structures has been demonstrated in several pathologies such as chronic kidney disease (CKD) and diabetes, and incriminated in the pathogenesis of the cardiovascular disturbances associated with these disease states. Recent in vitro and in vivo findings highlight the role of allosteric coactivators of the CaR, shown to interfere with the development of uremia-induced vascular calcification. Calcimimetics can prevent the vascular calcification process by controlling not only the uremia-induced secondary hyperparathyroidism, hypercalcemia and hyperphosphatemia, but also by directly modulating the activity of the CaR at the site of the vessel wall and thereby reduce vascular calcium and phosphate deposition. The mechanism(s) of this protective effect against vascular mineralization are under active evaluation. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis demonstrated that in these patients with moderate to severe secondary hyperparathyroidism, cinacalcet plus low-dose vitamin D sterols may attenuate vascular and cardiac valve calcification. The preliminary results of the Phase 3 EVOLVE(TM) (EValuation Of

Cinacalcet HCl Therapy to Lower CardioVascular Events) trial, which evaluated Sensipar®/Mimpara® (cinacalcet) for the reduction of the risk of mortality and cardiovascular (CV) events among 3,883 patients with secondary hyperparathyroidism (HPT) and chronic kidney disease (CKD) receiving dialysis. The primary endpoint of the study was time to the composite event comprising all-cause mortality or first non-fatal cardiovascular event, including myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event. Although patients in the Sensipar/Mimpara arm experienced numerically fewer composite primary events, the results were not statistically significant, and the trial did not meet its primary endpoint in the intent-to-treat analysis.

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MEBAZAA Alexandre, 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.

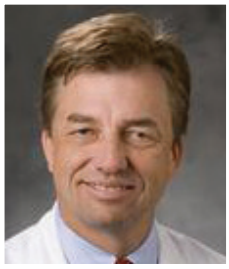
MEHRAN Roxana, New York, USA

Roxana Mehran, MD, FACC, FACP, FCCP, FESC, FAHA, FSCAI, is Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials at the Zena and Michael A. Weiner Cardiovascular Institute at Mount Sinai School of Medicine. Dr. Mehran completed her training in internal medicine at the University of Connecticut, where she was also a Chief Medical Resident, before continuing with Fellowships in Cardiovascular Disease and Interventional Cardiology at Mount Sinai Medical Center. Dr. Mehran is internationally recognized for her work as a clinical trial specialist with complex data analyses and outcomes research within the field of interventional cardiology and for her experience and expertise in working with regulatory agencies to conduct clinical trials.

Her research interests expand from mechanisms of restenosis to treatment and prevention of acute kidney injury in cardiac patients, as well as advancing treatments for acute coronary syndromes and acute myocardial infarction. In addition to founding a highly regarded academic research organization (ARO) within the Cardiovascular Research Foundation, she is also a widely published author and frequent invited speaker at national and international scientific conferences such as American Heart Association, American College of Cardiology, European Society of Cardiology, and EuroPCR.

She has served as Course Co-Director of the annual Transcatheter Cardiovascular Therapeutics (TCT) for the last 13 years.

Dr. Mehran serves on editorial board of multiple peer reviewed journals, including Journal of the American College of Cardiology, Circulation, and Circulation Research. She currently serves on the board of trustees of SCAI, as a member of the Program Committee for the American Heart Association Scientific Sessions, as a member of the board of directors for Harboring Hearts, and as Program Chair for Society of Cardiac Angiography and Interventions (SCAI- WIN (Women in Innovations)) Initiative, and is also the Chief Scientific Officer of the Clinical Trials Center at the Cardiovascular Research Foundation (NYC).



O'CONNOR Christopher, Durham, USA

Dr. O'Connor is the Director of the Heart Center and Division Chief of Cardiology and Clinical Pharmacology at Duke University. He is a Professor of Medicine and Associate Professor in Psychiatry and Behavior Sciences.

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 many 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 on over 20 national and international clinical trials with an extensive record of NIH/NHLBI and industry grants.

His 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 University of Maryland and his Internal Medicine residency and Cardiology Fellowships at Duke University.

PAIS Prem, Bangalore, IND

ABSTRACT

Epidemiology of type 2 diabetes mellitus in Asian Indians:

India has a high prevalence of type 2 diabetes mellitus (DM) and the highest absolute number of diabetic people in the world – 50 million in 2006, estimated to increase to70 million by 2025. While there is no representative national survey, cross sectional studies in different parts of the country have demonstrated an increasing prevalence in both rural and urban areas of the country. An early survey done between 1972 -1975 on 35 000 subjects aged over 14 years reported a prevalence of DM of 2.1% in urban and 1.5% in rural regions; in those aged over 40 years the prevalence was 5.0% and 2.8 % respectively. By 2010 a survey in adults aged over 20 years showed the prevalence to be as high as 13% and 7.8% in urban and rural areas respectively in the state of Tamil Nadu. Prediabetes – IGT and IFG – was an additional 9.8% (urban) and 7.1% (rural). In addition there is a high prevalence of undiagnosed disease.

Burden of complications: Indians with DM are at high risk of CVD especially CAD while risk of PVD seems to be less than in Western populations. In the CUPS study in Tamil Nadu, South India, the prevalence of CAD in diabetics was 21.4% compared to 9.1% in age matched non diabetic controls while the prevalence of PVD was 6.3% and 2.7% in diabetics and nondiabetics respectively. As regards microvascular complications, the prevalence is lower than is reported in other populations including the Chinese population. Overall retinopathy prevalence is 17.6%, microalbuminuria 26.9% and over nephropathy 2.2%.

Risk factors for DM. Risk factors for DM are no different from other populations – obesity, sedenteryness and a family predilection. However risks seem to rise at younger age and at lower BMI than in Caucasians. In addition for a given BMI, Indians have higher total abdominal and visceral fat. The genetic determinants of this are yet to be fully understood.

Risk score. To aid in population screening for DM a non-laboratory based risk scoring system has been developed and validated – the Indian Diabetes Risk Score (IDRS) with a sensitivity and specificity of over 60%.

Management status. Appropriate management and diagnosis of DM is unsatisfactory. In one survey in an urban South India, 68% of detected cases were previously undiagnosed. Of diagnosed patients, only 56% were on treatment and of these 29% had satisfactory control.

Regulatory Issues. Regulatory approval and monitoring of clinical trials in India are currently in a state of flux after an intense and often uninformed media focus. As new systems and regulations are being developed and enforced, approvals for new studies may take six months after submission. With specific reference to trials in DM, studies in subjects aged over 65 years require specific justification for their inclusion as such people are being viewed as a vulnerable population. Recently approval for a long term trial for cardiovascular safety of dulaglutide was denied because the product had not yet been approved for it hypoglycemic effect. The sponsor has reapplied for approval and is awaiting the response.

Suggested Reading

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PFEFFER Marc, Boston, USA

Dr. Marc A. Pfeffer, a graduate of Rockford College in Rockford, Illinois, received both his doctorate in physiology and biophysics and his medical degree from the University of Oklahoma in Oklahoma City.

He completed his internship, residency and clinical fellowship at the Peter Bent Brigham Hospital, Harvard Medical School in Boston.

Dr. Pfeffer is currently the Dzau Professor of Medicine at Harvard Medical School and physician in the Cardiology Division at Brigham and Women's Hospital.

Dr. Pfeffer also serves as medical director of Partners Research and Education Program (PREP).

Dr. Pfeffer has distinguished himself as a translational investigator. Along with his late wife, Dr. Janice Pfeffer, and Eugene Braunwald, M.D., their studies in an experimental model of myocardial infarction first introduced the concept of an insidious deleterious structural remodeling of the impaired ventricle.

They demonstrated in both animals and man that angiotensin converting enzyme (ACE) inhibitors could attenuate these adverse structural and functional changes providing the rationale for the use of these agents in patients experiencing a myocardial infarction.

Pfeffer led the first definitive clinical trial demonstrating that this use could prolong survival and prevent the development of heart failure, which has improved the prognosis of untold numbers of survivors of myocardial infarction.

From his major initial discovery, Dr. Pfeffer's career trajectory has been to lead a number of other key practicechanging, randomized controlled clinical trials. Indeed,a common theme for his substantial contributions has been in the utilization of the randomized controlled trial to enhance the academic mission.

Dr. Pfeffer has had a principal role in several practicechanging clinical trials such as SAVE, CARE, HEART, VALIANT, CHARM and PEACE. He is currently a leading investigator in ARISE, TOPCAT and TREAT.

He is generally considered as a team builder and takes pride in academic advancement of trainees and junior faculty collaborating on the trials, and embedding important mechanistic substudies within the major randomized trials to enhance our understanding of the pathophysiology of the disease processes.

Pfeffer's trials have set high standards for relationships with the sponsors whether industry or NHLBI. He is known for his fairness in data sharing and assisting others in developing meaningful scholarly works from study databases. His studies have improved medical practice and patient prognosis.

Ileana PIÑA, New York, USA

Professor of Medicine & Professor of Epidemiology/ Biostatistics.

Case Western Reserve University.

Graduated Quality Scholar.

Louis Stokes Administration of Veteran's Affairs.

