CVCT WASHINGTON, DC US

Maison Française, French Embassy

12th Global Cardio Vascular Clinical Trialists Forum

Course Directors:
Faiez ZANNAD, Nancy - FRA, Bertram PITT, Ann Arbor - USA
Christopher O'CONNOR, Washington, DC - USA

FINAL PROGRAM

DECEMBER 2015

THURSDAY 3 - SATURDAY 5

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GENERAL PRESENTATION

12th Global Cardio Vascular Clinical Trialists Forum

CVCT WASHINGTON, DC US

Over the years, the Global CardioVascular Clinical Trialists (CVCT) Forum has evolved as one of the most exciting meetings for clinical trialists in cardiology. It brings together investigators who are designing clinical studies, industry, regulators from around the world, statisticians, major journal editors and now also payers. It is an ideal platform for exchange on the latest analysis of clinical trials results and what we can expect in the future.

Moreover, CVCT Forum, now in its 12th year, provides an opportunity for us to learn together how to design better trials for the future.

We all bring different perspectives to the table at this meeting. Regulatory affairs and the principles that guide approval of therapies can differ from the principles that guide academicians, researchers and trialists in developing trials. The opportunity to understand why those differences exist and how to meet on common ground can lead to the development of better therapies, and CVCT Forum is ideally placed to be at the forefront of this major contribution.

Next year promises great things, as we continue to expand our reach with satellite CVCT conferences in Singapore and Abu Dhabi.

CVCT Middle East will be held for the first time, 14-15 April, allowing colleagues from the region to come together to discuss trials and unmet needs of their populations. Local and international experts address the specific health characteristics and opportunities for managing studies and medical conditions in the Middle East, with a view to growing local trialists' expertise and investigator networks.

From 15-17 July, we are in Singapore for the 2nd CVCT Asia meeting. There is a high burden of cardiovascular diseases in Asia in comparison with the western world. The epidemic of heart conditions is growing faster in Asia than elsewhere, which, in turn, is reflected in the growth in clinical trials in the region, meaning there is much to discuss and significant opportunities for developing new science.

We look forward to hearing your voice at CVCT meetings and welcome you to this free and collegial exchange of ideas, aiming to help improve treatment prospects for the world's many patients suffering from heart disease

Pr Faiez Zannad *Dr Bertram Pitt* *Dr Christopher O'Connor*

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- **Heart Rhythm Society:** David Van Wagoner (Cleveland, USA)

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Summary

SCIENTIFIC PROGRAM

PROGRAM AT-A-GLANCE

DAY 1 – **THURSDAY 3 DECEMBER 2015**

	12.00 noon 3.00 pm	3.00 pm 3.30 pm	3.30 pm 5.00 pm	5.00 pm 5.30 pm	5.30 pm 7.00 pm
BALLROOM	TRIAL PUBLICATIONS	Coffee break	AUTONOMIC MODULATION	Coffee break	AUTONOMIC MODULATION
THEATRE	HYPER-K		CKD TRIALS		CKD TRIALS

DAY 2 – **FRIDAY 4 DECEMBER 2015**

	8.00 am 10.00 am	10.00 am 10.30 am	10.30 am 12.00 noon	12.00 noon 12.30 pm	12.30 pm 1.30 pm	1.30 pm 3.00 pm	3.00 pm 3.30 pm	3.30 pm 6.00 pm
BALLROOM	DIABETES OBESITY	Coffee break	DIABETES OBESITY		Lunch break	HEART FAILURE	Coffee break	HEART FAILURE
THEATRE	RISK GUIDED ICD		RISK GUIDED ICD	Key Note Lecture Jean-Paul Clozel Actelion		THROMBOSIS		THROMBOSIS

DAY 3 – **SATURDAY 5 DECEMBER 2015**

	8.00 am 10.00 am	10.00 am 10.30 am	10.30 am 12.00 noon	12.00 noon 12.30 pm	12.30 pm 1.30 pm	1.30 pm 3.00 pm	3.00 pm 3.30 pm	3.30 pm 6.00 pm
BALLROOM	BIOMARKER IMAGING BIOSENSORS	Coffee break	BIOMARKER IMAGING BIOSENSORS		Lunch break	ATRIAL FIBRILLATION	Coffee break	ATRIAL FIBRILLATION
THEATRE	ANTIPLATELET THERAPY IN CAD		ANTIPLATELET THERAPY IN CAD	Key Note Lecture Rob Califf FDA		ATHERO-SCLROSIS		ATHERO-SCLROSIS

THURSDAY 3 DECEMBER 2015

BALLROOM

12.00 – 3.00 pm

TRIAL PUBLICATIONS: POINT AND COUNTERPOINT WITH MAJOR JOURNAL EDITORS

Moderators: Robert Golub (JAMA, USA); John Jarcho (NEJM, USA); Stuart Spencer (The Lancet, GBR)

- Over the past several years, a debate has arisen in the academic and research community. Should papers written by researchers be published as open-access? Some suggest papers written by researchers that use public funds should always be made available for free. Others insist that the only way to ensure quality and integrity is to have well respected journals accept only those papers worthy of publication via a peer review process. In some open access journals authors, not readers, pay the price of publication. The existence of this new payment system has encouraged entrepreneurs to set up companies to carry out the intermediate steps, including peer review. Open access has obvious merits but may have a number of limitations.
- Because randomized controlled trials provide the basis for change in clinical practice, concern that delays in publication of clinical trial results may harm patients, threaten originality, and risk results leaking out in the absence of context has prompted several journals to offer expedited publication for selected submissions. However, there are a number of limitations to fast track, expedited review publication.
- It has been suggested that the raw data gathered during clinical research, or an abstracted form of the raw data, should be posted at the time of publication of the primary report of the analyses arising from the data, to allow other investigators to confirm the results and to perform other useful analyses ("open data").
- Although clinical trials generate vast amounts of data, a large portion is never published or made available to other researchers. A number of stakeholders are clearly pushing for open data, and it is already happening in a limited way. Will it become a rule?
- Data sharing could advance scientific discovery and improve clinical care by maximizing knowledge production from data collected in trials. In response to public- and private-sector sponsors in the United States and abroad, the Institute of Medicine (IOM) develops guiding principles and a practical framework for the responsible sharing of clinical trial data.
- Sharing data is in the public interest, but a multi-stakeholder effort is needed to develop a culture, infrastructure, and policies that will foster responsible sharing.
- The European Medicines Agency has already adopted data sharing policies.
- A number of big pharmaceutical firms are also already pursuing open access.
  The website https://clinicalstudydatarequest.com/ provides access to trial data from participating companies including Astellas, Bayer, Boehringer Ingelheim, Eisai, GSK, Lilly, Novartis, Roche, Sanofi, Takeda, UCB and ViiV Healthcare.

Is peer review outdated?
Drummond Rennie (San Francisco, USA)
Stuart Spencer (The Lancet, GBR)

Fast track publication: advantages and dangers
John Jarcho (NEJM, USA)
Valentin Fuster (JACC, USA)

Should publications of trial results be made "open access"?
Zoë Mullan (The Lancet Global Health, GBR)

Should trial data be made "open data"? Is this realistic and useful?
- **Institute of Medicine**
  David DeMets (Madison, USA)
- **Statistician perspective**
  Janet Wittes (Washington, DC, USA)

Investigator/editor viewpoint
Joseph Hill (Circulation, USA)
Patrick O'Malley (JAMA Intern Med, USA)
Filippo Crea (EHJ, ITA)

Medical writing, publication ethics viewpoint: Wendy Gattis-Stough (Expert Medical Communication, USA)

Industry viewpoint: James Revkin (Pfizer, USA)

Regulatory viewpoint: Krishna Prasad (EMA, GBR)

The Forum: Moderated discussion with the audience

Panelists: Filippo Crea (EHJ, ITA); David DeMets (Madison, USA); Valentin Fuster (JACC, USA); Wendy Gattis-Stough (Cary, USA); Robert Golub (JAMA, USA); Joseph Hill (Circulation, USA); John Jarcho (NEJM, USA); Zoë Mullan (The Lancet Global Health, GBR); Gillian Murtagh (Abbott, USA); Christopher O'Connor (Washington, DC, USA); Patrick O'Malley (Vama intern Med, USA); Milton Packer (Dallas, USA); Krishna Prasad (EMA, GBR); Drummond Rennie (San Francisco, USA); James Revkin (Pfizer, USA); Stuart Spencer (The Lancet, GBR); Ken Stein (Boston Scientific, USA); Janet Wittes (Washington, DC, USA)

THEATRE

12.00 – 3.00 pm

CARDIORENAL TRIALS: PREVENTION AND MANAGEMENT OF HYPERKALEMIA

American Society of Nephrology – INI-CRCT – CVCT joint session

Moderators: Patrick Rossignol (Nancy, FRA); Theodore I. Steinman (Boston, USA)

Hyperkalemia, with both ZS9 and patiromer to enter the US and European market, both have several major trials that were recently completed that are the predecessor of a series of acute studies that will encounter ethical challenges of obtaining consent in critically ill vulnerable populations (many of the potential acute hyperkalemia candidates are enrolled in compassionate dialysis programs).

What level of K+ is associated with increased CV risk?
Alexandre Mebazaa (Paris, FRA)

New potassium binding agents: How do these work? Dose-effect relationship, other electrolyte effects: any concern with carry over, overshoot, rebound and other non K effects?
Robert Toto (Dallas, USA)

Importance of Hyperkalemia in the current treatment gap between clinical guidelines and the utilization of Renin-Angiotensin-Aldosterone System Inhibitors: a call to action
Murray Epstein (Miami, USA)

Acute and chronic hyperkalemia therapy future trials: unmet needs and newer opportunities for potassium binding agents

- **At the emergency department and ICU:** Alexandre Mebazaa (Paris, FRA)
- **In chronic heart failure:** Faiez Zannad (Nancy, FRA)
- **In chronic kidney disease:** Mikhail Kosiborod (Kansas City, USA)

Industry perspective: Lance Berman (Relypsa, USA); Henrik Rasmussen (ZS Pharma, USA)
Regulatory perspective: Amany El-Gazayerly (EMA, NED); Aliza Thompson (FDA, USA)

The Forum: Moderated discussion with the audience
Hyperkalemia therapy future trials

Panelists: Lance Berman (Relypsa, USA); Amany El-Gazayerly (EMA, NED); Murray Epstein (Miami, USA); Charles Herzog (Minneapolis, USA); Mikhail Kosiborod (Kansas City, USA); Alexandre Mebazaa (Paris, FRA); Bertram Pitt (Ann Arbor, USA); Henrik Rasmussen (ZS Pharma, USA); Patrick Rossignol (Nancy, FRA); Prabir Roy-Chaudhury (Tucson, USA); Theodore I. Steinman (Boston, USA); Aliza Thompson (FDA, USA); Robert Toto (Dallas, USA); Faiez Zannad (Nancy, FRA)

BALLROOM

3.30 pm – 7.00 pm

AUTONOMIC MODULATION DEVICE THERAPY: SHOULD WE RETHINK THE CLINICAL TRIAL STRATEGY?

American Society of Hypertension – CVCT joint session

Moderators: Murray Esler (Melbourne, AUS); William White (Farmington, USA)

- Several device-based approaches to autonomic nervous system modulation are under investigation for the treatment of resistant hypertension and heart failure. This line of research has evolved from the long-standing recognition that these diseases originate or are worsened by excess sympathetic activity and loss of parasympathetic tone.
- Drug therapies including beta-blockers, alpha-blockers, and centrally acting antihypertensive drugs can modulate these neurohormonal systems, but they are often insufficient to control blood pressure or are limited by side effects or patient non-adherence.
- Technological innovations have produced devices capable of modulating the autonomic nervous system, including renal denervation, carotid baroreceptor stimulation, vagal nerve stimulation, and spinal cord stimulation.
- Proof-of-concept and phase II studies have been completed for many autonomic modulation therapy devices. Pivotal, phase III trials are either ongoing or being planned.
- In Europe, several autonomic modulation therapy devices have received the Conformité Européenne (CE)mark. United States Food and Drug Administration (FDA) evaluation of these devices is ongoing. The need for adequately powered, randomized, controlled studies with longer follow-up has been noted.
- Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
- Approvability pathways and the requirements for reimbursement are still a matter of debate.
- This session is the continuation and update of the previous CVCT Forum discussions with panels of primary investigators of several ongoing trials, along with biostatisticians, National Institutes of Health (NIH) scientists, European and United States regulators, and medical device and pharmaceutical industry scientists and payers representatives about the strengths and limitations of current clinical trials, optimal designs for future trials, approvability of new devices, and considerations for integrating these technologies into practice.