Dr. Piña, a cardiologist and heart failure/transplant expert received her MD at the University of Miami in 1976. She continued her education and received her Masters of Public Health in 2009 after completing a 3 year Fellowship in Quality at the Cleveland VA. She has served as Director of the Exercise Laboratory at the University of Miami, of Heart Failure and Cardiac Rehabilitation at Hahnemann University, of Cardiomyopathy at Temple University and Heart Failure/ Transplantation at University Hospitals Health System at Case Medical Center. Dr. Piña is the Principal Investigator of as well as has participated in many studies focused on improving heart failure and rehabilitation.

She serves as an advisor/consultant to the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health and the Division of Epidemiology which allows her to assist in evaluation and review cardiovascular medical devices, epidemiologic research studies while working with the FDA staff.

Dr. Piña is internationally recognized for her research in rehabilitation and recovery of heart failure patients. She has over 70 publications and is a world-renown speaker on this subject. She has been a recurrent presenter/speaker in the World Congress of Cardiology in Spain, Argentina, Berlin, and Beijing. She is also a National Spokesperson for Go Red for Women and the Heart Truth of Ohio in which she is dedicated to finding out why and coming up with solutions for women who suffer from Heart Disease, which will enable them to live healthier, longer, lives.

In 1995, Dr. Piña established and initiated The National Heart Failure Training Program (N-Heft™) at Case Western Reserve University with Hector Ventura of Ochsner Medical Center in New Orleans, Louisiana which is a program that seeks to educate physicians and other healthcare professionals in best practices for treating heart failure.

Dr. Piña is a recipient of many Outstanding Service Awards and Best Doctors recognition Awards 2010. She sits on numerous committees and chairs countless scientific sessions and meetings and is currently a member for the AHA (American Heart Association) Writing Group Women's Cardiovascular Diseases Prevention Guidelines. She also representes the AHA at the Electronic Health Inititaive (eHI) and AHRQ Task Force on Workplace.

PITT Bertram, Ann Arbor, USA

BERTRAM PITT, M.D.

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.

POCOCK Stuart, London, GBR

Stuart 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. His particular methodologic interests include: standards for the statistical reporting of trials and epidemiological studies, the statistical ethical and organisational principles for data monitoring including early stopping guidelines, the presentation of time-to-event (survival) data, the pros and cons of equivalence trials, and problems of multiplicity in trial reporting eg subgroup analyses, multiple outcomes and covariate adjustment.

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 Cardiovascular Research Foundation in New York and the New England Research Institutes in Boston. He is a frequent lecturer on a variety of clinical trial issues.

PRASAD Krishna, MHRA, GBR

Dr Krishna Prasad, MB BS, MD, FRCP.

Clinical Assessor/ Consultant Cardiologist, MHRA, UK.

Krishna Prasad is currently a Expert Clinical assessor at the MHRA, the UK regulatory Agency and a cardiologist with a special interest in cardiology, cardiovascular disease and personalised medicine. His special areas of interest are Pharmacogenomics/ stratified medicine, drug innovation, CV genetics and risk stratification. Prior to joining the regulatory agency, he worked as an academic and has number of publications. He is a member of the Cardiovascular Working party and of the Pharmacogenomics working parties of CHMP. He is currently the chair of the Pharmacogenomics Working party. As the Coordinator/co-chairs for the ICH E-14 expert group, and as the chair of the QT subgroup of CHMP he has a keen interest in CV risk associated with pharmaceutical intervention including antidiabetics, and others. He has a specific interest in development of regulatory guidance and has continued to work in developing regulatory guidelines and reflection papers in areas of pharmacogenetics/genomics and cardiovascular medicine He is keen on enhancing the interaction between academia, regulators and the other stakeholders.

ABSTRACT

For "Endpoints, pitfalls and regulatory issues. Expectations";

The impact of control of diabetes and CV end points has been debated topic for sometime. Since 2007 this interest has taken an unusual turn due to the controversy relating to the effect of certain glucose lowering agents and their intrinsic effect on CV risk. This has lead to specific demand on long term safety of these agents and the new guidances being issued. All these events raise the fundamental question; what end points to use in diabetes trials and what are likely to be the pitfalls, short and long term. It also raises the discussion point that what should the regulatory requirement be for these glucose lowering agents in treating an inherently vascular disease? Expressing a predominantly personal view of these, the talk will aim to highlight the debate.

RAY Kausik, London, GBR

Professor Kausik Ray, BSc (hons), MBChB, FRCP, MD, MPhil (Cantab), FACC, FESC.

Professor Ray completed his basic medical and cardiology training from Birmingham University and in the West Midlands. He completed his MD in Sheffield University as a British Heart Foundation Junior Fellow, then a post-doctoral fellowship at Harvard Medical School funded by the British Heart Foundation, working in the TIMI group under Professor Eugene Braunwald and Prof Christopher Cannon. He was appointed as aConsultant Cardiologist in 2006 in Cambridge and as a British Heart Foundation Intermediate Fellow at the University of Cambridge, where he also completed a masters in Epidemiology. He was appointed as Professor of Cardiovascular Disease Prevention at St George's University of London in 2010. Professor Ray's research interests focus on cardiometabolic risk and preventative cardiology, cardiovascular epidemiology and clinical trials. He has published some of the most definitive studies to date on lipid lowering and observational epidemiology from the PROVE IT trial and Emerging Risk Factors Collaboration), as well as the relationship between glycaemia and CVD and intensive glycaemic control and CVD outcomes. His work on statins and diabetes risk has led to a change in the FDA label for statins. More recently his work demonstrated the modest effect of aspirin for the primary prevention of CVD outcomes at the expense of excessive bleeding. His work has contributed to national and international guidelines such as EAS, ESC and AHA, ACC. Currently his goals are to develop CVD prevention in the community to reduce CV disease in South West London and establish a biorepository in the unique ethnic mix of south London for identifying novel markers of risk, targets for treatment and clinical intervention trials. Professor Ray has over 100 publications and sits on the editorial board of several medical journals such as the EHJ and is a reviewer for the Medical Research Council and an external expert for NICE.

REDBERG Rita, San Francisco, USA

Rita F. Redberg, MD, MSc, has been a cardiologist and Professor of Medicine at the University of California, San Francisco since 1990. Dr. Redberg is currently the Chief Editor of Archives of Internal Medicine and has spearheaded the journal's new focus on health care reform and "less is more", which highlights areas of health care with no known benefit and definite risks. Her research interests are in the area of health policy and technology assessment focusing on how evidence relates to FDA approval, insurance coverage and medical guidelines and practice, particularly in the area of medical devices.

Dr. Redberg is a member of the Medicare Payment Advisory Commission, which advises Congress on Medicare payment issues. She also served on the Medicare Evidence, Development and Coverage Advisory Committee from 2003-2006 and was reappointed in 2012 as Chair of MEDCAC. Dr Redberg is a member of the California Technology Assessment Forum, the Medical Policy Technology and Advisory Committee, and the Food and Drug Administration Cardiovascular Devices Expert Panel, and is a consultant for the Center for Medical Technology Policy. She gave Congressional testimony four times in 2011 in hearings related to the issue of balancing safety and innovation in medical device approvals Dr. Redberg worked in the office of Senator Hatch and with the Senate Judiciary Committee on FDA-related matters during her tenure as a Robert Wood Johnson Health Policy Fellow, 2003-2006.

Dr. Redberg was a member of the Institute of Medicine's Learning Health Care Committee, which produced the report Best Care at Lower Cost in September 2012. She chaired the AHA/ACC Writing Group on Primary Prevention Performance Measures and is a member of the American College of Cardiology's (ACC) Clinical Quality Committee and serves on the Quality in Technology Work Group. She does comparative effectiveness research, and serves on the American College of Cardiology's Comparative Effectiveness Work Group, represents the ACC on the Institute of Clinical and Economic Review Advisory Board and serves on other ACC Committees, including several on appropriate use of cardiac imaging. She was honored by receiving the Women's Day Red Dress Award in 2011 for her leadership in the area of heart disease in women. Dr. Redberg graduated from Cornell University and the University of Pennsylvania Medical School and has a Master of Science in Health Policy and Administration from the London School of Economics.

ROSENBERG Yves, NHLBI, USA

Yves Rosenberg, M.D., M.P.H.

Dr. Rosenberg 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 from the University of Lyon, France. 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 17 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. The major studies he currently is involved include: ACCORDION (Action to Control Cardiovascular Risk in Diabetes Follow-On Study); FREEDOM (Future Revascularization Evaluation in Patients with Diabetes mellitus Optimal Management of Multivessel Disease). Dr. Rosenberg is also the lead NIH Project Scientist for a randomized trial of genotype-guided warfarin therapy (COAG), the first large scale (1,200 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.

ROSENSON Robert, New York, USA

Robert S. Rosenson, MD, FACC, FACP, FAHA, FNLA,

Robert S. Rosenson, MD, is Professor of Medicine at the Mount Sinai School of Medicine where he serves as Director of Cardiometabolic Disorders.

Dr. Rosenson earned his medical degree from Tulane University in New Orleans, Louisiana. He then served his residency in medicine at Brigham and Women's Hospital in Boston, Massachusetts. He later completed a fellowship in cardiology at the University of Chicago that was followed by an additional year of training as a Research Associate in lipoprotein metabolism.