Autonomic modulation therapy: a critical appraisal of recent and ongoing trials in hypertension, heart failure and arrhythmias - recommendations for future trials
Speaker: John Bisognano (Rochester, USA)
Discussant: William White (Farmington, USA)
Discussant: Faiez Zannad (Nancy, FRA)

Need for blinding, placebo effects and regression to the mean
Nancy Geller (NHLBI, USA)

How can we manage dose-response and dose finding? Is preclinical testing sufficient?
Gaetano De Ferrari (Pavia, ITA)

Autonomic modulation readouts for patient selection, dose finding and/or response prediction/monitoring: any simple test?
Murray Esler (Melbourne, AUS)

How important are center-related factors in device/procedure clinical trials, i.e. volume of patients and degree of experience with the procedure?
Felix Mahfoud (Hamburg, GER)

The challenge of continuous technological innovations: how might the results of the ongoing trials apply to novel/future technologies?
Ken Stein (Boston Scientific, USA)

Rethinking future hypertension trials? Insight from the Systolic Blood Pressure Intervention Trial (SPRINT)
William Cushman (Memphis, USA)

Industry viewpoint: Steve Ruble (Boston Scientific, USA); Elizabeth Galle (CVRx, USA)

Regulatory viewpoint: Bram Zuckerman (FDA/CDRH, USA)

Medicare's approach to coverage of clinical trials and evidence development
Tamara Syrek Jensen and Joe Chin (Medicare and Medicaid Services, USA)

The Forum: Moderated discussion with the audience
How can we improve the design of device trials?

Panelists: John Bisognano (Rochester, USA); Joe Chin (Medicare and Medicaid Services, USA); William Cushman (Memphis, USA); Gaetano De Ferrari (Pavia, ITA); Murray Esler (Melbourne, AUS); Elizabeth Galle (CVRx, USA); Nancy Geller (NHLBI, USA); Felix Mahfoud (Hamburg, GER); Steve Ruble (Boston Scientific, USA); Ken Stein (Boston Scientific, USA); Tamara Syrek Jensen (Medicare and Medicaid Services, USA); William White (Farmington, USA); Faiez Zannad (Nancy, FRA); Bram Zuckerman (FDA/CDRH, USA)

THEATRE

3.30 pm – 7.00 pm

CARDIOVASCULAR OUTCOME TRIALS IN CKD PATIENTS

American Society of Nephrology – INI-CRCT – CVCT joint session

Moderators: Vlado Perkovic (Sydney, AUS); Prabir Roy-Chaudhury (Tucson, USA)

- In patients presenting with CV disease, declining renal function has been associated with increased risk for adverse clinical outcomes. In spite of the high risk of adverse events in this population, CKD patients have largely been excluded from or underrepresented in CV randomized controlled trials. This presents a challenging situation for clinicians to make evidence-based medication choices. Important considerations are necessary to balance benefit and the chance for harm.
- Classical CV risk factors do not have the same significance in CKD patients. Some bear an inverse relationship to CV outcomes, a phenomenon called reverse-epidemiology. Also the significance and predictive value of bio-markers needs to be specifically examined in CKD patients.
- Causes and modes of the majority of CV deaths differ and are more frequently attributable to sudden cardiac death and arrhythmia, with relatively few from vasculo-occlusive. The definition of heart failure events is challenging in hemodialysis patients.
- The use of emerging medications that have not been formally studied in patients with CKD is challenging and the extent to which those medications need to be investigated in CKD patients is an important issue to discuss.
- Inclusion and better representation of patients with CKD in CV outcome randomized clinical trials seem to be necessary to accurately assess the risks and benefits of medications in this population
- This is currently being remedied. FIGARO, FIDELIO, FINESSE, ALCHEMIST, PHASE, SAPPHIRE are few examples of CV outcome trials specifically conducted in CKD patients.
- Updating the regulatory guidance and recommendations for the pharmaceutical industry on the design and conduct of pharmacokinetic studies and/or specific CV outcome trials in patients with impaired renal function is another important issue for debate.

Unmet need and challenges related to CV outcomes in CKD and dialysis patients: prevalence, epidemiology and the differing significance of biomarkers
Speaker: Daniel Weiner (Boston, USA)
Discussant: James de Lemos (Boston, USA)

Running CV therapy trials specifically in patients with significant renal impairment, or including CKD patients in common CV therapy trials? Pros and cons and insight from recent and ongoing trials
Speaker: Patrick Rossignol (Nancy, FRA)
Discussant: Bertram Pitt (Ann Arbor, USA)

Cardiovascular endpoints in CKD and hemodialysis trials: are specific event definitions and adjudication needed?
Patrick Rossignol (Nancy, FRA)

Basis to date for providing dosing recommendations in this population: strengths and limitations of using of PK data
Raj Madabushi (FDA, USA)

Sudden cardiac death in the ESRD population: new opportunities for diagnosis and therapy
Prabir Roy-Chaudhury (Tucson, USA)

Recommendations moving forward

- **Investigator viewpoint:** Charles Herzog (Minneapolis, USA)
- **Regulatory viewpoint:** Peter Mol (EMA, NED); Aliza Thompson (FDA, USA)
- **Industry viewpoints:** Michael Hanna (BMS, USA); Christina Nowack (Bayer, GER)

The Forum: Moderated discussion with the audience
Cardiorenal trials - how to move the field forward?

Panelists: Julio Chirinos (Philadelphia, USA); Murray Epstein (Miami, USA); Michael Hanna (BMS, USA); Charles Herzog (Minneapolis, USA); So-Young Kim (Bayer, GER), James de Lemos (Boston, USA); Raj Madabushi (FDA, USA); Peter Mol (EMA, NED); Christina Nowack (Bayer, GER); Vlado Perkovic (Sydney, AUS); Bertram Pitt (Ann Arbor, USA); Patrick Rossignol (Nancy, FRA); Prabir Roy-Chaudhury (Tucson, USA); Aliza Thompson (FDA, USA); Daniel Weiner (Boston, USA); Faiez Zannad (Nancy, FRA)

FRIDAY 4 DECEMBER 2015

BALLROOM

8.00 am – 12.00 noon

DIABETES CV OUTCOME TRIALS

International Society of Cardiovascular Pharmacology – CVCT joint session

Moderators: Felipe Martinez (Cordoba, ARG); Marc Pfeffer (Boston, USA)

- Regulatory guidance allows informing filing of new products supported by interim analysis (e.g. Diabetes or Obesity safety CVOT to demonstrate HR upper CL <1.8). However, to maintain trail integrity for the continuation of the study post approval, this still should be done while keeping the trial team, investigators and patients blinded. Absent of a clear idea of how to bridge these in themselves contradictory objectives, some companies have decided to delay the US filing until the full safety study is finalized (e.g. Sanofi with ELIXA). The FDA recently convened a public input meeting to discuss how to precisely do this risk of interim analyses would be important to discuss.
- The LIGHT trial designed to study the cardiovascular safety of the weight-loss drug Contrave (Orexigen/Takeda Pharmaceutical), a naltrexone/bupropion combination, has been halted after the sponsor publicly released data through a patent and securities filing without knowledge from the study's clinical-trial leaders. This unfortunate episode highlights the challenge of applying the regulatory guidance.
- The consistency of evidence generated since the implementation of the FDA guidance on assessing cardiovascular safety of DM drugs raises the question of whether cardiovascular safety outcome studies remain necessary for all new DM drugs. A more tailored approach might now be appropriate, where the need for cardiovascular outcome studies would be determined by regulators for each individual drug based on its mechanism of action, pre-clinical or phase 1-2 data, and the safety database. Only requiring cardiovascular outcome safety trials when there is suspicion or a signal of an adverse effect seems reasonable given the number of recent studies that have demonstrated non-inferiority and the resources and time involved in conducting these large-scale trials.
- In CV safety trials, the MACE composite trial endpoint capturing mortality and morbidity have substantial room for improvement. Should heart failure events be captured in the primary endpoint? Should components be weighted? How to determine whether to capture first events versus total events (first and recurrent)? Which other components should be considered (e.g. hospitalization-equivalent outpatient visits for HF, etc.)
- The question arises the guidance should be updated since the several first Diabetes CV safety studies have shown no increase in CV mortality or morbidity. How to readdress the question whether glucose lowering reduces CV M&M (trial options, patient populations, etc.)?
- Importantly, with EMPA-REC OUTCOME trial, for the first time ever, a type 2 diabetes drug is shown to improve survival and prevent CV outcome in a population of diabetics with established heart disease, suggesting that the way HbA1c is lowered may be important. Additional pharmacological effects may also play a role. The full results of this disruptive trial will be examined in details in this session. Interpretation and consequences on clinical practice and the future of diabetes trials will be discussed.

Diabetes CV safety trials: learnings and recommendations - review of SAVOR, EXAMINE, TECOS, and ELIXA Marc Pfeffer (Boston, USA)

The EMPA-REG OUTCOME trial

- **Rationale and study design:** Hans Juergen Woerle (Boehringer Ingelheim, GER)
- **Survival MACE and heart failure findings:**
  Speaker: Uli Broedl (Boehringer Ingelheim, GER)
  Discussant: Faiez Zannad (Nancy, FRA)
- **Microvascular findings:** Hans Juergen Woerle (Boehringer Ingelheim, GER)
- **Implication for the patients the physicians and the trialists:** Marc Pfeffer (Boston, USA)

CV safety trials: Seeing the trees for the forest - are we losing the prospect for CV protection? John Cleland (London, GBR)

General methodological issues with FDA-guided CV safety trials: Stuart Pocock (London, GBR)

Interim analysis during pivotal studies
Speaker: Steven Nissen (Cleveland, USA)
Discussant: Nancy Geller (NHLBI, USA)

Use and misuse of on-off treatment analyses
Janet Wittes (Washington, DC, USA)

Industry viewpoint: Mads Engelmann (Novo Nordisk, DEN); Stuart Kupfer (Takeda, USA); Christina Stahre (AstraZeneca, SWE)

Regulatory perspective: Kristina Dunder (EMA, SWE); Jean-Marc Guettier (FDA, USA); Norman Stockbridge (FDA, USA))

The Forum: Moderated discussion with the audience
Diabetes and obesity CV safety trials: how to move the field forward?

Panelists: Uli Broedl (Boehringer Ingelheim, GER); Luther Clark (Merck, USA); Kristina Dunder (EMA, SWE); John Cleland (London, GBR); Mads Engelmann (Novo Nordisk, DEN); Nancy Geller (NHLBI, USA); Jean-Marc Guettier (FDA, USA); Stuart Kupfer (Takeda, USA); Felipe Martinez (Cordoba, ARG); Steven Nissen (Cleveland, USA); Marc Pfeffer (Boston, USA); Stuart Pocock (London, GBR); Jeffrey S Riesmeyer (Lilly, USA); James Smith (FDA, USA); Christina Stahre (AstraZeneca, SWE); Norman Stockbridge (FDA, USA); Colette Strnadova (Health Canada, CAN); Janet Wittes (Washington, DC, USA); Hans-Juergen Woerle (Boehringer Ingelheim, GER); Faiez Zannad (Nancy, FRA)

THEATRE

8.00 am - 12.00 noon

THE TRIAL ROADMAP FOR RISK GUIDED ICD THERAPY

Heart Rhythm Society – CVCT joint session

Moderators: Jeffrey Goldberger (Chicago, USA); Milton Packer (Dallas, USA)

- ICD therapy has proven effective in preventing sudden cardiac death (SCD) in patients with low EF and a variety. However, within the patients with an impaired LVEF patients can be identified who may not benefit from an ICD implantation.
- On another hand, other populations have high risk of SCD independently from LVEF, and are yet to be identified by risk markers.
- In addition, ICD implant and care is not affordable in many regions.
- Remote monitoring of implanted devices may provide novel data for better understanding the factors promoting ectopy and for assessing arrhythmia burden. How do we best utilize remote monitoring?
- Optimizing risk stratification and appropriately triaging individual patients to these invasive options to improve clinical outcomes remains a clinical challenge.
- Markers of autonomic tone, cardiac repolarization, LV remodeling, fibrosis and scarring are candidates for a better discrimination of patients at risk versus not at risk of SCD.
- Risk prediction is primarily based on well-conducted prospective observational studies. However, few actionable markers have been validated so far.
- Certain populations such as patients with CKD, diabetes or LVH/preserved EF may have different risk bioprofiles and should be analyzed separately in risk prediction studies.
- The most robust evidence for a direct impact of a test on overall health derives from a properly designed randomized comparative clinical study showing meaningful benefit for patient outcomes from test-guided care compared to usual care.