Dr. Rosenson has been involved in numerous grant-supported research investigations studying the effects of lipid-lowering therapy, hypoglycemic therapy, and antihypertensive agents in inflammation, thrombogenesis, and rheology. He has served as Principal Investigator on a number of NIH-funded research studies, pharmaceutical-sponsored drug trials, and multicenter studies. Recently, he served as Global Principal Investigator of the PLASMA I, PLASMA II and FRANCIS trials. He has been an invited speaker at more than 200 national and international association meetings, grand rounds, and symposia. He has authored nearly a total of 700 journal articles, book chapters, abstracts, and electronic publications for Up To Date Medicine.

ABSTRACT

HDL and Cardiovascular Disease: Risk Marker or Risk Factor?

Low levels of HDL cholesterol (HDL-C) are an established biomarker for the future development of atherosclerosis

and atherosclerotic cardiovascular disease (ASCVD) events in both population-based observational studies and clinical trials of cholesterol-lowering therapies.[1-3] HDL-C are inversely associated with high levels of apolipoprotein B-containing lipoproteins so the risk associated with low HDL-C may be primarily due to excess atherogenic lipoproteins. Thus, it remains uncertain whether HDL-C is a biomarker or risk factor. In a Mendelian randomization study that investigated the association between HDL-C and the risk of myocardial infarction, certain polymorphisms associated with an increase in HDL-C were selected from a genome wide association study (GWAS).[4] The endothelial lipase polymorphism, LIPG Asn396Ser, was associated with higher HDL-C levels, but no différence in the risk of myocardial infarction. However, CETP polymorphisms were associated with higher HDL-C levels and lower LDL-C levels, and reduced risk of myocardial infarction. Based on this analysis, it was concluded that HDL-C is an insufficient biomarker of ASCVD risk.

The reliance on HDL-C, a measure of the cholesterol content of HDL particles, has resulted in an underappreciation of the contribution of the protein-enriched HDL particles in modulating critical atheroprotective functions.[5] Specifically, protein-enriched populations of small HDL particles are associated with anti-oxidant, anti-inflammatory and anti-infective properties of HDL.

Analyses of prospective population studies,[6,7] and clinical trials of lipid modifying-therapies[8,9] have shown that small HDL particle subclasses and total HDL particle concentration are more robust predictors of ASCVD risk than HDL-C. In contrast to endothelial lipase polymorphisms, polymorphisms in the phospholipid transfer protein (PLTP) gene were not accompanied by différences in HDL-C, but they were associated with higher concentrations of small HDL particles and reduced ASCVD risk.[10] These analyses suggest that the proteome of HDL has more important contributions to HDL-associated ASCVD risk than the cholesterol content of circulating HDL particles.

Of the pharmacological agents, peroxisome proliferator activating protein alpha (PPAR-a) agonists increase HDL particle concentration more than HDL-C levels.[11] The heterotypic CETP agent torcetrapib increases the cholesterol carrying capacity of HDL particles without expanding the pool of HDL particles, and thus the importance of these changes will require furhter investigation. It is unlikely that clinical trials with CETP inhibitors will be sufficient to test the HDL hypothesis since these agents reduce LDL-C. The use of multivariate regression analyses will be required to determine whether there is additional benefit from increasing HDL-C beyond that predicted by the reduction in LDL-C.

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Dr. Rossi has served in Editorial Boards including the Journal of Hypertension and currently belongs to the Editorial Board of Hypertension. He is Specialist in Hypertension of the European Society of Hypertension, Fellow of the American College of Cardiology and of the American Heart Association, Member and former Treasurer of the Executive Board of the European Council for Cardiovascular Research (ECCR), Member of the European Society of Hypertension and of the International Society of Hypertension, Coordinator of the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension, Coordinator of the Working Group on Primary Aldosteronism of the Italian Society of Hypertension. In 2004 Dr. Rossi was nominated International Expert of the French INSERM (Institute Nationale de la Santè e Recherche Medicale) and acted as external reviewer for on site visits at French INSERM. From 2006 he acts as grants reviewer for National Research Council of Hong-Kong, the German Ministry of Health, the Austrian Ministry of Health, The Austrian Ministry of Health, The Wellcome Trust Foundation and The French Foundation for Research in Arterial Hypertension (FRHA).

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RUDD James, Cambridge, GBR

I am a HEFCE Senior Lecturer and Consultant in Cardiology at Addenbrooke's Hospital and the University of Cambridge.

My specialty interest is cardiac and atherosclerosis imaging, using CT, MRI and nuclear methods. After medical training in UK and Australia, my PhD at the University of Cambridge described the first use of FDG PET for atherosclerotic plaque imaging and was funded by a British Heart Foundation Clinical Fellowship, under the supervision of Professor Peter Weissberg.

As a post-doctoral researcher, I won a BHF International Fellowship to work with Zahi Fayad at Mount Sinai Hospital in New York. This allowed me to develop further my interest in plaque imaging with novel techniques and targeted contrast agents. In 2007, I returned to Cambridge to complete specialist training as a Cardiologist. I now work on both basic and clinical research projects with collaborators worldwide.

My research is supported by HEFCE, the BHF, the Evelyn Trust, the Academy of Medical Sciences and the NIHR Cambridge Biomedical Research Centre.

I was a British Atherosclerosis Society Young Investigator Finalist in 2003, and the Society of Nuclear Medicine Young Investigator in 2006.

Most recently, collaborative work on NaF PET imaging of atherosclerosis between myself and colleagues in Edinburgh has won the 2011 RSNA Young Investigator Prize and both the Young Investigator and Parmley prize at the 2012 American College of Cardiology meeting.

RUILOPE Luis, Madrid, ESP

Ruilope is Associate Professor of Internal Medicine at Complutense University and Head of the Hypertension Unit at the 12 de Octubre Hospital in Madrid, Spain.

His principal area of interest is hypertension and the kidney.

Professor Ruilope received his MD degree from the University of Madrid and completed his residency and fellowship in nephrology at the Jiménez Díaz Foundation in Madrid. A member of the Scientific Council of the International Society of Hypertension and an International Fellow of the Council of High Blood Pressure Research, Professor Ruilope is on the editorial boards of the Journal of Hypertension, Blood Pressure, High Blood Pressure & Cardiovascular Prevention, Medicina Clinica, Nephrology Dialysis Transplantation, and the Journal of Human Hypertension.

He is a board member of the Spanish Society of Hypertension and a member of the Council on the Kidney in Cardiovascular Disease (American Heart Association). He served on the ISH 2000 International Scientific Program Committee and was a member of the Steering Committee in the studies Hypertension Optimal Treatment (HOT), INtervention aS a Goal In HyperTension (INSIGHT), Study on Cognition and Prognosis in the Elderly (SCOPE), and Controlled Onset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE).

SCOTT Robert, Amgen, USA

Dr Rob Scott is Zimbabwean born and began his career in the industry in 1987 with J&J in South Africa. In 1992 he joined Pfizer and became the Global Therapeutic Head for CV and Metabolic, responsible for the world's largest pharmaceutical product and the largest cardiovascular product – Lipitor and Norvasc. He helped set up the most ambitious evidence based program ever, with over 80,000 patients in long term Lipitor studies alone, six of which have subsequently impacted guidelines. In 2002, he became the Chief Medical Officer and Executive Vice President of R&D of AtheroGenics, an emerging Pharma company in Atlanta Georgia. In 2008, he became the CMO and Head of Development of Cerenis Therapeutics, a micro

biotech in Toulouse, France. In 2010, he joined Amgen, the world's largest Biotech company, as the Global Therapeutic Area Head for Cardiovascular Development. At Amgen, he is leading the development of a new class of lipid lowering drugs which target PCSK9, a protein which regulates the LDL receptor. AMG 145 is a fully human monoclonal antibody to PCSK9 which is currently in a large Phase 2 program involving 1,900 subjects. Dr Scott is the Industry Representative on the FDA Cardiac and Renal Drug Advisory Committee since 2012. During his career, he has been involved with almost every therapeutic area and mode of drug delivery as well as both small molecules and biologics. He developed the first drug combination to simultaneously treat two different disease states - Caduet.

SHINAGAWA Kaori, PMDA, JAP

MD, PhD

Dr. Kaori Shinagawa 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.

ABSTRACT

Dosing issues in clinical development of antithrombotic agents~ from the Japanese regulatory viewpoint

Once patients with non-valvular atrial fibrillation (AF) develop cardioembolic stroke, the outcome is poor. Therefore, prevention of cardioembolic stroke is important in those with AF. But with growing awareness of the limitations of vitamin K antagonists, efforts were and are still underway for the development of novel oral anticoagulants (NOACs), which display better efficacy and safety profile.

The development of NOACs for AF is a challenging area. Because of low event rate and lack of any established surrogate markers for stroke prevention study in patients with AF, it is hard to design formal phase 2 dose-finding study. No long-term pharmacodynamic objective tool for NOAC like PT-INR for warfarin is available. On top of that, ethnic differences are indicated in this area. Japanese are smaller than Caucasians. Some studies indicate ethnic differences related to bleeding risks of antithrombotic agents between Japanese and Caucasians. Japanese guidelines recommend INR levels between 1.6 and 2.6 for elderly patients ages 70 years or more with AF and between 2.0 and 3.0 for patients younger than 70 years. The Japanese care more about bleeding than Americans do. There are issues about weighing risk and benefit. When developing this type of global drug this has to be taken into account.

The recommended clinical dose may be different between Japanese and non-Japanese patients when their pharmacokinetic profiles are markedly different. Therefore, to facilitate drug development and reach regulatory approval in Japan at the same time as approvals overseas, it is recommended to include Japanese patients into a dose-finding study to identify inter-ethnic difference, and subsequently design a confirmatory study.

Should you consider supplying the drug for the Japanese at the different dose compared to the other areas, the consequence is that the clinical trial needs to be conduct among Japanese. Still the results in Japan should be compared to those in western countries.

In the case, the same dose as for non-Japanese patients seems to be acceptable for Japanese patients from the data of early clinical development, a global phase 3 trial including Japanese patients is usually conducted.

However, the number of Japanese patients including these trials is so small, there are several issues you have to take into account when you provide the agent in Japan. There are examples of regulatory agencies of different countries that have looked at the same compound of the same data and come to different conclusions for which dosage should be approved. Conducting global studies makes it of the utmost importance to take into consideration body weight, age, renal function etc and adjust the dosage accordingly to the subgroups.

Pivotal phase 3 study of two dose level of the agent is one of the strategies to provide meaningful information for each area. The situation in Japan is not unique, and all countries should receive information from the global trial that can be used to improve dosage for different target groups.

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Professor Sobhy is Immediate Past President of Egyptian Society of Cardiology and currently the Chairman of the Working Group of Cardiovascular Drug Therapy. He is a Fellow of both the American College of Cardiology and European Society of Cardiology (FACC and FESC, respectively). He is also a Fellow of the Emory University Hospital (USA), a Fellow of the Henry Ford Institute (USA), and a Fellow of the University of Lausanne, Switzerland. Professor Sobhy is a Board Member of the Working Group of Interventional Cardiology, and an active member of the Middle East Focus of the American College of Cardiology being the vice president in 2012, he is nominated as the Governor of Egypt chapter of American College of Cardiology ACC and of various advisory boards.

ABSTRACT

Diabetes in Egypt, Middle East and Asia

Diabetes is one of the major public health problems worldwide due to its chronic nature and severe complications; it's projected to become one of the world's main disablers and killers within the next twenty five years as the number of people with diabetes is increasing in every country.

The global epidemic of Diabetes Mellitus disproportionately affects indigenous and developing populations. Most people with diabetes live in the economically less developed regions of the world in middle and low income countries with the greatest number of people with diabetes between 40 to 59 years of age and this may be due to lack of investment in the treatment of people with diabetes in low-income countries.This difference in diabetes expenditures may explain the high relative mortality rate between low and high income countries.

There are several etiological factors leading to this increase in the prevalence of diabetes, from the most important factors are: ethnicity-based differences, Obesity, Sedentary life style, childhood obesity as well as genetic Susceptibility. These factors are the main reasons that Africa, Middle East & Asia have the highest increasing percentage of diabetes between 2011 and 2030 as estimated from IDF Diabetes Atlas 2011.

According to IDF Diabetes Atlas 2011, the prevalence of Diabetes in Egypt is 15.2%, in Middle East 9.1% and in Asia 8.3%.

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STEIN Kenneth, Boston Scientific, USA

Kenneth Stein, MD, FACC, FHRS, Senior Vice President & Chief Medical Officer Cardiac Rhythm Management.

Ken Stein, MD, FACC, FHRS, is currently Chief Medical Officer and Senior Vice President for Boston Scientific's Cardiac Rhythm Management (CRM) division of the Cardiology, Rhythm and Vascular (CRV) Group.

Dr. Stein held the position of Associate Director of Clinical Cardiac Electrophysiology at Weill Cornell Medical Center and Associate Professor of Medicine at Cornell University prior to joining Boston Scientific in September of 2009.

Dr. Stein currently oversees the development and execution of clinical strategy for the Company's CRM division.

Ken is a Phi Beta Kappa graduate of Harvard College (magna cum laude in Economics), and he earned his MD from New York University School of Medicine. He completed his medical internship and residency at The New York-Presbyterian Hospital/Weill Cornell Medical Center, where he also completed his cardiology and electrophysiology training. He has published widely in the areas of cardiac electrophysiology with special interest in cardiac resynchronization therapy and risk stratification for sudden cardiac arrest.

STROES Eric, Amsterdam, NED

Prof Dr ESG Stroes, MD

Chair Department of Vascular medicine, AMC, Amsterdam.

Over 2 decades now, Stroes has focused at the role of the vessel wall in atherogenesis development. In the late nineties, modulation of endothelial nitric oxide synthase (co-factor suppletion, gene therapy) was a major topic for research,

leading to the first demonstration of the relevance of nitric oxide synthase uncoupling in humans with dyslipidemia.

Since his transition to the AMC, Stroes have focused at lipid disorders in relation to atherogenesis. He has participated in numerous lipid lowering trials using surrogate markers such as intima media thickness (ENHANCE study) and flow mediated dilation. More recently, 3T-MRI has been added as surrogate marker for vascular disease progression.

In addition, novel gene defects contributing to lipid disorders (HDLc, hypertriglyceridemia) have been pursued by collecting autosomal dominant families with these disorders.

In parallel, Stroes has been involved in the development of novel therapeutic moieties for dyslipidemia, such as Lipoprotein lipase gene therapy, apoB antisense, reconstituted HDL-infusion and other novel compounds. Stroes has published more than 195 papers in peer reviewed journals. He currently chairs the department of vascular medicine at the AMC, Amsterdam. The Netherlands.

Honors and awards : Vascular biology science price 1998.

ABSTRACT

Cholesteryl-ester transfer protein inhibition and Cardiovascular prevention:

Viable or Finished?

Cholesteryl ester transfer protein is a pivotal enzyme transferring cholesteryl esters from high-density lipoprotein (HDL) to the apolipoprotein B-containing lipoproteins. Consequently, CETP-inhibitors have the capacity to induce potent HDL-c increases. In analogy to the strong, inverse relation between HDLc and cardiovascular (CV) risk in epidemiological surveys, it has been assumed that pharmacological strategies increasing HDLc would offer significant CV-benefit. However, this concept has been challenged in recent years. Thus, Voight et al (Lancet 2012) recently demonstrated that genetic mechanisms raising plasma HDLc do not seem to lower the risk of myocardial infarction, whereas a clear relation is present between plasma HDLc concentration and CV-risk. These data have challenged the concept that raising plasma HDLc uniformly decreases CV-risk. In parallel, several studies have emphasized the potential importance of HDL functionality, besides HDLc concentration only (Landmesser, JCI 2012).

In this complicated area, CETP inhibition has been tested. The first CETP inhibitor, Torcetrapib, was taken from the market following increased CV-mortality in Torcetrapib-treated subjects, which has in part been attributed to a wide array of non-CETP-dependent adverse effects (Vergeer, Am J Cardiol 2009). Following extensive safety studies, Dalcetrapib, void of any of the adverse effects, was continued in the dal-OUTCOMES study. Yet, a recent interim analysis of this study, has shown a lack of clinically meaningful benefit. Two CETP inhibitors that are much more potent than dalcetrapib, including a potent LDLc lowering effect, are still being tested (anacetrapib, evacetrapib). In the meantime, evidence for CETP inhibition, as well as for HDLc increase in general as a valid target for CV-prevention remains to be established.

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Ulf Landmesser, et al.European Heart Journal (2012) 33, 1712–1715.

TARDIF Jean-Claude, Montréal, CAN

Jean-Claude Tardif, MD, FRCPC, FACC, FCAHS, Director, Montreal Heart Institute (MHI) Research Centre, Professor of Medicine, University of Montreal, University of Montreal Endowed Research Chair in Atherosclerosis.

Jean-Claude Tardif is the Director of the Research Centre at the Montreal Heart Institute and Professor of Medicine at the University of Montreal. Dr Tardif graduated from the University of Montreal with his medical degree in 1987 and completed his training in cardiology and research in Montreal and Boston in 1994. Dr Tardif holds the University of Montreal endowed research chair in atherosclerosis. He is the Scientific Director of the Montreal Heart Institute Coordinating Centre (MHICC) and Chairman of the steering committees of the CIHR-funded Canadian Atherosclerosis Imaging Network (CAIN) and Medical Imaging Trials NEtwork of Canada (MITNEC).

Dr Tardif has authored and co-authored more than 600 articles and abstracts in peer-reviewed publications including The New England Journal of Medicine, The Journal of the American Medical Association, The Lancet, Circulation, the Journal of the American College of Cardiology, the European Heart Journal, Nature Genetics, Genes and Development, the British Journal of Pharmacology, and Cardiovascular Research. In addition, he has written more than 30 book chapters (including in Braunwald's Textbook

of Heart Disease) and has edited several books. He has given approximately 400 invited lectures around the world.

His research covers the molecular and genomic aspects of atherosclerosis and related diseases and also involves animal models, mechanistic and observational clinical studies as well as large international randomized clinical trials. Dr Tardif is or has been the international principal investigator or part of the study leadership of several large clinical trials in the field of atherosclerosis and other cardiovascular diseases including DAL-OUTCOMES-1, DAL-OUTCOMES-2, DAL-PLAQUE-2, ILLUSTRATE, ILLUMINATE, ASTEROID, ALECARDIO, ELIXA, SELECT-CABG, SELECT-ACS, A-PLUS, ERASE, CHI-SQUARE, INITIATIVE, ASSOCIATE, SHIFT and SIGNIFY.