The roadmap for risk guided ICD therapy
Jeffrey Goldberger (Chicago, USA)

Risk-guided strategy trials

- **Omics based risk stratification. PROSE-ICD:** Gordon Tomaselli (Baltimore, USA)
- **Abnormal repolarization alternans (TWA), impaired heart rate turbulence (HRT)**

  REFINE-ICD: Derek Exner (Calgary, CAN)

  PREDICTION: Johannes Brachmann (Coburg, GER)
- **MIBG Adreview imaging: ADMIRE-ICD** Faiez Zannad (Nancy, FRA)

Ongoing observational risk prediction studies

- **Genetics, biomarkers and MRI imaging: pre-DETERMINE:** Christine Albert (Boston, USA)
- **Using remote monitoring data from implanted devices:** David Slotwiner (New York, USA)

Other risk categories eligible for ICD trials

- **Diabetes post MI patients. MADIT-SICD:** Valentina Kutyifa (Rochester, USA)
- **Post MI preserved EF:** Konstantinos Gatzoulis (Athens, GRE)
- **End stage renal disease:** Alfred Buxton (Boston, USA)

Industry viewpoint: Jean-Claude Provost (GE Healthcare, GBR); Ken Stein (Boston Scientific, USA)

Regulatory viewpoint: Angeles Alonso (EMA, GBR), Mitchell Shein (FDA, USA)

Medicare's coverage process: Tamara Syrek Jensen and Joe Chin (Medicare and Medicaid Services, USA)

The Forum: Moderated discussion with the audience
How to overcome methodological, design, operational and regulatory challenges for risk-guided ICD therapy?

Panelists: Christine Albert (Boston, USA); Angeles Alonso (EMA, GBR); Johannes Brachmann (Coburg, GER); Alfred Buxton (Boston, USA); Joe Chin (Medicare and Medicaid Services, USA); Gaetano De Ferrari (Pavia, ITA); Derek Exner (Calgary, CAN); Konstantinos Gatzoulis (Athens, GRE); Jeffrey Goldberger (Chicago, USA); Valentina Kutyifa (Rochester, USA); Milton Packer (Dallas, USA); Jean-Claude Provost (GE Healthcare, GBR); Mitchell Shein (FDA, USA); David Slotwiner (New York, USA); Ken Stein (Boston Scientific, USA); Tamara Syrek Jensen (Medicare and Medicaid Services, USA) Gordon Tomaselli (Baltimore, USA); Faiez Zannad (Nancy, FRA)

12.00 noon - 12.30 pm
KEY NOTE LECTURE
DRUG DEVELOPMENT FOR ORPHAN CARDIOVASCULAR DISEASES: A VIEW FROM THE INDUSTRY
Jean Paul Clozel, CEO – Actelion Pharmaceutical, CHE

BALLROOM

1.30 pm – 6.00 pm

PHENOTYPING HEART FAILURE – IS PRECISION MEDICINE THE WAY FORWARD?

Heart Failure Society of America – CVCT joint session

Moderators: Christopher O'Connor (Washington, DC, USA), Bertram Pitt (Ann Arbor, USA)

- There are but a few areas in medicine where progress has been as remarkable as that observed with HF therapy over the last three decades. In chronic HF with reduced ejection fraction (HFREF), the cumulative mortality benefit of evidence-based therapy translates to a three-fold decrease in death rate.
- However, progress has been consistent only for chronic HFREF. In acutely decompensated HF and HF with preserved ejection fraction (HFPEF), despite a reasonable number of trials, none of the therapies tested to date have definitively proven to be effective.
- So far, driven by a trialists' approach, clinically actionable classifiers of HF are limited to ejection fraction (EF), i.e. HFREF and HFPEF and chronic and acute HF. Heart rate and LBBB are also classifiers which guide lifesaving therapies, respectively, ivabradine and CRT.
- A disruptive strategic approach is based on combining knowledge based on underlying mechanisms, hemodynamic, omics and imaging bioprofiling, co-morbidities to define mechanistically relevant and clinically actionable bioprofiles.
- This session explores the potential of generating new HF classifiers with the ultimate aim of improving patient outcomes using mechanistically targeted therapies.

Phenotyping heart failure: helpful new tools for patient selection in trials?

- **Phenotyping heart failure:**
  Speaker: Michael Felker (Durham, USA)
  Discussant: David Kao (Aurora, USA)
- **Diabetes HF phenotype(s):**
  Brian Lindman (St Louis, USA)
- **The pulmonary hypertension phenotypes**
  Stephan Rosenkranz (Cologne, GER)

The right drug for the right patient: how to select mechanistically phenotyped patients for bio-targeted therapies?

- **LCZ 696 trial program, may change the landscape of future HF trials:** Milton Packer (Dallas, USA)
- **Ivabradine crosses the Atlantic: is this good enough?** Jeffrey Borer (New York, USA)
- **Could finerenone beat eplerenone? Results from ARTS-HF trial and perspectives with FINESSE:** Bertram Pitt (Ann Arbor, USA)
- **Cyclic GMP activators and stimulators (Vericiguat):** Carolyn Lam (Singapore, SGP)
- **Endothelin antagonists and Future design of clinical trials in pulmonary hypertension** Andrew Peacock (Glasgow, GBR)
- **Mitochondrial protectants (Bendavia):** John Cleland (London, GBR)
- **Levosimendan**: Alexandre Mebazaa (Paris, FRA)
- **Cardiac myosin activation**: John Teerlink (San Francisco, USA)

How best to design a personalized medicine trial? What can be learnt from oncology trialists?
Richard Simon (NCI, NIH, USA)

Are heart failure trial investigators ready for it? Insight from the NHLBI heart failure networks
Monica Shah (NHLBI, USA)

Translational science perspective: Joseph Hill (Dallas, USA)

Industry viewpoint: James Carr (Stealth Peptides, USA); Fady Malik (Cytokinetics, USA)

Regulatory viewpoints: Angeles Alonso (EMA, GBR), Norman Stockbridge (FDA, USA)

The Forum: Moderated discussion with the audience
Rethinking trial design and regulatory pathway to meet the precision medicine agenda in heart

Panelists: Kirkwood Adams (Chapel Hill, USA); Angeles Alonso (EMA, GBR); Jeffrey Borer (New York, USA); James Carr (Stealth Peptides, USA); John Cleland (London, GBR); Jean-Paul Clozel (Actelion, CHE); Michael Felker (Durham, USA); Mona Fiuzat (FDA, USA); Karen Hicks (FDA, USA), Joseph Hill (Dallas, USA); James Januzzi (Boston, USA); David Kao (Aurora, USA); Mark Kowala (Lilly, USA); Carolyn Lam (Singapore, SGP); Brian Lindman (St Louis, USA); Olivier Madonna (Quantum Genomics, FRA); Fady Malik (Cytokinetics, USA); Alexandre Mebazaa (Paris, FRA), Gillian Murtagh (Abbott, USA); Christopher O'Connor (Washington, DC, USA); Milton Packer (Dallas, USA); Andrew Peacock (Glasgow, GBR); Ileana Piña (New York, USA), Marc Pfeffer (Boston, USA); Bertram Pitt (Ann Arbor, USA); Lothar Roessig (Bayer, GER), Stephan Rosenkranz (Cologne, GER); Sebastien Roux (Actelion, CHE); Monica Shah (NHLBI, USA); Richard Simon (NCI, NIH, USA); Norman Stockbridge (FDA, USA); John Teerlink (San Francisco, USA); Janet Wittes (Washington, DC, USA); Faiez Zannad (Nancy, FRA)

THEATRE

1.30 pm – 6.00 pm

THROMBOSIS TRIALS: NEW FRONTIERS AND SAFETY CHALLENGES

Moderators: Ken Borow (Bryn Mawr, USA); Freek Verheugt (Amsterdam, NED)

Non-valvular atrial fibrillation and stroke trials: who should be treated?
Elaine Hylek (Boston, USA)

How should one decide when to use an anticoagulant, ablation therapy, or a LAA closure device?
David Slotwiner (New York, USA)

Should NOAC dose be adjusted on exposure (drug blood level) or pharmacodynamics (coagulation test)?
Paul Reilly (Boehringer Ingelheim, USA)

The twist on efficacy vs. safety: going patient specific?
Roxana Mehran (New York, USA)

The National Medication Safety, Outcomes and Adherence Program (NMSOAP) study of real world comparative effectiveness of NOACs and Warfarin
Ken Borow (Bryn Mawr, USA)

Antidote trials and how will reversal agents impact use of NOACs? Freek Verheugt (Amsterdam, NED)

Regulatory perspective:

- **FDA/CDER perspective:** Robert Temple (FDA, USA)
- **FDA/CDRH perspective:** Andrew Farb (FDA, USA)
- **EMA perspective:** Antonio Gómez-Outes (EMA, ESP)

Industry perspective: Pete DiBattiste (Janssen, USA); Michele Mercuri (Daiichi Sankyo, USA); James Rusnak (Pfizer, USA);

The Forum: Moderated discussion with the audience
Benefit/risk issues

Panelists: Ken Borow (Bryn Mawr, USA); Joe Chin (Medicare and Medicaid Services, USA); Pete DiBattiste (Janssen, USA); Andrew Farb (FDA, USA); Antonio Gómez-Outes (EMA, ESP); Michael Hanna (BMS, USA); Elaine Hylek (Boston, USA); Cecilia Linde (Stockholm, SWE); Raj Madabushi (FDA, USA); Michele Mercuri (Daiichi Sankyo, USA); Roxana Mehran (New York, USA); Paul Reilly (Boehringer Ingelheim, USA); James Rusnak (Pfizer, USA); David Slotwiner (New York, USA); Tamara Syrek Jensen (Medicare and Medicaid Services, USA); Robert Temple (FDA, USA); Freek Verheugt (Amsterdam, NED)

SATURDAY 5 DECEMBER 2015

BALLROOM

8.00 am - 12.00 noon

USE IN TRIALS AND IN CLINICAL PRACTICE OF BIOMARKERS AND BIOSENSORS

INI CRCT – GREAT network – CVCT joint session

Moderators: Kirkwood Adams (Chapel Hill, USA); Alexandre Mebazaa (Paris, FRA)

- Natriuretic peptides are useful for diagnosis and prognosis, but novel biomarkers have been described that may assess HF severity and prognosis additively (and sometimes superiorly) to natriuretic peptides. Is a one biomarker-fits-all concept still true in HF?
- Recent literature assessed novel metabolism pathways for natriuretic peptides (glycosylation, effects of neprilysin), it is however unclear whether this will change our practice.
- Acute HF trials have been disappointing. Among the reasons of failure is the fact that selecting the right patients in each of the several hundred centers is still difficult. Indeed, assessing the level of congestion and myocardial dysfunction in patients that should be included within few hours after admission is still a challenge. Biomarkers, in addition to clinical signs may help introducing homogeneity in the studied cohort.
- Novel biomarkers, imaging and biosensor technology data can improve the efficiency and technical success at developing novel drug therapies. Many trials of innovative mechanistically targeted therapies failed probably because they enrolled untargeted patient populations. Novel biomarkers and biosensor data should enable new therapies to target patient segments. Across both patient populations novel biomarkers, imaging and biosensor data may also provide a mechanistic understanding that supports explaining the outcome benefit to the mode of action.
- This session objective is to assess the assess the utility of biomarkers and novel biosensor monitoring technology into heart failure and atrial fibrillation clinical trials to screen patients, identify likely responders and to increase the mechanistic understanding of efficacy. What is the current and future state of these technologies, what is the clinical value of remote monitoring, what is known and unknown about the utility in clinical trials?
- An explicit classification system for approval of biological molecules (biomarkers); morphological or functional imaging or physiological sensing with innovative biosensors could be the following: Class 3 would mean you measure what you claim to; Class 2 would add that the biomarker had a known association with clinical outcome; Class 1 would mean you had actually shown its use to improve outcomes.