Dr Tardif and his team have created the Beaulieu-Saucier Pharmacogenomics Center at the Montreal Heart Institute and he has created the Center of Excellence in Personalized Medicine (CEPMed), the latter funded by the Network of Centers of Excellence (NCE) of Canada and which is also supported by multiple pharmaceutical and biotechnological companies. He is one of the founding fathers of the Critical Markers Of Disease (CMOD) organization, which focuses on the development and better use of biomarkers (www.cmod.org).

Dr Tardif has won multiple awards during his career, including the Research Achievement Award of the Canadian Cardiovascular Society, the Genesis Award of Bio-Québec (for his outstanding contributions to life sciences) and the Armand-Frappier Award of the Government of Quebec. He was also named scientific personality of the year by La Presse newspaper. Because of his accomplishments, Dr Tardif was named Fellow of the Canadian Academy of Health Sciences (FCAHS).

TAVAZZI Luigi, Cotignola, ITA

Luigi Tavazzi (Cotignola, Italy) is currently Scientific Director of GVM Care& Research - E.S. Health Science Foundation at Maria Cecilia Hospital in Cotignola.

***Other activities:** Prof. Tavazzi is a member of several professional societies. including the European Society of Cardiology (ESC), where he is Chairman of the Oversight Committee of the EURObservational Research Programme, member of the Cardiovascular Round Table, and past-Chairman for the Working Group on Myocardial and Pericardial Diseases of the ESC.*

***Member of executive or steering committees of the following studies:** GISSI -1, GISSI 2, GISSI 3, International t PA SK mortality study, GISSI-Prevention, GISSI-prognosis, ACE-inhibitor myocardial infarction overview, Val-Heft, PREAMI, EARISA, IN-CHF Registry, SEOSI study, PARI-MI, RECOVER, BRING-UP, BRING-Up 2, HHH, SET-UP study, MAHLER , SENIORS, CARE-HF, DESIRE, PROSPECT, TEMISTOCLE, BALANCE, URGENT survey, SHIFT, IGNITE, OPTILINK, OPERA, GISSI-HF, AHF Italian Survey, IN-HF registry, EMPHASIS, HORIZON, CANDHEART, I-PRESERVE, EUROPA, RED-HF, EVEREST, SIGNIFY.*

***Additional activities:** member of the editorial board of several peer reviews journal such as, the European Journal of Heart Failure, author or co-author of 546 publications and 24 books (participation).*

TORP-PEDERSEN Christian, Copenhagen, DEN

ABSTRACT

Cardiovascular medicine and drug development: time for a new trial paradigm

Over several decades the event rates in trials have come down and this is frequently attributed to improved treatment of patients. Nevertheless, epidemiological studies of populations have failed to confirm the dramatic decline of event rates in the diseases studies. Over the same decades the conduct of clinical trials have become increasingly industrialized and the introduction of multiple interests that conflict with the scientific conduct of trials have been introduced. To understand the changes and devise a remedy it is important to examine the two key components of a trial – the patient and the investigator.

A patient generally enters a trial for his own interest rather than a dedication to science. A trial must therefore be designed to increase the interest of patients and keep the burden at a minimum. The study must be explained briefly and accurately in the patient information. Multiple pages of information decrease the interest and also decrease the understanding. The number of physical visits must be kept at a minimum, in particular multiple screening visits during the initiation of a study is a burden. While double blind treatment is important, it should be avoided when the actual treatment is revealed for many patients which is the case when the effect or side effect of treatment are obvious.

The investigator should be put in a situation where the motivation is to include representative patients without bias. This involves the protocol, the monitoring and the contract. A key motivation is a feeling of ownership. Trials are better when run by a moderate group of dedicated investigators rather than hundreds spread over the planet. The paperwork of trials must be kept at a minimum rather than the current maximum where even the work load of signing papers is significant. The contract is most likely the key to better conduct. The current contract design place all uncertainty on the investigator and trials can be postponed or stopped with no warning and no compensation. If a patients discontinues in a trial payment stops motivating investigators only to include patients that are unlikely to stop. Sick patients requiring multiple visits increase the cost for investigators without compensation.

The remedy for trial design can only come about from a combined understanding and effort of industry and authorities. Both parties need to understand not only the principles of double blind but the effect is has on patients. Inclusion of representative patients is as important as other main principles of trial design. Authorities and industry need to accept that international patient representation may hamper good trial conduct. And the contracts need to change so that investigators are encouraged to include representative patients rather than patients that protect the economy of a trial.

VERHEUGT Freek, Amsterdam, NED

Freek W.A, Verheugt, M.D., F.E.S.C. , F.A.C.C., F.A.H.A.(63) 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 VrouweGasthuis (OLVG) in Amsterdam, The Netherlands.

Professor Verheugt graduated from the University of Amsterdam in 1974 and wrote a thesis on platelet and granulocyte 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 medine and Circulation.

He has over 14,000 citations.

His main fields of scientific interest are pharmacological and interventional treatments of acute coronary syndromes and atrial fibrillation.

ABSTRACT

Different doses, different indications for the noacs?

In the last decade oral agents have been developed that directly block the activity of thrombin (factor IIa), as well as drugs that directly inhibit activated factor X (Xa), which is the first component in the final common pathway to the activation of thrombin. These agents (new oral anticoagulants, or NOACs) have advantages in that they do not need monitoring and have a fast onset and offset of action. Another major advantage is that there seems to be no drug tolerance and food interaction and these agents also lack the need of monitoring. They have a fast onset of activity and a relatively short duration of action, which in case of bleeding is another advantage over vitamin K antagonists. On the other hand, some agents need twice daily dosing and the fast offset of action may be problematic in case of poor compliance, e.g. when 2 or 3 doses in sequence are not taken by the patient. Furthermore, there is a relative narrow therapeutic window and an antidote algorithm has not been developed yet, where for warfarin this is well established.

The direct oral thrombin blocker dabigatran as well as the oral Xa blockers rivaroxaban and apixaban have shown to be more effective and safer than warfarin for stroke prevention in atrial fibrillation. Especially, intracranial bleeding is reduced with 50% by the new agents.1 They are also effective and safe in the prevention and treatment of deep vein thrombosis and pulmonary embolism.[1] Dosing here is also important. The NOACS have also been tested in the secondary prevention of acute coronary syndrome.[2] Here the dosing is even more critical. Only low dose rivaroxaban has been successful in reducing mortality and stent thrombosis. High doses of dabigatran and apixaban were associated with a high bleeding rate and were not protective.

Finally, a dose finding trial with the oral thrombin blocker dabigatran in patient recovering from heart valve replacement had to stopped because of excess thrombosis with dabigatran.

Conclusion

From the current trials it has come clear, that oral direct inhibition of the major hemostatic proteins factor IIa or factor Xa is as effective as warfarin in stroke prevention of atrial fibrillation with a safety profile which is more favorable than warfarin. The same has been observed in the prevention and treatment of venous thromboembolism. Their role in secondary prevention after acute coronary syndrome is less clear as of now. The same holds true for thrombosis prevention in carriers of artificial heart valves.

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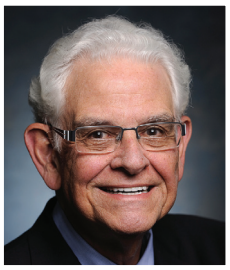
VOORS Adrian, Groningen, GER

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, Associate Professor of Cardiology, 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 23 PhD students. He (co)authored more than 220 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. Finally, he has a large experience in the design and conduction of phase II/III clinical trials in heart failure (principal investigator of 6 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).



WARNOCK David, Birmingham, USA

My focus is on the factors, genetic and environmental that contribute to hypertension and chronic kidney disease. The spectrum extends from basic studies of salt and water transport systems to population based studies of the prevalence of CKD and the association with stroke and heart disease. Another focus is inherited disorders of renal function, with a current emphasis on the renal manifestations of Fabry disease. Over 40 patients with Fabry disease have been identified in Alabama and approximately 20 of them have been started on Enzyme Replacement Therapy.

A major part of current nephrology practice is focused on management of kidney disease in adults with type 2 diabetes, the most common cause of end-stage renal disease in many parts of the world. I participated as an investigator in the phase 2B studies of bardoxolone methy in the treatment of moderate to severe chronic kidney disease in type 2 diabetics, and now serve as a Senior Medial Advisor to Reata Pharmaceuticals in Irving, Texas as bardoxolone methyl undergoes testing in a phase 3 outcome study (BEACON Trial) in partnership with Abbott Pharmaceuticals.

I was born in Parker, Arizona on March 5, 1945. I received a BA degree in 1966 from the University of California at Berkeley and my MD degree in 1970 from the University of California, San Francisco. My clinical training was completed at the University of California, San Francisco, including a 1 year research fellowship with Isidore Edelman, MD in the Cardiovascular Research Institute. Following a fellowship with Maurice Burg, MD at the NIH, I returned to UCSF as a faculty member. I served as the Section Chief at the San Francisco VA Medical Center during the last 5 years of my appointment at UCSF. Following a sabbatical with Bernard Rossier, MD at the Institute of Pharmacology in Lausanne, Switzerland, I was recruited to UAB, and served as the Director of Nephrology from 1988 to 2008. I also served at the Director of the Office of Human Research at UAB from May 1, 2005 through September 30, 2008. I then spent a 6-month sabbatical in 2008 at the College de France in Paris with Frederic Jaisser and Pierre Corvol. My research research interests include acid-base physiology, sodium transport mechanisms, chronic kidney disease, diabetes and kidney disease, and inherited renal diseases.