Opportunities and limitations of natriuretic peptides for use in clinical trials
James Januzzi (Boston, USA)

Should we change our views on the use of NPs in a world with LCZ696 and DPPIV inhibitors?

- **LCZ696, NPs and neprilysin intercations:** Nicolas Vodovar (Paris, FRA)
- **What NP to measure in patients on LCZ696?** Milton Packer (Dallas, USA)

Are there alternative biomarkers to NPs to judge of congestion in heart failure? Etienne Gayat (Paris, FRA)

Biomarkers, and biosensor technology and how they may help rethinking clinical trials

- **Pressure, impedance and other sensors of congestion:** William Abraham (Colombus, USA)
- **eHealth Heart rhythm monitoring and other Biosensor technologies:** Johannes Brachmann (Coburg, GER)
- **Biomarkers to improve success in HF trials:** Michael Felker (Durham, USA)

Methodological challenges in designing precision medicine trials using biomarker-biosensor: what can be learned from oncologists? Richard Simon (NCI, NIH, USA)

How can pharma, imaging, biomarker and device companies synergize? How may regulatory bodies help? Robert Califf (FDA, USA)

Industry perspective: Gillian Murtagh (Abbott, USA); Jean-Claude Provost (GE Healthcare, GBR); Ken Stein (Boston Scientific, USA)

Regulatory perspective: Fernando Aguel (FDA, USA); Krishna Prasad (EMA, GBR); Mitchell Shein (FDA, USA)

The Forum: Moderated discussion with the audience
Rethinking the regulatory pathway for biomarkers and biosensor technology

Panelists: William Abraham (Columbus, USA); Kirkwood Adams (Chapel Hill, USA); Fernando Aguel (FDA, USA); Johannes Brachmann (Coburg, GER); Julian Braz (Roche Diagnostics, CH); Robert Califf (FDA, USA); Michael Felker (Durham, USA); Etienne Gayat (Paris, FRA); David Guez (Servier, FRA); James Januzzi (Boston, USA); Peter Kowey (Wynnewood, USA); Daniel Krainak (FDA, USA); Carolyn Lam (Singapore, SIN); Lars Lund (Stockholm, SWE); Elizabeth Mansfield (FDA, USA); Alexandre Mebazaa (Paris, FRA); Gillian Murtagh (Abbott, USA); Milton Packer (Dallas, USA); Ileana Pina (FDA, USA); Krishna Prasad (EMA, GBR); Jean-Claude Provost (GE Healthcare, GBR); Mitchell Shein (FDA/CDRH, USA), Monica Shah (NHLBI, USA); Richard Simon (NCI, NIH, USA); Ken Stein (Boston Scientific, USA); Norman Stockbridge (FDA, USA); Nicolas Vodovar (Paris, FRA); Faiez Zannad (Nancy, FRA)

THEATRE

8.00 am - 12.00 noon

LONG-TERM ANTIPLATELET TREATMENT IN CORONARY ARTERY DISEASE

European Association of Clinical Pharmacology and Therapeutics - CVCT joint session

Moderators: Roxana Mehran (New York, USA); Tabassome Simon (Paris, FRA)

Dual antiplatelet treatment for chronic post MI secondary CV prevention: review of the evidence so far and the input from PEGASUS
Tabassome Simon (Paris, FRA)

Duration of DAPT post PCI: how to generate further needed evidence?
Patrick Serruys (Rotterdam, NED)

Endpoint related issues

- MACE components vs. bleeding types across the various indications (ACS, post ACS). Freek Verheugt (Amsterdam, NED)
- And what if we ask the patients? Patient preferences on which outcome matters the most. Joe Selby (PCORI, USA)

Triple therapy in concomitant coronary artery disease and atrial fibrillation – what do we know? What evidence do we need and what future trial strategy?
Roxana Mehran (New York, USA)

First PCORNET pragmatic clinical trial to evaluate Aspirin dosing in patients with cardiovascular disease
Adrian Hernandez (Durham, USA)

Industry viewpoint: Tomas Andersson (AstraZeneca, SWE)

Regulatory viewpoints:

- FDA/CDER perspective: Martin Rose (FDA, USA); Ellis Unger (FDA, USA)
- FDA/CDRH perspective: Andrew Farb (FDA, USA)
- EMA perspective: Antonio Gómez-Outes (EMA, ESP)

The Forum: Moderated discussion with the audience
How to better involve patients?

Panelists: Angeles Alonso (EMA, GBR); Tomas Andersson (AstraZeneca, SWE); Corine Bernaud (AstraZeneca, GBR); Andrew Farb (FDA, USA); Antonio Gómez-Outes (EMA, ESP); Michael Hanna (BMS, USA); Adrian Hernandez (Durham, USA); Roxana Mehran (New York, USA); Martin Rose (FDA, USA); Howard Rutman (Daiichi Sankyo, USA); Joe Selby (PCORI, USA); Patrick Serruys (Rotterdam, NED); Tabassome Simon (Paris, FRA); Freek Verheugt (Amsterdam, NED); Ellis Unger (FDA, USA)

12.00 noon – 12.30 pm
KEY NOTE LECTURE
Robert Califf, Deputy Commissioner, Office of Medical Products and Tobacco, US Food and Drug Administration

BALLROOM

1.30 pm – 6.00 pm

ATRIAL FIBRILLATION PREVENTION AND TREATMENT TRIALS

Heart Rhythm Society – CVCT joint session

Moderators: Cecilia Linde (Stockholm, SWE); David Van Wagoner (Cleveland, USA)

- Analysis of clinical practice guidelines reveals a gap between the need for evidence and its availability and more research is required to support evidence-based recommendations as part of a comprehensive approach to prevention and treatment of AF. Developing an evidence base from which we can adequately predict and prevent AF is an important public health goal.
- The Heart Rhythm Society recently sought to identify key deficiencies and opportunities in research infrastructure, operations, and methodologies as well as basic research targets and how clinical AF research could be improved in the current health care environment.
- Catheter ablation is usually undertaken in patients with symptomatic paroxysmal AF that is resistant to at least one antiarrhythmic drug. This practice is supported by the results of multiple single center randomized studies showing a significantly better rhythm outcome after ablation. Most of these studies have included patients already resistant to antiarrhythmic drug treatment with no or minimal organic heart disease, and the follow-up was relatively short.
- Australian trials have shown a significant impact of structured weight loss programs on AF burden. What is the role of lifestyle interventions in the prevention and management of AF?
- For patients with either persistent AF or long-standing persistent AF, and, the treatment strategies and the benefit–risk ratio of catheter ablation are less well established.
- Currently available evidence suggests that occurrence of AF in patients with heart failure (HF), in addition to the risk of thromboembolism, leads to a decline in exercise tolerance, worsened quality of life, increased hospitalization, and in many studies an increase in mortality. Results from ongoing prospective multicenter trials in patient subgroups such as AF in congestive heart failure (e.g. CASTLE-AF, ARC-AF and AMICA) are still pending.
- RAFT-AF compares the effect of catheter ablation-based atrial fibrillation rhythm control to rate control in patients with heart failure and AF on the composite endpoint of all-cause mortality and hospitalization for heart failure.
- More generally, there is no evidence so far that successful AF ablation will result in reduced mortality. CABANA is a large prospective worldwide trial is exploring this.
- Technological innovation is racing at fast speed, and it is expected that some would argue that the results of the ongoing trials may not be generalizable, and may not apply to all centers (center-related factors and learning curve), to all procedures (technology related factors) and to all patients (history of AF and concomitant heart disease…) and to all outcomes (hard, AF recurrence and patient reported outcomes)

Aim of this session: Examine and compare the design of recent and ongoing trials and discuss the possible outcomes and future impact on clinical practice.

Atrial fibrillation prevention and treatment: clinical trials as part of the research agenda

- **At the Heart Rhythm Society:** David Van Wagoner (Cleveland, USA)
- **At the NHLBI:** Yves Rosenberg (NHLBI, USA)
- **At the ESC – European Heart Rhythm Association:** Cecilia Linde (Stockholm, SWE)

Targeting the right patient population: are current trials addressing personalized AFib prevention/treatment strategies? Hugh Calkins (Baltimore, USA)

How important are center-related factors in clinical trials of interventional procedures, i.e. volume of patients and degree of experience with the procedure? Tom Wong (London, GBR)

What are clinically meaningful endpoints in AF trials?

- **AF burden and the role of novel biosensors in AF trials:** Peter Kowey (Wynnewood, USA)
- **Patient reported outcomes, symptoms, quality of life:** Heather Ross (Phoenix, USA)

The challenge of continuous technological innovations: how might the results of the ongoing trials apply to novel ablation technologies? Kevin Heist (Boston, USA)

Industry perspective: Timothy Meyer (Boston Scientific, USA)

Regulatory perspective: Karsten Bruins Slot (EMA, NOR); Jun Dong (FDA, USA)

The Forum: Moderated discussion with the audience
Preparing for evidence based AF prevention/treatment trials

Panelists: Karsten Bruins Slot (EMA, NOR); Hugh Calkins (Baltimore, USA); Jun Dong (FDA, USA), Mark Fellman (FDA, USA), David Gordon (NHLBI, USA); Kevin Heist (Boston, USA); Peter Kowey (Wynnewood, USA); Cecilia Linde (Stockholm, SWE); Timothy Meyer (Boston Scientific, USA); Yves Rosenberg (NHLBI, USA); Heather Ross (Phoenix, USA); Martin Unverdorben (Daiichi Sankyo, USA); David Van Wagoner (Cleveland, USA); Tom Wong (London, GBR)

THEATRE

1.30 pm – 6.00 pm
ATHEROSCLEROSIS TRIALS

Moderators: Wolfgang Koenig (Munich, GER); Jean Claude Tardif (Montreal, CAN)

Causes and consequences of the underutilization of high intensity statins in ACS patients
Robert Rosenson (New York, USA)

PCSK9 inhibitors: almost all said already? Just waiting for results of outcome trials?
Evan Stein (Cincinnati, USA)

Is targeting inflammation still an option in patients on very low LDL cholesterol levels? The inflammation theory of atherosclerosis and ongoing trials (CIRT, CANTOS, COLCOT)
Wolgang Koenig (Munich, GER)

Ongoing clinical trials in cardiovascular disease with antisense oligonucleotides: Targeting ApoB-100, ApoC-III, Lp(a), ANGPTL3, FXI and angiotensinogen
Sam Tsimikas (Isis Pharmaceuticals, USA)

Would a biomarker risk score help identifying high-risk subjects for randomized clinical trials?
James de Lemos (Boston, USA)

Optical coherence tomography: ready for the inclusion in clinical trial?
Evelyn Regar (Rotterdam, NED)

Personalized medicine: how far have we come? (DalGENE): Jean Claude Tardif (Montreal, CAN

Pharmacogenomic studies: potentials and limitations: Klaus Lindpaintner (Newark, USA)

Mendelian randomization studies

- Lipoprotein and Inflammatory targets Daniel Swerdlow (London, GBR)

Industry viewpoint: Andrew Hamer (AMGEN, USA)

Regulatory viewpoint: Pieter de Graeff (EMA, NED)

The Forum: Moderated discussion with the audience
Tailoring mechanistically targeted therapy to targeted patient populations

Panelists: Pieter de Graeff (EMA, NED); James de Lemos (Boston, USA); Andrew Hamer (Amgen, USA); Wolfgang Koenig (Munich, GER); Klaus Lindpaintner (Newark, USA); Evelyn Regar (Rotterdam, NED); James Revkin (Pfizer, USA), Robert Rosenson (New York, USA); Evan Stein (Cincinnati, USA); Daniel Swerdlow (London, GBR); Jean Claude Tardif (Montreal, CAN); Sam Tsimikas (Isis Pharmaceuticals, USA)

CVCT YOUNG TRIALISTS

The 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. At CVCT they 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.
Our scientific committee learns about candidates in the following ways:

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

We are pleased to welcome the following young trialists to CVCT Forum 2015:

Tariq Ahmad, USA
Christos Konstantinos Antoniou, GRE
Marwan Badri,USA
David Briceno, USA
Jeffrey Bruckel, USA
Sara Burgardt, USA
Mike Cahill, USA
Neal Chatterjee, USA
Lisandro Colantonio, USA
Geoffrey Cole, USA
Robert Cole, USA
Lauren Cooper, USA
Adam Devore, USA
João Pedro Ferreira, FRA
Camilla Hage, SWE
Robert Hawkins, USA
Nasrien Ibrahim , USA
Antwan Jones, USA
Anu Lala, USA
Ulrika Löfström, SWE
Tom Lumbers, GBR
Sonomi Maruyama, USA
James Mehaffey, USA
Robert J. Mentz, USA
Michael Nassif, USA
Kishan Parikh, USA
Nish Patel, USA
Pierpaolo Pellicori, GBR
Ali Poyan Mehr, USA
Mitchell Psotka, USA
Yader Sandoval, USA
Marilina Santero, ARG
Marvin Schwarz, GER
Abhinav Sharma, USA
Ali Tanweer Siddiquee, BGD
Marc Sintek, USA
Tobias Daniel Trippel, GER
Rosita Zakeri, GBR

CVCT LIBRARY and CVCT PUBLICATIONS

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

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

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

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

CVCT publications reference list - Visit www.globalcvctforum.com to read the articles in full.

▸ 2015

Agents with vasodilator properties in acute heart failure: how to design successful trials
Mebazaa A, Longrois D, Metra M, Mueller C, Richards AM, Roessig L, Seronde MF, Sato N, Stockbridge N, Gattis Stough W, Alonso A, Cody R, Cook Bruns N, Gheorghiade M, Holzmeister J, Laribi S, Zannad F
European Journal of Heart Failure (2015) 17, 652–664 doi:10.1002/ejhf.294. Review.

Cardiac resynchronization therapy in heart failure patients with less severe left ventricular dysfunction
Hai OY, Mentz RJ, Zannad F, Gasparini M, De Ferrari GM, Daubert JC, Holzmeister J, Lam CS, Pochet T, Vincent A, Linde C
Eur J Heart Fail. 2015 Feb;17(2):135-43. doi: 10.1002/ejhf.208. Epub 2014 Dec 3.

Patient selection in heart failure with preserved ejection fraction clinical trials
Kelly JP, Mentz RJ, Mebazaa A, Voors AA, Butler J, Roessig L, Fiuzat M, Zannad F, Pitt B, O'Connor CM, Lam CS
J Am Coll Cardiol. 2015 Apr 28;65(16):1668-82. doi: 10.1016/j.jacc.2015.03.043.

Atherosclerosis: recent trials, new targets and future directions
Ladeiras-Lopes R, Agewall S, Tawakol A, Staels B, Stein E, Mentz RJ, Leite-Moreira A, Zannad F, Koenig W
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CONTINUING MEDICAL EDUCATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Medical Society of Virginia (MSV) through the joint providership of Inova Health System Office of Continuing Medical Education and Overcome. The Inova Health System Office of Continuing Medical Education is accredited by the Medical Society of Virginia to provide continuing medical education for physicians.

The Inova Office of Continuing Medical Education designates this live activity for a maximum of 22 AMA PRA Category 1 Credits ™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Physicians may claim up to 22 credits in Type 1 CME on the Virginia Board of Medicine Continued Competency and Assessment Form required for renewal of an active medical license in Virginia.

Learning Objectives

- To identify and recognize the science of clinical trials from trial protocol design to trial result interpretation.
- To identify continued investigation in the CV trial arena, and to provide new approaches to treatment.
- To identify and analyze the evidence from clinical trials and how trial results may be incorporated into treatment guidelines.

ORGANISED BY THE CLINICAL INVESTIGATION CENTER

Nancy Inserm 1433 Clinical Plurithematic Investigation Centre (CIC-P), headed by Pr Faiez Zannad, is supported by the **National Institution for Health Care and Medical Research** (Inserm), **Nancy University Hospital**, and the **Université de Lorraine**.

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.

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The **Heart Failure Society of America** provides a forum for all those interested in heart function, heart failure, and congestive heart failure (CHF) research and patient care. Membership is open to all health care professionals with an interest in cardiovascular medicine, including cardiologists, cardiac surgeons, internists, geriatricians, general and family practitioners, scientists, cardiac rehabilitation specialists, nurses, industry or allied personnel.
http://www.hfsa.org/

The **American Society of Nephrology** (ASN) leads the fight against kidney disease by educating health professionals, sharing new knowledge, advancing research, and advocating the highest quality care for patients.
www.asn-online.org

The **Heart Rhythm Society** aims to improve the care of patients by advancing research, education and optimal health care policies and standards. The Heart Rhythm Society is a leading resource on cardiac pacing and electrophysiology. This specialty organization represents medical, allied health, and science professionals from more than 70 countries who specialize in cardiac rhythm disorders.
www.hrsonline.org

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The **Food and Drug Administration** (FDA or USFDA) is a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics, animal foods & feed and veterinary products.
www.fda.gov

The **National Heart, Lung, and Blood Institute** (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives.
www.nhlbi.nih.gov

The **European Medicines Agency** is a decentralised agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It began operating in 1995. *www.ema.europa.eu*

American Society of Hypertension

Established in 1985 to provide a forum for the exchange of information among basic scientists, clinical investigators and health care clinicians involved in the study or management of high blood pressure, the American Society of Hypertension is dedicated to the advancement of science, prevention and treatment of high blood pressure and its cardio-renal consequences--including obesity and diabetes--with special emphasis on treating cases of resistant and complex hypertension. ASH has a domestic and international membership of basic science & clinical investigators, physicians, physician assistants, nurse practitioners, pharmacists, as well as individuals with a scientific interest in hypertension. ASH remains committed to eliminating hypertension and its consequences through a renewed and vigorous focus on translational research leading to effective treatment strategies for patients. *www.ash-us.org*

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*

The **European Association for Clinical Pharmacology and Therapeutics** (EACPT) is a learned society in the field of clinical pharmacology. It is the leading society in Europe serving the European and global clinical pharmacology and therapeutics community. The EACPT includes all national organisations for clinical pharmacology in Europe and provides educational and scientific support for the more than 4000 individual professionals interested in clinical pharmacology and therapeutics throughout the European region, with its congresses - the next in Madrid in 2015 - attended by a global audience. The EACPT also holds summer schools and organises other scientific and professional activities. *www.eacpt.org*

EDDH, **European Drug Development Hub** is an academic clinical research organisation, under the aegis of the Foundation Transplantation, 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 investigators 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.
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Ranked among the top 10 heart programs in the United States, **Duke Heart Center** provides state-of-the-art cardiac care to help thousands of heart patients lead longer, healthier lives. Decades of experience in caring for patients with heart disease have established Duke as one of the world's leading programs in cardiac care, research, and education. *www.dukemedicine.org*

F-CRIN, **French Clinical Research Infrastructure Network**, hosted by Inserm, is an operational excellence network encompassing the major French academic actors in clinical research. FCRIN aims to support and promote ambitious and competitive multinational academic investigator-driven trials proposed in France and early development proof of concept with industry sponsored trials. FCRIN acts as a multifunctional platform able to provide all necessary services to the duo Investigator/Sponsor and works in tight connection with ECRIN, ERIC of which France is one of the founding member. *www.fcrin.org*

INI (**Investigation Network Initiative**)-CRCT (**Cardiovascular and Renal Clinical Trialists**), coordinated by Pr Patrick Rossignol (Nancy, France) has been approved by the "F-CRIN" (French Clinical Research Infrastructure Network). It has established a national multidisciplinary network of research excellence comprised of the French leaders in the cardiorenal field (nephrology, cardiology, intensivists, internists trialists, epidemiologists, methodologists, basic researchers), an Academic Research Organisation, disease management programs in Chronic Kidney disease (CKD) and heart failure, the French Biomedecine agency, and University of Lorraine Foundation. It aims at designing and realizing research programs both nationally and internationally, to improve cardiovascular and renal outcomes in CKD patients. *www.inicrt.org*

Speaker biographies & abstracts

William Abraham (Columbus, USA)

William T. Abraham, MD, FACP, FACC, FAHA, FESC, FRCP, is Professor of Internal Medicine and Chief of the Division of Cardiovascular Medicine at The Ohio State University College of Medicine. Dr Abraham earned his medical degree from Harvard Medical School in Boston, Massachusetts, following which he completed his residency in Internal Medicine and fellowships in Cardiovascular Disease and Advanced Heart Failure/Transplant Cardiology at the University of Colorado Health Sciences Center. He previously held faculty appointments at the University of Colorado, the University of Cincinnati, and the University of Kentucky. He is board certified in Internal Medicine, Cardiovascular Diseases, and Advanced Heart Failure and Transplant Cardiology. Dr Abraham spends the majority of his clinical time managing heart failure patients in the inpatient and outpatient settings. Dr Abraham has been recognized as one of the "Best Doctors in America" for thirteen consecutive years and has been ranked among the top 10% of physicians nationally in patient satisfaction. Dr Abraham's research interests include hemodynamic and neurohormonal mechanisms in heart failure, sleep disordered breathing in heart failure, and clinical drug and device trials in heart failure. Dr Abraham has received grants from the National Institutes of Health, American College of Cardiology, and Aetna Quality Care Foundation and has participated as a site Principal Investigator in more than 100 multicenter clinical drug and device trials. He has also served as national or international Principal Investigator and on the Executive or Steering Committees of more than 30 multicenter clinical drug and device trials. Dr Abraham has participated in all regulatory phases of new drug and device development from pre-clinical evaluation to Pre-Market Approval (PMA) and New Drug Application (NDA) submission and approval. He is an experienced US Food and Drug Administration panel presenter and a consultant to various CE Marking Notified Bodies of the European Union. His work has led to the approval and adoption of new therapies for heart failure, including cardiac resynchronization therapy and implantable hemodynamic monitoring devices. Dr Abraham has authored more than 700 original papers, abstracts, book chapters, and review articles. His work has been published in high impact journals, including The New England Journal of Medicine, The Lancet, the Journal of the American Medical Association, Circulation, the European Heart Journal, and the Journal of the American College of Cardiology. Dr Abraham has co-authored national heart failure practice guidelines and co-edited a leading textbook on heart failure entitled Heart Failure: A Practical Approach to Treatment. Dr Abraham serves on the editorial boards of several major journals. In 2014 and again in 2015, he was named to the Thomson Reuters Highly Cited Researchers list and as one of The World's Most Influential Scientific Minds.[1] 1 Highly Cited Researchers represents some of world's leading scientific minds. Only 3,000 researchers worldwide earned the distinction by writing the greatest numbers of reports officially designated by Essential Science Indicators as Highly Cited Papers—ranking among the top 1% most cited for their subject field and year of publication, earning them the mark of exceptional impact

Kirkwood Adams (Chapel Hill, USA)

Kirkwood F. Adams Jr., MD, is Associate Professor of Medicine and Radiology in the Division of Cardiology, University of North Carolina at Chapel Hill, where he founded and for many years directed the UNC Heart Failure Program and served as the first transplant cardiologist for two decades, helping to establish this treatment at UNC. Dr Adams is currently involved in numerous research activities related to heart failure with particular focus on novel drug development in acute heart failure and translational research concerning the identification and clinical application of cardiovascular biomarkers and pharmacogenomics. Dr Adams 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 including RELAX-2 and COSMIC. He has been involved in several registry and database studies, and in three completed NHLBIfunded 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. He has published more than 175 manuscripts in refereed journals, a number of book chapters and monographs, and more than 150 abstracts. Dr Adams 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. In addition to drug development for acute and chronic heart failure, 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 helped design and is very actively involved on the Executive Commit-

tee of the NHLBI sponsored trial of NT- proBNP guided therapy known as the GUIDE-IT Trial. He is the principal investigator of the Point of Care substudy of this trial. He is involved in ongoing studies of the clinical role of proBNP and ST2 with particular focus on using these markers in patient management and drug selection.