References:

Effect of Bardoxolone Methyl on Kidney Function in Patients with T2D and Stage 3b–4 CKD. Pablo E. Pergola, Melissa Krauth, J. Warren Huff, Deborah A. Ferguson, Stacey Ruiz, Colin J. Meyer, David G. Warnock. Am J Nephrol 2011;33:469–476 Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes Pablo E. Pergola, M.D., Ph.D., Philip Raskin, M.D., Robert D. Toto, M.D., Colin J. Meyer, M.D., J. Warren Huff, J.D., Eric B. Grossman, M.D., Melissa Krauth, M.B.A., Stacey Ruiz, Ph.D., Paul Audhya, M.D., Heidi Christ-Schmidt, M.S.E., Janet Wittes, Ph.D., and David G. Warnock, M.D., for the BEAM Study Investigators*. N Engl J Med 2011.

WASSERMAN Scott, Amgen, USA

Dr. Wasserman 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. During more than seven years at Amgen, he has taken new therapies, including small and large molecules, from phase 1 through phase 3 clinical development. He set strategy and led numerous critical programs in heart failure, anemia, osteoporosis, fracture healing, and lipid metabolism. Most recently, Dr. Wasserman's efforts focus on the design and execution of global clinical trials in heart failure, hypercholesterolemia, and the emerging cardiovascular pipeline.

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.*

WIERZBICKI Anthony, London, GBR

Dr Anthony Wierzbicki trained at the University of Cambridge and attended clinical school in Oxford. He qualified in 1986. He specialised in metabolic medicine and chemical pathology and after a MRC Research Fellowship at Oxford completed his training in Cardiff and Imperial College London. He was appointed consultant in chemical pathology and director of the lipid unit at Guy's & St. Thomas' Hospitals in 1994 and as honorary Reader (Assistant Professor) in Lipids & Cardiometabolic Disease at the university - King's College London in 2010. His work in the field of atherosclerosis, which comprises more than 280 publications, has led to

appointments as a Fellow of National Association of Clinical Biochemistry (USA) and the American Heart Association. He has been a trustee of HEART-UK and was chairman of this charity's medical and scientific committee (2004-11). He has sat on many UK and European government panels in cardiovascular medicine including NICE and the South East London Cardiac Network. He is the chair of the Lipid Modification Guideline Development Group at NICE. His research interests are in the molecular genetics of hyperlipidaemia, molecular diagnostics, the relationship of lipids to atherosclerosis and the role of lipids in peroxisomal and neurological disease (Refsum's disease).

YARED Nadim, CVRx, USA

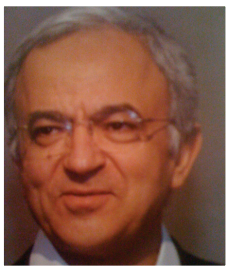
Mr. Yared was hired by CVRx, Inc. as President & CEO in 2006. CVRx is a privately-held company which has developed proprietary active implantable technology for the treatment of hypertension and heart failure.

He had previously served as Vice President and General Manager of Medtronic Navigation, the leading supplier of integrated image-guided surgery products, from 2002 - 2006.

He also held positions with GE Medical for ten years, where he was Vice President of Global Marketing for OEC Medical Systems and Vice President and General Manager of GE's European X-ray business based in Paris.

Mr. Yared has an engineering degree from Ecole Nationale Supérieure des Télécommunications, and an MBA from Insead in Paris, France.

Mr. Yared is a member of the Board of Directors for AdvaMed, Hansen Medical, Intio and CVRx.



ZANNAD Faiez, 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.

In 1981 he served as a Research Fellow at the Clinical Pharmacology Medical Research Unit of Oxford University, UK and in 1986 he obtained his PhD in cardiovascular clinical pharmacology at the University of Lyon. 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 Past Chairman of the Board of the French Society of Hypertension, Fellow of the European Society of Cardiology (ESC), Chairman of the ESC Working group on pharmacology and drug therapy as well as Board member of the ESC Heart Failure Association.

He 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. : Executive Steering committee member: CIBIS 11, RALES VALIANT, RECOVER, MOXCON, EPHESUS,, EVEREST, AURORA, EXAMINE, ASTRONAUT, AXIOM-ACS, SERVE-HF, HF-ACTION; NECTAR-HF, PEARL-HF, ALBATROSS, REMINDRE, FOSIDIAL (Chairman), EMPHASIS-HF (Chairman) Steering Committee membership: APSI, FIRST, CIBIS I, ASCEND-HF, CAPRICORN, Critical Event Committee: CAPRICORN, RESPECT, SCOUT, EchoCRT Data and Safety Monitoring Board HEAAL, ASPIRE.

POSTERS

PROACTIVELY EVALUATING IMPACT OF MODIFIED ELIGIBILITY CRITERIA ON ENROLLMENT AND STATISTICAL POWER IN CARDIOVASCULAR CLINICAL TRIALS

Authors:
LEE, Jae Eun and SUNG, Jung Hye

Co Author:
Lee, Ji-Young

Purpose:
Achieving enrollment goal is essential to conducting a successful clinical trial. When recruitment delayed, modifying the patient inclusion/exclusion criteria may be one of the steps to be considered. However, little is known about guideline to proactively evaluate the effect of modified eligibility criteria on enrollment and study goal. This study is to propose an empirical practice to proactively examine how much enrollment can be increased through the revised eligibility criteria and how the revision impacts the statistical power.

Methods:
Key eligibility criteria used for the evaluation were obtained from 21 clinical trials registered in ClinicalTRials.gov website as of September 28, 2012: age 18-70, low serum vitamin D levels (≥10 and ≤ 25 ng/ml), BMI ≥ 25 kg/m2, well controlled blood pressure (systolic BP<160 mmHg and diastolic BP <105 mmHg), and non-diabetes patients. Search rule for selecting relevant clinical trials was “vitamin D” AND (“Vascular” OR “cardio”) AND “Intervention” AND “deficiency” AND “randomized”. For the illustrative purposes, we started data analysis with 1,543 adults who met the initial eligibility criteria from the National Health and Nutrition Examination Survey data 2005-6. Potential eligible enrollees were estimated for every 1 unit decrease in the BMI low limit cutoff. Statistical power to detect the relationship between serum vitamin D levels and vascular function (cardiovascular disease and CRP) by each low limit of BM cutoff was calculated using multiple regression models (SURVEYREG for binary outcome and SURVEYREG for continuous outcome) after controlling age, gender and race.

Results:
Our analysis revealed that those who met select criteria increased by about 7% with every 1 unit decrease of BMI lower limit: marginal percent change decreased with decrease of BMI lower limit. There was no gender and race difference in percent increase of the potential enrollees, but younger age group was more likely to increase. Statistical power to detect the association of serum vitamin D level with cardiovascular disease (5 % at 25 of BMI low limit and 7 % at 20 of BMI low limit) and CRP (40% at 25 of BMI low limit and 48% at 20 of BMI low limit) went up with decreasing the BMI low limit.

Conclusion:
Our analyses suggested that modifying the BMI low limit cutoff increased potential enrollment as well as statistical power to detect the association between cardiovascular outcome and serum vitamin D level. However, modification increased potential enrollees only in a specific demographic subgroup (<30 year age group in our study), which may cause increased statistical power. This selection bias caused by modification may misguide the results of the clinical trials. Therefore, change of the eligibility criteria should be carefully done after evaluating its impact on the study goal by using the open source data.

INCIDENCE OF THROMBOEMEBOLIC EVENTS IN PATIENTS WITH CATANIA STENT IN FRANCE AND MIDDLE EAST

Authors:
Pr Emmanuel Teiger, Henri Mondor University Hospital, France

Co Authors:

Stephane Champagne, Henri Mondor University Hospital, France
Gauthier Mouillet, Henri Mondor University Hospital, France Jean Armangaud,Clinique St Hilaire, AGEN, France, Sulaiman Gharib,Kasr El-Aini H. Cairo University, Cairo, Egypt,Jean-Paul Faure

Purpose:
Bare metal stents are associated with an increased risk of restenosis whereas drug eluting stents are associated with an increased risk of stent thrombosis requiring long-term dual antiplatelet therapy. However, the long-term dual antiplatelet therapy increases the risk of bleeding. To overcome the concerns, the CATANIA stent (CeloNova BioSciences), a stent coated with an anti-thrombotic and anti-inflammatory polymer has been developed; this stent only requires a one-month dual antiplatelet therapy. This study aims at assessing the long-term efficacy and safety of the CATANIA stent in a large multinational cohort in a real life setting.

Methods:
We are performing an observational, multinational study in France and Middle East (ME) assessing the 1-year incidence of stent thrombosis and major adverse cardiovascular events (MACE) in patients who are receiving the CATANIA stent and following 1 year after stent implantation. The expected size of the cohort is approximately 1300 patients. We did an interim analysis on patients who have completed the 1-year follow-up.

Results:
The study population consisted of 244 patients (73% men, mean age 67.4 years). 86% of patients had cardiovascular comorbidities. Diabetes was reported in 18% of patients. The main clinical indications for coronary-stent placement were

stable angina (40.2%) and myocardial infarction (36.8%). The mean number of treated lesions per patient was 1.37±0.61 with a mean reference vessel diameter of 3.14±0.49 mm and a target-lesion length of 15.7±7.15 mm. Over the 1-year follow-up, one definite subacute stent thrombosis occurred. The cumulative incidence of MACE at 1 year was 7.8%. The cumulative cardiac death and target lesion revascularization (TLR) at 1-year follow-up was 2.8% and 4.3%, respectively. No significant differences in MACE rates were observed according to diabetes status or clinical indication.