Christine Albert (Boston, USA)

Christine Albert, MD, MPH is the Director of the Center for Arrhythmia Prevention at Brigham and Women's Hospital and Professor of Medicine at Harvard Medical School. Dr Albert received her MD from Harvard Medical School and MPH from the Harvard School of Public Health. She completed her Internal Medicine, Cardiology, and Cardiac Electrophysiology training at the Massachusetts General Hospital in Boston. She currently holds joint appointments as a clinical cardiac electrophysiologist and epidemiologist within the Divisions of Cardiovascular and Preventive Medicine at Brigham and Women's Hospital. Dr Albert's research focuses on epidemiology, risk stratification, and prevention of sudden cardiac death and atrial fibrillation in large prospective cohort designs and in multi-center clinical studies, most notably seminal contributions regarding the contribution of diet, lifestyle, and genetics to the burden of heart rhythm disorders. Dr Albert is an author on over 100 peer-reviewed original publications in prestigious journals. Dr Albert serves as an Associate Editor for Circulation and as a Trustee for the Heart Rhythm Society.

Genetics, biomarkers and MRI imaging: pre-DETERMINE

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Angeles Alonso (EMA, GBR)

Honorary Consultant in Cardiology. Imperial College Healthcare. NHS. United Kingdom

Senior Medical Assessor in the Medicines and Healthcare products Regulatory Agency (MHRA)

Cardiology Member of the Scientific Advice Working Party (SAWP) of the European Medicines Agency (EMA) Active member in the European Society of Cardiology. Active member in the Spanish Society of Cardiology.

Dr Alonso graduated from the School of Medicine at the Universidad Autónoma de Madrid (1979). PhD 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 Program Committee, Registries and Pharma Working Group).

Tomas Andersson (AstraZeneca, SWE)

Tomas Andersson, MD, PhD, is Vice President, Clinical Cardiovascular and Chronic Kidney Disease, AstraZeneca, heading up the medical teams for late phase clinical development in these areas. Dr Andersson obtained his MD degree at Lund University, Sweden in 1991, and his PhD in 1990. He was post-doctoral research fellow at The William Harvey Research Institute in London (GBR), 1992-1994, and subsequently became Board Certified as specialist in Clinical Pharmacology at the University Hospital, Lund, Sweden. Dr Andersson has a long standing interest in cardiovascular pharmacology and late phase drug development, having worked in senior positions in both Cardiovascular/CKD and Respiratory with Brilinta and Symbicort. Recently he was medically responsible for the readout, interpretation and regulatory submission of the Pegasus study, investigating the effects of Brilinta in patients with a history of myocardial infarction

Lance Berman (Relypsa, USA)

Dr Berman joined Relypsa in December 2011 as Senior Vice President, Commercial Strategy and Medical Affairs and was promoted in October 2012 to Senior Vice President and Chief Medical Officer. Prior to Relypsa, Dr Berman was the Chief Medical Officer of CPEX Pharmaceuticals where he was responsible for the clinical development of the Company's late stage clinical product as well as its in-licensing and acquisition strategies. Prior to that, Dr Berman served in various medical leadership roles at Pfizer Inc. from June 2003 to January 2009, where he was responsible for atherosclerosis, hypertension and endocrinology products serving at various times as US or Global Medical Team Leader. Previously, Dr Berman held roles of increasing responsibility at Schering-Plough Corporation (merged with Merck) and Janssen Pharmaceuticals, Inc. (Johnson & Johnson). Dr Berman received his Bachelor of Medicine and Bachelor of Surgery degrees at the University of Cape Town in Cape Town, South Africa, and an MS in Pharmaceutical Medicine from Hibernia College.

ABSTRACT

Acute and chronic hyperkalemia therapy future trials: unmet needs and newer opportunities for potassium binding agents - industry perspective

Hyperkalemia represents a serious condition that can result in life-threatening cardiac arrhythmias and is associated with increased mortality risk. Patients most at risk of hyperkalemia are those with compromised renal excretion of potassium, primarily patients with chronic kidney disease (CKD). Hyperkalemia frequently occurs in settings where the underlying disorder is persistent and generally progressive. Given the sustained or recurring nature of hyperkalemia in these conditions, treatment of hyperkalemia may need to be continued for long periods of time and/or may need to be repeated. Current options for the ongoing management of recurrent or persistent hyperkalemia have

limited utility and include dietary potassium restriction, diuretics, sodium bicarbonate and the cation exchange resins sodium and calcium polystyrene sulfonate. Up until recently, sodium polystyrene sulfonate (Kayexalate®), which was approved by the FDA in 1958, was the only medication in the US specifically indicated for the treatment of hyperkalemia. Since effective lowering of serum potassium with sodium polystyrene sulfonate may take hours to days, treatment with this drug alone may not be sufficient to rapidly correct severe hyperkalemia associated with states of rapid tissue breakdown or marked hyperkalemia that is considered to be a medical emergency. While sodium polystyrene sulfonate may be an appropriate treatment option for some patients, Warning and Precautions added to the Kayexelate label in 2009 and 2011 may limit its use in certain circumstances. Cases of intestinal necrosis and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with sodium polystyrene sulfonate use. Further, sodium is used as the counter exchange ion in sodium polystyrene sulfonate and caution is advised in patients who cannot tolerate even a small increase in sodium loads such as patients with heart failure, severe hypertension, or marked edema. Given the limitations with current therapies and the need for a better tolerated potassium binder to be used in diverse clinical settings, Relypsa applied its polymer technology with the intent to design an orally administered, non-absorbed potassium binder with physicochemical characteristics that would provide effective and sustained reductions in serum potassium and with a safety and tolerability profile that would support long term chronic use.

VELTASSATM (patiromer) for oral suspension was recently approved by FDA for the treatment of hyperkalemia. Given its delayed onset of action, it should not be used as an emergency treatment for life-threatening hyperkalemia. The active moiety, patiromer, is a sodium-free, non-absorbed polymer that binds potassium in exchange for calcium in the gastrointestinal tract, increasing fecal potassium excretion and lowering serum potassium levels. A comprehensive nonclinical testing program was conducted that supported the safety of the product for its intended use in humans for the treatment of hyperkalemia. Of note, nonclinical ADME studies in two species using 14C-labeled drug demonstrated the non-absorbed nature of the polymer. The primary objectives of the clinical development program were as follows:

- To evaluate safety and efficacy in subjects with underlying conditions that are common causes of hyperkalemia in the clinical setting, primarily patients with CKD, heart failure, and receiving RAAS inhibitor therapies.
- To demonstrate a reduction in serum potassium to within the normal range.
- The onset of action should occur early after treatment and within 12 hours to have utility in both acute and chronic settings.
- Efficacy should be durable and sustained to enable treatment in patients with hyperkalemia that is more chronic in nature.
- To assess safety and tolerability, particularly in support of repeated and long term use.

Following the recent approval of VELTASSA, additional questions remain on the safety, efficacy and clinical utility of VELTASSA in certain treatment settings and patient types that were not assessed as part of the initial clinical development program. The talk will provide perspective on post-approval clinical development and considerations for clinical trial design.

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John Bisognano (Rochester, USA)

John Bisognano MD, PhD, is a professor of medicine and director of outpatient cardiology at the University of Rochester Medical Center in Rochester, New York. He obtained bachelor's degrees in Biology and Political Science from Massachusetts Institute of Technology and went on to obtain a PhD in Physical Chemistry from the State University of New York at Binghamton. He received his medical degree at the State University of New York at Syracuse and did residency at the University of Michigan followed by a fellowship in preventive cardiology. He did a fellowship in cardiology with specialty in heart failure and transplantation at the University of Colorado before accepting a position in the faculty at the University of

Michigan. He subsequently joined the faculty at the University of Rochester. He has been involved in many clinical and basic science studies that include approaches to treatment of patients with resistant and refractory hypertension, including clinical trials testing new medical devices. He is also engaged in community-wide efforts at blood pressure reduction as well as NIH funded in investigating novel methods for treatment of patients with Stage I hypertension. He is a frequent lecturer on hypertension guidelines, treatment approaches, and clinical research both locally as well as internationally.
Dr Bisognano is member of numerous editorial boards and has served as President of the New York State Chapter of the American College of Cardiology, Secretary-Treasurer of the American Society of Hypertension, and Director of the ASH Comprehensive Hypertension Center at the University of Rochester.

ABSTRACT

Autonomic modulation therapy: a critical appraisal of recent and ongoing trials in hypertension, heart failure and arrhythmias - recommendations for future trials

The sympathetic nervous system remains an attractive therapeutic target for therapies in hypertension, heart failure, and arrhythmias. Although great progress has been made in treating these diseases using robust pharmacological therapy, there remains a relatively large population in desperate need for additional clinical tools. Despite ample evidence supporting the benefits of treating patients with hypertension (particularly those with more severe hypertension), there is an inappropriate expectation among clinicians and patients that the therapies be completely free of risk and free of side effect. This thinking has stalled much of autonomic modulation therapy for many decades, as most interventions require surgical procedures and come with a risk that generally exceeds that of most drug trials. But approaching such clinical trials using the same tools as huge-scale drug trials makes progress in that area move at a relative snail's pace, as surgical trials are inherently difficult to be amenable to placebo control arms and strict regulation of other medications. This talk will review some of the recent and ongoing trials is hypertension, heart failure, and arrhythmia with an eye on how the trials can be streamlined in the future to discover clinical results that can quickly be offered to the many patients in need.

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Jeffrey Borer (New York, USA)

Jeffrey S. Borer, MD, is Professor of Medicine, Cell Biology, Radiology and Surgery at the SUNY Downstate Medical Center where for several years was Chief, Division of Cardiology and Chairman, Department of Medicine, administrative positions he recently relinquished to direct two research institutes and to establish a clinical trials unit at Downstate. Dr Borer's BA is from Harvard, MD from Cornell, and training at the Massachusetts General Hospital. He spent 7 years in the Cardiology Branch, NHLBI, and a year at Guy's Hospital (London) as Senior Fullbright Hays Scholar, completing the first clinical demonstration of nitroglycerin's utility in acute MI. Returning to the NIH, he developed stress radionuclide cineangiography, enabling the first 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, Division of Cardiovascular Pathophysiology. He performs clinical service, teaching and research, primarily developing prognosticators for regurgitant valve diseases, and assessing the effects of therapeutic heart rate modification. He has been Advisor to the USFDA for 38 years, chaired the CardioRenal Drugs Advisory Committee for 3 terms and the Circulatory Devices Advisory Panel for one term, was a life sciences Advisor to NASA for 24 years, has served as officer/board member of several national professional societies, has published almost 500 scientific papers and 6 books, is editor-in-chief of the journal, Cardiology, and has received several awards and other recognitions.

Ivabradine crosses the Atlantic: is this good enough?

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Ken Borow (Bryn Mawr, USA)

Dr Borow, MD, is a highly experienced clinician, clinical investigator and trialist, and businessman. He is a Harvard-trained adult cardiologist and pediatric cardiologist with >30 years of clinical research experience. As a faculty member at Harvard Medical School and subsequently Professor of Medicine and Pediatrics at the University of Chicago, he was the author of >100 publications dealing with a wide array of CV and other disease states. He also oversaw a large research group focused on atherosclerosis and heart failure. Dr Borow's direct biopharmaceutical industry experience includes responsibility for Clinical Research Operations in the US for Merck Research Laboratories. In this role, he was involved in >200 different clinical trials conducted at >2,500 investigative sites. For the eight years beginning in 2000, Dr Borow was President/CEO of a NASDAQ traded multinational CRO with operations in >30 countries. In this role he helped design/conduct >60 clinical trials including Pfizer's landmark REVERSAL and CAMELOT studies, Mylan' nebivolol development program in hypertension, and Portola Pharmaceutical's Phase 2 Factor Xa inhibitor (betrixaban) oral anticoagulant development program. In 2008, Dr Borow founded Borow Consulting Group, LLC in order to devote more attention to issues associated with clinical trial strategic design and development as well as global healthcare processes and analytics. He has had extensive experience in clinical outcomes trials as well as broad interactions with regulatory authorities. Currently, Dr Borow is President and Chief Medical Officer of an innovative health information technology company (MediMergent, LLC) that has a public-private partnership with FDA focused on the collection and integration of clinical data acquired from the "voice-of-the-patient" and electronic medical records for pre- and post-approval assessments of safety, clinical outcomes, medication adherence, and comparative effectiveness.

ABSTRACT

The National Medication Safety, Outcomes and Adherence Program (NMSOAP) study of real world comparative effectiveness of NOACs and Warfarin

Background:

Under a Research Collaboration Agreement with the US FDA and its Center for Drug Evaluation Research (CDER), MediMergent, LLC established the **National Medication Safety, Outcomes and Adherence Program (NMSOAP)** to longitudinally assess real-world safety, outcomes, drug adherence/persistence, and comparative effectiveness using innovative and prospective early warning approaches towards adverse events associated with use of targeted medications and procedures.

Methods:

NMSOAP collects, integrates and analyzes structured and unstructured health data acquired directly in the "Voice-of-the-Patient" (VoP) using PCs, tablets, web applications, and call centers. Data focus on medication associated adverse effects, clinical outcomes, drug adherence/persistence, impact of concomitant branded and over-the-counter (OTC) medications, and the patient's sense of well-being. The customized survey data are integrated with other patient information collected from medical records (EMR when available), prescription data and insurance claims. Patients are primarily engaged and enrolled into NMSOAP at the Point- of-Care (POC) at select community pharmacies and physician practices across the United States. Pharmacists and care providers as well as the patient have access to the VoP information on a monthly basis. In the case of oral anticoagulants (OAC), NMSOAP provides early prospective warning signs that might act as harbingers of adverse safety and other issues that can result in either costly treatments and/or poor medication adherence.

MediMergent's relationships for the NMSOAP extend well beyond the FDA and CDER and ,for example, include:

- **Kroger & Co.,** a top 5 global retailer with over 2000 pharmacies and 7,000 pharmacists in the U.S.
- **Cardinal Health,** a Fortune 500 health care services company with >500 Medicine Shoppe pharmacies;

working closely with NMSOAP to provide patient access, enrollment, and retention.

- **American Pharmacists Association (APhA),** the largest association of pharmacists in the US (>65,000); provides development/implementation of national training programs to pharmacists & staff.
- **Multiple Physician and other Care-provider Groups** which are involved in the identification/recruitment of patients directly from provider practices into NMSOAP.

The NMSOAP NOAC-Warfarin Trial

"Real World Assessments of Safety, Outcomes, Medication Adherence and Comparative Effectiveness of Novel Oral Anticoagulants [NOACs: Rivaroxaban (Xarelto™), Apixaban (Eliquis™) and Dabigatran (Pradaxa™)] or the Standard-of-Care Comparator Warfarin".

- Open label, non-randomized, real world study designed to enroll approximately 48,000 patients who are undergoing chronic treatment with a FDA approved OAC indicated for prevention of clinical events associated with atrial fibrillation (AFib) or venous thromboembolism (VTE). An interim analysis is planned when ~12,000 patients have been enrolled.
- Designed to evaluate safety and clinical outcomes as well as medication adherence, possible REMS applicability, and aspects of comparative effectiveness for NOACs and Warfarin.
- Recruitment occurs at community retail pharmacies or physicians practices throughout the US. New and ongoing OAC users are being enrolled independent of whether they have an on-label or off-label indication.
- Consented patients provide self-reported baseline data and access to their medical/pharmacy and other health care data. Study participation entails baseline and monthly VoP surveys for up to 2 years. The VoP surveys collect salient patient health characteristics/experiences (e.g., bleeding, bruising, stroke, pulmonary embolus, MI), changes in perceived well-being, and adherence/use patterns of prescription anti-platelet agents and/or targeted OTC drugs (e.g., aspirin).
- Prospective medical data are available from updates to the medical records (including EMR when available), pharmacy/pharmacist data, and other healthcare providers. Laboratory data, provider data and claims data are incorporated when available and as needed.

Conclusions:

The NMSOAP approach brings the patient, the ultimate end-user of the healthcare system, into the forefront of his/her own disease management by creating prospective interactive relationships between health care providers, pharmacies, and patients. The result is the ability to detect early warning signals of adverse events and serve as a comprehensive digital platform for evaluating patient safety and clinical outcomes.

Johannes Brachmann (Coburg, GER)

Professor of medecine Johannes Brachmann was born in Kiel, Germany in 1952. He went to Medical School at the University of Heidelberg from 1973 to 1979 then earned the approbation for his Medical licence in May 1979. In 1980 and 1981 Prof Dr Brachmann did Reaserch fellowship of the German Research Foundation at the University of Oklahoma, USA (Prof. Lazzara, Prof Scherlag). Then from 1982 and 1985 Prof Dr Brachmann had his Cardiology Training at the University of Heidelberg, Dept of Cardiology (Director Prof Dr W. Kübler) where he had already worked in 1979.

Since 1985, Prof Dr Bachmann is head of the clinical and experimental electrophysiological laboratory of the University of Heidelberg, attending cardiologist at the University of Heidelberg. He also is an active participator and principel investigator of more than 20 clinical studies mostly in the area of cardiac electrophysiology (atiarrhythmics, ICD, PM) and interventional cardiology (stents, atherectomy), as well as the principal investigator in several multicenter studies on arrhythmias and coronary intervention Coburg. He wrote more than 200 Publications and published abstracts.

In 1991, Prof Dr Brachmann became a member of the scientific committees of the German Cardiac Society and the European Society of Cardiology and a member of the Nucleus of the Working Group "Electrophysiology" of the German Cardiac Society. In 1995, he became deputy chief of Cardiology at the University of Heidelberg. In 1998, Prof Dr Brachmann became chief of Cardiology at II Med Hospital Klinikum Coburg, Teaching Hospital of the University of Würzburg.

Uli Broedl (Boehringer Ingelheim, GER)

Dr Uli C. Broedl, MD, is Global Head of Late Clinical Development and Deputy Global Therapeutic Area Head, Therapeutic Area Metabolism, at Boehringer Ingelheim. He is board certified in Internal Medicine, Endocrinology and Metabolism, and is adjunct Professor of Internal Medicine at the University of Munich School of Medicine, Germany.

Dr Broedl received his MD degree from the University of Munich in 1999. Following a Postdoctoral Fellowship in Dr Daniel Rader´s lab, Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, USA, he completed his residency and fellowship in Internal Medicine, Endocrinology, and Metabolism at the University of Munich. Uli Broedl joined Boehringer Ingelheim in 2009, and oversees global late clinical development, submission and registration

strategy within the Therapeutic Area Metabolism. He is member of the EMPA-REG OUTCOME (Empagliflozin CVOT), CAROLINA and CARMELINA (Linagliptin CVOTs) steering committees.

ABSTRACT

Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes

Bernard Zinman, Christoph Wanner, John M. Lachin, David Fitchett, Erich Bluhmki, Stefan Hantel, Michaela Mattheus, Theresa Devins, Odd Erik Johansen, Hans J. Woerle, Uli C. Broedl, Silvio E. Inzucchi on behalf of the EMPA-REG OUTCOME investigators

Objective:

To examine the effects of empagliflozin, in addition to standard of care, on cardiovascular morbidity and mortality in patients with type 2 diabetes and high cardiovascular risk.

Methods:

Patients were randomized to receive empagliflozin 10 mg, 25 mg, or placebo once daily. The primary outcome was time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, analyzedby empagliflozin (pooled dose groups) versus placebo.

Results:

A total of 7020 patients were treated. The median observation time was 3.1 years. The primary outcome occurred in a significantly lower percentage of patients on empagliflozin (10.5%) than placebo (12.1%) (hazard ratio [HR] 0.86; 95.02% confidence interval [CI] 0.74–0.99; p=0.04 for superiority). There was no significant difference in myocardial infarction or stroke between empagliflozin and placebo. Empagliflozin reduced the risk of cardiovascular death by 38% (HR 0.62; 95% CI 0.49–0.77; p<0.001) and the risk of hospitalization for heart failure by 35% (HR 0.65; 95% CI 0.50–0.85; p=0.002). Empagliflozin reduced the risk of all-cause mortality by 32% (HR 0.68; 95% CI 0.57–0.82; p<0.001), which corresponds to a number needed to treat of 39 over 3 years to prevent one death. Empagliflozin was well tolerated but associated with an increase in genital infections.

Conclusion:

Empagliflozin is the first glucose-lowering agent to demonstrate a reduction in overall mortality, in cardiovascular death, and in hospitalization for heart failure in patients with type 2 diabetes and high cardiovascular risk when used in addition to standard of care.

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Karsten Bruins Slot (EMA, NOR)

Dr Bruins Slot received his MD degree in 2002 (University of Groningen, The Netherlands) and a PhD in cerebrovascular medicine in 2009 (University of Oslo, Norway). Prior to joining the Norwegian Medicines Agency (NoMA), he worked as a physician and research fellow at the Oslo University Hospital and Western General Hospital (University of Edinburgh, GBR). Dr Bruins Slot has been a member of EMA's Committee for Medicinal Products for Human Use (CHMP) and Cardiovascular Working Party since 2010. He still holds a postdoctoral research position in cerebrovascular medicine at the Oslo University Hospital and has recently published on thrombolytic stroke treatment and the use of factor Xa inhibitors for prevention of stroke in patients with atrial fibrillation.

Robert Califf (FDA, USA)

Robert M. Califf, MD, MACC, was named Deputy Commissioner for Medical Products and Tobacco for the Food and Drug Administration (FDA) in February of 2015. Dr Califf provides executive leadership to the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Tobacco Products. He also oversees the Office of Special Medical Programs and provides direction for cross-cutting clinical, scientific, and regulatory initiatives, including precision medicine, combination products, orphan drugs, pediatric therapeutics, and the advisory committee system.

Prior to joining the FDA, Dr Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University. He also served as director of the Duke Translational Medicine Institute and founding director of the Duke Clinical Research Institute. A nationally and internationally recognized expert in cardiovascular medicine, health outcomes research, healthcare quality, and clinical research, Dr Califf has led many landmark clinical trials and is one of the most frequently cited authors in biomedical science, with more than 1,200 publications in the peer-reviewed literature. Dr Califf has served on the Institute of Medicine (IOM) committees that recommended Medicare coverage

of clinical trials and the removal of ephedra from the market, as well as on the IOM Committee on Identifying and Preventing Medication Errors and the IOM Health Sciences Policy Board. He has served as a member of the FDA Cardiorenal Advisory Panel and FDA Science Board's Subcommittee on Science and Technology. Dr Califf has also served on the Board of Scientific Counselors for the National Institutes of Health and the National Library of Medicine, as well as on advisory committees for the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Environmental Health Sciences and the Council of the National Institute on Aging.

While at Duke, Dr Califf led major initiatives aimed at improving methods and infrastructure for clinical research, including the Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by the FDA and Duke. He also served as the principal investigator for Duke's Clinical and Translational Science Award and the NIH Health Care Systems Research Collaboratory coordinating center.

Dr Califf is a graduate of Duke University School of Medicine.

He completed a residency in internal medicine at the University of California, San Francisco and a fellowship in cardiology at Duke.

Hugh Calkins (Baltimore, USA)

Dr Hugh Calkins is the Nicholas J. Fortuin MD Professor of Cardiology and Professor of Medicine at the Johns Hopkins University School of Medicine. He also is the Director of the Clinical Electrophysiology Laboratory, the Arrhythmia Service, and the Arrhythmogenic Right Ventricular Dysplasia Program at the Johns Hopkins Hospital. Dr Calkins graduated Magna Cum Laude with Highest Honors in Chemistry from Williams College. He then attended Harvard Medical School before training in Internal Medicine at the Massachusetts General Hospital. He received his cardiology fellowship training at Johns Hopkins. Dr Calkins trained in electrophysiology at Johns Hopkins and at the University of Michigan. His first faculty position was at the University of Michigan. He returned to Johns Hopkins as Director of the Clinical Electrophysiology Laboratory and Arrhythmia Service in 2002. Dr Calkins has published more than 470 manuscripts and more than 50 book chapters.

He is recognized nationally and internationally for the pioneering role he has played in the development of radiofrequency catheter ablation for treatment of cardiac arrhythmias as well as for his research on arrhythmogenic right ventricular dysplasia. Dr Calkins received 1st prize in the NASPE Young Investigator Competition in 1988, was recipient of the Helen B. Taussig Award of the Maryland American Heart Association Affiliate in 1999, and was awarded the Van Ruyven Medal of the Heart Lung Foundation Utrecht, the Netherlands in 2012.