Conclusion:
The results of this interim analysis suggest that the CATANIA stent that only requires a one-month dual antiplatelet therapy is safe and effective in a real life setting. This assumption has to be further supported with the final analysis of the entire cohort.

CARDIOPROTECTIVE EFFECT OF AN ORIGINAL SPIROCYCLIC OXINDOLE DERIVATIVE

Author:
Redkin R.G.

Co Author:
Tsubanova N.A., Shtrygol S.Yu.

According to preclinical results, compound R-77-371 in the dose of 5 mg/kg has an evident cardioprotective activity. Based on the myocardial infarction model, the efficacy of compound R-77-371 is equal to that of Mexidol in the dose of 100 mg/kg. The cardioprotective activity of compound R-77-371 confirmed by the ECG indices is related to the potent antioxidant effect of the substance. In addition to cardioprotective effect, compound R-77-371 has an antioxidant and membrane-protective effect based on the acute isoproterenol-induced model.

Purpose:
Achieving enrollment goal is essential to conducting a successful clinical trial. When recruitment delayed, modifying the patient inclusion/exclusion criteria may be one of the steps to be considered. However, little is known about guideline to proactively evaluate the effect of modified eligibility criteria on enrollment and study goal. This study is to propose an empirical practice to proactively examine how much enrollment can be increased through revising eligibility criteria and how the revision impacts the statistical power.

Methods: :
Key eligibility criteria used for the evaluation were obtained from 21 clinical trials registered in ClinicalTRials.gov website as of September 28, 2012: age 18-70, low serum vitamin D levels (≥10 and ≤ 25 ng/ml), BMI ≥ 25 kg/m2, well controlled blood pressure (systolic BP<160 mmHg and diastolic BP <105 mmHg), and non-diabetes patients. Search rule for selecting relevant clinical trials was “vitamin D” AND (“Vascular” OR “cardio”) AND “Intervention” AND “deficiency” AND “randomized”. For the illustrative purposes, we started data analysis with 1,543 adults who met the initial eligibility criteria from the National Health and Nutrition Examination Survey data 2005-6. Potential eligible enrollees were estimated for every 1 unit decrease in the BMI low limit cutoff. Statistical power to detect the relationship between serum vitamin D levels and vascular function (cardiovascular disease and C-reactive protein (CRP) as a potential vascular function mediator) by each low limit of BMI cutoff was calculated using multiple regression models (SURVEYREG for binary outcome and SURVEYREG for continuous outcome) after controlling age, gender and race.

Results:
Key eligibility criteria used for the evaluation were obtained from 21 clinical trials registered in ClinicalTRials.gov website Our analysis revealed that those who met select criteria increased by about 7% with every 1 unit decrease of BMI lower limit: marginal percent change decreased with decrease of BMI lower limit. There was no gender and race difference in percent increase of the potential enrollees, but younger age group was more likely to increase. Statistical power to detect the association of serum vitamin D level with cardiovascular disease (5 % at 25 of BMI low limit and 7 % at 20 of BMI low limit) and CRP (40% at 25 of BMI low limit and 48% at 20 of BMI low limit) went up with decreasing the BMI low limit.

Conclusion:
Our analyses suggested that modifying the BMI low limit cutoff was likely to increase potential enrollment as well as statistical power to detect the association between cardiovascular outcome and serum vitamin D level. However, increase in potential enrollees was greater in a certain demographic subgroup (<30 year age group), which may cause increased statistical power. This selection bias caused by modification may misguide the results of the clinical trials. Therefore, change of the eligibility criteria should be carefully done after evaluating its impact on the study goal by using the open source data.

PATIROMER (RLY5016) LOWERS SERUM POTASSIUM IN SUBJECTS WITH CHRONIC KIDNEY DISEASE AND DIABETES: RESULTS OF THE AMETHYST-DN STUDY

George L. Bakris, MD, FASN[1], Bertram Pitt[2], MD, Jamie Cope, PhD[3], Yuri Stasiv, PhD[3], Patricia A Feeney[4], Alicia Y Toledano[4], Jerry Buysse, PhD[3] and Lance Berman, MbChB[3].

[1]University of Chicago, Chicago, IL, United States; [2]University of Michigan, Ann Arbor, MI, United States; [3]Relypsa, Inc., Santa Clara, CA, United States and [4]Statistics Collaborative, Inc., Washington, DC, United States.

Purpose:
Patients with advanced chronic kidney disease (CKD) are at high risk of hyperkalemia (HK), especially when guideline-recommended renin angiotensin-aldosterone system inhibitors (RAASi) are used. HK limits appropriate dosing of RAASi, thus attenuating cardio-renal protective benefits conferred by the drugs. In the PEARL-HF study, patiromer (previously designated RLY5016), a non-absorbed potassium-binding polymer, prevented HK after 4 weeks of increased spironolactone dosing in a placebo-controlled heart failure trial.

Method:
AMETHYST-DN tested the ability of patiromer to reduce potassium (K+) in subjects with either pre-existing HK (K+>5.0 mEq/L) or HK that developed following a RAASi intensification run-in period of 100mg/d losartan. Due to the inherent risks of HK and daily treatment for up to 1 year in the ongoing long-term maintenance phase, an active polymer control or placebo was unethical and the study was conducted as an open label study. AMETHYST-DN enrolled 306 CKD subjects with T2DM into two K+ strata (S1 = K+ >5.0 -5.5 mEq/L and S2 = K+ >5.5 - <6.0 mEq/L). Mean eGFR was 42ml/min/m2; 49% of subjects had ACR >300 mg/g and 34% had heart failure.

Results:
Approximately 40% of screened patients were enrolled in the study immediately because they were found to have pre-existing HK. Seventy percent of normokalemic subjects at screening developed hyperkalemia following the RAASi intensification run-period within an average of ~2 weeks. Twenty-five percent of these subjects developed a K+ ≥5.5mEq/L. The primary outcome, mean change from baseline in serum K+ (mEq/L) at week 4 or first patiromer dose titration analyzed using a parallel lines ANCOVA model, was -0.47±0.038 ($p<0.001$) in S1 and -0.90±0.076 ($p<0.001$) in S2. Mean serum K+ reduction after a median 2 days of treatment was 0.29±0.03 (S1) and 0.55±0.05 mEq/L (S2). Table 1 summarizes the means and changes from baseline, allowing patiromer titration. No treatment-related SAEs occurred and a low incidence of hypokalemia was observed (2% during the 8 weeks). Adverse events were infrequent and were mild to moderate in severity.

Table 1.

	Stratum 1 ([S1], BL K+ >5.0-5.5 mEq/L)			Stratum 2 ([S2], BL K >5.5+-<6.0 mEq/L)		
	Baseline (n=217)	Week 4 (n=197)	Week 8 (n=185)	Baseline (N=84)	Week 4 (n=70)	Week 8 (n=70)
Mean K+ (SE) (mEq/L)	5.15 (0.02)	4.54 (0.03)	4.59 (0.03)	5.64 (0.04)	4.65 (0.06)	4.52 (0.06)
LS Mean change (SE) (mEq/L)	-	-0,61 (0.03)	-0,55 (0.03)	-	-0.97 (0.06)	-1.10 (0.06)

Conclusions:
Patiromer reduced serum K+ within days of treatment initiation, an effect sustained over two months without significant adverse effects, including hypokalemia.

ECHOCRT - ECHOCARDIOGRAPHY GUIDED CARDIAC RESYNCHRONIZATION THERAPY CLINICAL INVESTIGATION

Authors:
J. Holzmeister, F. Ruschitzka (both University Hospital Zurich, CHE), W.T. Abraham (Ohio State Univ.,USA), J. Singh (Mass. General Hospital, Boston, USA) et al.

Rationale & Objective:
Currently CRT is indicated for HF patients with a wide QRS complex. The EchoCRT trial evaluates the effects of CRT on mortality and morbidity of subjects with HF due to LV systolic dysfunction, already receiving current standard HF medication, with a narrow QRS and echocardiographic evidence of dyssynchrony.

Design:
Randomized, prospective, parallel, double-blinded, multi-center, international trial, regulated by the FDA. 1258 subjects will be 1:1 randomized at approximately 125 sites to detect a 25% risk-reduction between treatment groups with 80% power. EchoCRT is an event driven trial, 381 events are needed to meet the primary endpoint.

Primary Endpoint 1:
Evaluate the effect of CRT=ON vs. CRT=OFF in time to event of combined endpoint of death or first hospitalization for worsening heart failure.

Primary Endpoint 2:
Evaluate the complication-free rate at 6 months for the Lumax HF-T devices in the narrow QRS population.

Key Inclusion Criteria:
ICD indication, NYHA III/IV, OPT, QRS < 130ms, ventricular dyssynchrony (TDI opposing wall delay > 80ms or Speckle-tracking radial strain > 130 ms)

Key Exclusion Criteria:
Bradycardia pacing indication, primary valvular disease, acute CABG PCI or MI, atrial fibrillation, life expectancy < 6 months, renal or liver insufficiency

Organization:
Executive Committee responsible for protocol development and oversight of study conduct, Clinical Events Committee responsible for reviewing all hospitalizations and deaths, DSMB conducting semi-annual safety reviews and interim efficacy analyses, 3 Core Labs for assessments of Echo, ECG and LV lead placement.

Sponsor:
BIOTRONIK SE & Co. KG, Hartmannstr. 65, 91052 Erlangen, Germany”

Ariane SZCZYGIEL MOEYS
Biotronik France

Paclitaxel Releasing Balloon with an Inert BTHC Excipient: Twelve-Month Results on 1'064 Patients of the International DELUX Registry

Gert Richardt,[1] Stefan Hoffmann[2], Huret Bruno[3], Ran Kornowski[4], Ton Slagboom[5], Christoph Naber[6], Bernhard Witzenbichler[7], Kristof Graf[8], Ralph Tölg[1], Béla Merkely[9], Andrejs Erglis[10]

[1]Segeberger Kliniken, Bad Segeberg, Germany [2]Vivantes Klinikum im Friedrichshain, Berlin, Germany, [3]CHP Saint Martin, Caen, France, [4]Rabin Medical Center, Petah-Tikva, Israel, [5]OLVG, Amsterdam, Netherlands,[6]Elisabeth-Krankenhaus Essen, Essen, Germany, [7]Charité Campus Benjamin Franklin, Berlin, Germany [8]Jüdisches Krankenhaus, Berlin, Germany,, [9]Semmelweis Egyetem, Budapest, Hungary, [10]P. Stadins Clinical University Hospital, Riga, Latvia

Pantera Lux[1] Paclitaxel Releasing Balloon

Drug
- Paclitaxel (3.0 µg/mm²)
- Anti-proliferative, lipophilic and allows fast absorption

Excipient
- BTHC[2]
- Keeps paclitaxel in micro-crystalline structure
- Degrades to citric acid and alcohol

Matrix Coating
- Guarantees high bioavailability of paclitaxel at target lesion for rapid drug absorption by tissue

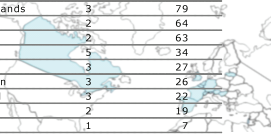
Balloon platform
- Pantera
- Semi-compliant, good deliverability and flexible balloon folds to protect drug

Pantera Lux

[1]Manufactured and distributed by BIOTRONIK
[2]Butyryl-tri-hexyl citrate, known as additive in blood bags to keep the plastic malleable

Enrolment

Country	Sites	Patients
Germany	22	518
France	12	123
Israel	4	82
The Netherlands	3	79
Latvia	2	64
Hungary	2	63
Belgium	5	34
Austria	3	27
Great Britain	3	26
Switzerland	3	22
Spain	2	19
Canada	1	7
Total	62	1064



Lesion Characteristics and Procedural Data

Lesion dimension	
Length (mm)	15.7 ± 7.5
Diameter (mm)	3.0 ± 0.5

ISR lesion: Mehran classification	
Class I (focal)	31.8%
Class II (diffuse intra stent)	47.6%
Class III (proliferative)	13.6%
Class IV (total occlusion)	4.3%

Procedural data	Pre-dilatation	DEB
Pre-dilatation performed	85.3%	-
Balloon diameter (mm)	2.8 ± 0.6	3.0 ± 0.5
Balloon length (mm)	15.7 ± 5.2	20.7 ± 5.9
Inflation pressure (atm)	15.4 ± 4.5	12.7 ± 3.0
Cutting/scoring balloons	20.2%	-
Inflation time (sec)	-	53.1 ± 24.7
Multiple DEB per lesion	-	3.7%
Clinical device success[1]	-	98.2%

[1] Defined as successful deployment of device and <50% residual stenosis of target lesion by visual estimation, without use of a device outside the assigned treatment strategy

Drug REleasing Pantera LUX PTCA Balloon Cathete Registry (DELUX)

Design
Prospective, multicenter, non-randomized, international, non-interventional registry[1] of the Pantera Lux Paclitaxel Releasing Balloon

Objective
Evaluation of the safety and efficacy of the Pantera Lux for coronary arteries in daily clinical practice

Principal Investigator
Ralph Tölg, MD
Herzzentrum Segeberger Kliniken
Bad Segeberg, Germany

ClinicalTrials.gov
NCT01081366

1'064 pts enrolled between April 2010 and April 2011

1'059 pts / 1'137 lesions treated[2] with Pantera Lux

6 M FUP: 1033 pts (97.5%)

12 M FUP: 1004 pts (94.8%)

[1] 10% data source verification, randomly chosen
[2] Pre-dilation recommended with an uncoated balloon at least 5 mm shorter than study device

Baseline Characteristics

Demographics	
Age (years)	66.5 ± 10.7
Male gender	74.6%

Medical history / risk factors[1]	
Hyperlipidemia	83.2%
Hypertension	84.2%
History of MI	51.8%
Smoking (current or previous)	60.4%
Diabetes	34.1%
Renal insufficiency	7.3%
Congestive heart failure	20.6%
History of stroke / TIA	7.8%

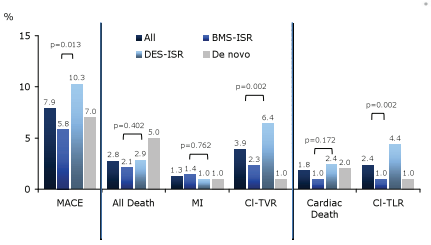
Ischemic status	
No ischemic symptoms	10.6%
Stable angina	49.6%
Unstable angina	32.9%
Documented silent ischemia	6.8%

Target lesion	
Right coronary artery	36.1%
Left main	1.7%
Left anterior descending	38.3%
Circumflex	23.4%
CABG	0.5%

Lesions per patient	
Single lesion	93.6%
Multiple lesions	6.4%

[1] Multiple answers possible

6-Month Clinical Results – MACE[1]



[1] Hierachical MACE, composite of all death, non-fatal MI and clinically driven target vessel revascularization (TVR)
[1] Adjudicated by clinical events committee

Registry Endpoints

Primary Endpoint
MACE[1] at 6 months
- Hierarchical MACE, composite of all death, non-fatal MI and clinically driven target vessel revascularization (TVR)

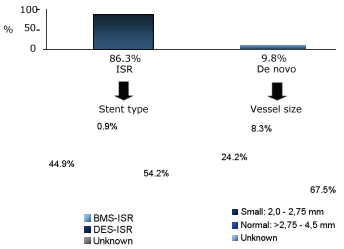
Secondary Endpoints
MACE at 1 & 12 months
- Hierarchical MACE, composite of all death, non-fatal MI and clinically driven target vessel revascularization (TVR)

Clinically driven TVR at 1, 6 and 12 months

Acute success (clinical device & clinical procedure success)

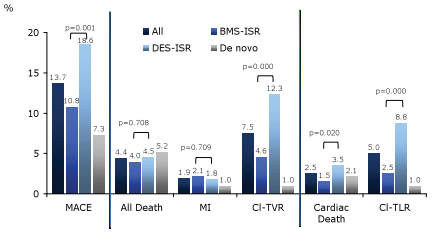
[1] Adjudicated by clinical events committee

Indications[1]



[1] 3.9% unknown

12-Month Clinical Results – MACE[1]



[1] Hierachical MACE, composite of all death, non-fatal MI and clinically driven target vessel revascularization (TVR)
[1] Adjudicated by clinical events committee

Conclusions

- These are the final endpoint data of a registry that enrolled more than 1'000 patients.
- Treatment with the Pantera Lux Paclitaxel Releasing Balloon showed excellent acute to 12-month outcomes in an international real world setting in a challenging ISR population (high rate of DES-ISR and high rate of diffuse in-stent restenosis).
- Efficacy and safety are demonstrated by low revascularization, MI and cardiac death rates and confirm previous clinical results of this device releasing paclitaxel from a BTHC excipient.
- Treatment of DES-ISR seems to be a risk factor for further revascularization. This might be due to the fact that DES were primarily used for lesions with a higher risk for stenosis, while lesions with a lower risk factor have been treated with BMS. Furthermore a DES-ISR constitutes already a failure of local anti-proliferative drug therapy.
- Results are both favourable in the overall population and particularly in the de novo lesion subgroup with MACE rates of 13.7% and 7.3% respectively at 12-month.

Preliminary Data –database not closed yet

SEGEBERGER KLINIKEN HERZZENTRUM

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GENERAL INFORMATION

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On-site registration: 770 euros

Participant registration fee includes:
Access to all scientific sessions
Access to the clinical gathering space
Congress materials
Lunches on November 30th and December 1st 2012
Daily coffee breaks
Congress Dinner on Friday November 30th 2012,
at Espace 56 in the Tour Montparnasse.
Upon invitation only. Please ask at the welcome desk of the Forum

Opening hours of the registration desk
Thursday November 29, 2012: 02:00 pm - 07:00 pm
Friday November 30, 2012: 07:30 am - 07:30 pm
Saturday December 1st, 2012: 07:30 am -07:30 pm

CLINICAL GATHERING SPACE

The Clinical Gathering Space will be located in the Foyer.
Morning coffee breaks will take place in the 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.

TRANSPORTATION

AIR FRANCE
KLM

By plane: "9th global cardiovascular clinical trialists forum"
Code AF 17232AF – validité du 25/11/2012 au 08/12/2012

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