Dr Calkins has been recognized for his clinical excellence by Best Doctors in America, America's Top Physicians, and Baltimore Magazine. Dr Calkins serves on the editorial board of Circulation, the Journal of the American College of Cardiology, Heart Rhythm, the Journal of Interventional Electrophysiology, and the Journal of Cardiovascular Electrophysiology. He served as President of the Heart Rhythm Society from 2014-2015.

James Carr (Stealth Peptides, USA)

Jim Carr is Vice President of Clinical Development at Stealth Biotherapeutics. Jim received his Doctor of Pharmacy degree at the University of Minnesota and subsequently pursued a post-doctoral fellowship at the same institution. Prior to joining the pharmaceutical industry, Jim spent 7 years in various hospital-based academic roles. Collectively, Jim has 20 years of experience in the pharmaceutical industry, in both large and small companies.

In his current role, he leads the clinical research efforts focused on cardiovascular and rare disease indications.

ABSTRACT

Phenotyping heart failure – is precision medicine the way forward? Industry viewpoint

Individualization of therapies in chronic heart failure may offer several advantages. First, the ability to identify the highest risk sub-populations would likely reduce the sample size of the trial. This might be particularly relevant for Stage B heart failure patients. This would also reduce the number needed to treat to prevent an event, which would likely be viewed as more attractive for payers.

Another advantage of individualization is that personalized therapies likely lead to better medication adherence.

Lastly, the most compelling reason to individualize is to avoid toxicity, which is more molecule specific. For example, the identification of patients that have a genetic predisposition to display toxicity with a particular therapy would allow the prescriber to reduce the risk of this occurrence. Further, the ability to identify likely responders, for drugs that possess some off-target toxicities, would lead to the ability to favorably impact the risk versus benefit profile.

John Cleland (London, GBR)

Professor Cleland qualified in medicine at the University of Glasgow in 1977 and was appointed Senior Lecturer in Cardiology at St Mary's Hospital, Paddington and the Hammersmith Hospital, London in 1989. In 1994, he was awarded a Senior Research Fellowship by the British Heart Foundation to transfer to the Medical Research Council's Clinical Research Initiative in Heart Failure in Glasgow. Subsequently, he was appointed Professor of Cardiology at the University of Hull in 1999 and, in 2013, Professor of Clinical Cardiology, National Heart & Lung Institute, Imperial College London and Honorary Consultant Cardiologist to the Royal Brompton, Harefield and Hammersmith Hospitals.

His main area of interest is in heart failure, extending from its epidemiology and prevention, through the development and implementation of guidelines for the application of current knowledge, to large randomized trials. Particular current interests include the influence of myocardial substrate on therapeutic response, novel methods of delivering care and theranostics.

He is a Past Chairman of the European Society of Cardiology's Working Group on Heart Failure and of the British Society for Heart Failure, Founded the European Journal of Heart Failure, is a National Institute of Health Research Senior Investigator and Heart Failure Lead for England & Wales, is an editor on the Cochrane Collaboration's Cardiovascular Group and was recently appointed to lead the European Heart Health's Institute on "Innovation & Implementation". He has published more than 800 papers in peer reviewed journals and is a Thomson Reuters Highly Cited Researcher.

ABSTRACT

CV safety trials: Seeing the trees for the forest - are we losing the prospect for CV protection?

There is the old adage "primum non nocere". This is a useful concept when the treatment being considered carries a great deal of risk, there is no evidence that this risk outweighs the benefit and the disease is relatively benign. Otherwise "primum non nocere" is a stupid and dangerous concept that serves only to benefit doctors and snake-oil merchants but not patients. It's totally wrong-headed when it is possible to assess therapeutic interventions in well-designed trials. I don't care how safe an ineffective treatment is, I can just avoid it or give placebo (although placebo is not risk free). Primum efficatum should be the watch-word of the physician who wants to help patients rather than just lead a quiet life.

Cardiovascular safety trials may fail at the design stage (before the first patient is enrolled) for several reasons:

1. The intervention is ineffective and therefore even if it's safe it's not needed. Fortunately, this is now rare
2. The intervention alters a marker (like HbA1c) that has not been shown to translate into improved outcome. Most trials of treatments to improve glycaemic control fall into this category
3. The intervention is compared to something that is not known to be effective – for instance, any long-term trial that uses aspirin as a control group.

Mitochondrial protectants

Mitochondrial exist inside almost all mammalian cells. On the inner membrane, sits the electron transport chain (ETC) that provides 95% of the bodies energy supply in the form of adenosine triphosphate (ATP). ATP is recycled about 1500 times per day from adenosine diphosphate (ADP). This represents the production of 50-75kg of ATP. About 20% of the internal membrane is composed of cardiolipin that forms a lattice on which the ETC complexes sit. ETC dysfunction may lead to increased production of free radicals and oxidative stress and reduced production of ATP which could impair myocyte relaxation and contraction. Mitochondrial 'behaviour' also changes in heart failure; there position in the cell changes and they become smaller.

Several promising agents target mitochondrial function more or less specifically including iron, co-enzyme Q10 and elamipretide.Randomized trials suggest that intravenous iron improves symptoms and possible outcome in patients with heart failure and iron deficiency. Two recent small studies of co-enzyme Q10 suggest a substantial reduction in mortality. Initial studies of elamipretide suggest possible improvement in cardiac and renal function. Ongoing trials of all three interventions exist.

Jean-Paul Clozel (Actelion, CHE)

Jean-Paul Clozel is a cardiologist educated in France, with further training in pharmacology and physiology at the University of Montreal, Canada, and the University of California, San Francisco. After eleven years as a clinician, he decided to move to applied research. During his 12 years at F. Hoffmann-La Roche Ltd, he was responsible for the selection of the first T-channel blocker. He also participated in the characterization of renin inhibitors as well as several endothelin receptor antagonists such as bosentan and clazosentan. Overall, the group he was heading discovered seven compounds that entered clinical trials. During his 25-year career in cardiology, he has published widely in peer-reviewed medical and scientific journals. At the same time, his passion has remained unchanged: being involved as closely as possible in bringing innovative medicine to "his" patients. He has developed various, novel experi-

mental models allowing the differentiation of these drugs, work honored with the 1997 Hoffmann-La Roche Research Prize. In 2007 he was nominated professor at the Collège de France in Paris, France (Chair of Technical Innovation). At the end of 1997, Jean-Paul founded Actelion, together with his wife, Martine, and work colleagues and friends Walter Fischli, Thomas Widmann and André J. Mueller, first mainly focusing on Research and Development. Since 2000 he has been the CEO of Actelion.

ABSTRACT

Drug development for orphan cardiovascular diseases: a view from the industry

During the last 15 years new drugs indicated for orphan cardiovascular diseases have appeared. The number of these drugs has rapidly increased and many more are in the development phase. For example, for a disease such as pulmonary arterial hypertension, there was only one i.v. drug approved in 2000. 15 years later there are now 4 i.v. drugs, 7 oral drugs and 2 nebulized drugs available!

Many regulatory and economic incentives explain the extensive efforts that are made in this area. In order to continue to innovate and bring new drugs to these patients, several challenges need to be considered and will be the topic of this presentation.

- Pressure from the patients and some drug companies to approve such drugs with limited information is an issue. The consequences of the approval of a drug with a low level of evidence on further approvals need to be considered.
- The definition of clinically meaningful end points and the feasibility of phase III studies remains a significant issue.
- The notion of surrogacy for phase III end points is extremely difficult to assess.
- Dose finding studies are challenging, taking the low number of patients in account.
- Pediatric studies have - up till now - not resulted in specific pediatric indications.
- With a low number of options, the benefit/risk ratio determination is extremely difficult to determine precisely.
- The use of registries for regulatory purposes is still limited.
- The involvement of patients within the clinical development process needs to increase.

All these challenges are actively discussed between the different parties involved. I am confident that methodological and regulatory progress will allow many new drugs to be developed for the treatment of orphan cardiovascular diseases.

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William Cushman (Memphis, USA)

Dr Cushman, MD is Chief of the Preventive Medicine Section at the Veterans Affairs (VA) Medical Center and Professor of Preventive Medicine, Medicine, and Physiology at the University of Tennessee College of Medicine in Memphis, Tennessee. He graduated Magna cum Laude from the University of Mississippi School of Medicine, completed his Medicine residency training at the University of Mississippi in Jackson, Mississippi, where he served on the faculty from 1977-1988, when he moved to the VA and University of Tennessee in Memphis. He has been an investigator in many clinical studies relating to hypertension, lipid therapy, and diabetes mellitus, including chairman for two VA Cooperative Studies, VA Chair for ALLHAT, and VA Principal Investigator for the ACCORD and SPRINT trials. He was on the Executive Committee for the Seventh (2003) Joint National Committee Report on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC 7) and was on the JNC 8 Panel (2014). He was the VA Champion for the 2014 VA-Department of Defense (VA-DoD) Hypertension Clinical Practice Guideline committee. He has over 200 journal articles in peer reviewed journals, including a number of publications in NEJM, JAMA, and Lancet, and has received approximately $60 million in research funding. In 2010, he received the inaugural John Blair Barnwell Award for Outstanding Achievement in Clinical Science, the Department of Veterans Affairs Clinical Science Research and Development's highest honor for scientific achievement.

ABSTRACT

Rethinking future hypertension trials? Insight from the Systolic Blood Pressure Intervention Trial (SPRINT)

The Systolic Blood Pressure Intervention Trial (SPRINT) was a randomized controlled trial in 9,361 participants, testing whether an intensive systolic blood pressure (SBP) treatment goal <120 mm Hg would lower a composite cardiovascular (CV) outcome compared with a standard treatment goal <140 mm Hg. Eligibility included age ≥50 years, SBP 130-180 mm Hg on 0-4 medications (upper limit reduced based on number of antihypertensive medications participant was on at screening), and no diabetes mellitus, prior stroke, or polycystic kidney disease, since these were being studied on other NIH trials testing lower BP goals. The primary composite outcome was myocardial infarction (MI), other acute coronary syndromes (ACS), stroke, heart failure, or death from CV causes. All major classes of drugs were provided for use on both groups, as needed; chlorthalidone, furosemide (e.g., for more severe CKD), and spironolactone were the preferred diuretics, and amlodipine or diltiazem were preferred calcium channel blockers (CCBs). Investigators were encouraged to initiate therapy with drug classes with the best CV outcome data (diuretics, calcium channel blockers, ACE inhibitors or angiotensin receptor blockers (ARBs). Intensive participants were converted to at least a 2-drug regimen at randomization. Other drugs could be added as needed for BP control. In the standard group medication dose or drug could be reduced if SBP was <130 mm Hg on a single visit or <135 mm Hg on 2 consecutive visits.

At 1 year, the mean systolic blood pressure was 121 mm Hg in the intensive treatment group and 136 mm Hg in the standard-treatment group, and these levels and separation was well maintained through follow-up. Nearly 3 drug average was used in the intensive treatment group and nearly 2 in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.3 years because of a significantly lower rate of the primary outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; HR 0.75; 95% CI 0.64-0.89; p<0.001). All-cause mortality was also lower in the intensive treatment group (HR 0.73; 95% CI 0.60-0.90; p=0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group. We concluded that among patients at high risk for CV events, targeting a SBP <120 mm Hg, as compared with <140 mm Hg, resulted in lower rates of MACE, although significantly higher rates of some adverse events were observed in the intensive-treatment group.

These results will likely lead to guideline recommendations to treat most high-risk hypertensive patients, including many populations excluded fro SRINT, to <120-130 mm Hg. It is possible resistant hypertension will be redefined – perhaps SBP >120 or 130 mm Hg on 3 or more antihypertensive medications. Something like this may become an eligibility criterion for using device therapy in hypertension. It is also possible that if adequate SBP control is considered <120 or 130 mm Hg, device therapy may be more desirable and feasible as ancillary therapy to limit numbers of, or delay or avoid antihypertensive drugs. More research may be needed to assess the efficacy of device therapy at lower levels of BP. Answering these questions may require quite different study designs than has been employed previously for device therapy.

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Gaetano De Ferrari (Pavia, ITA)

Gaetano M. De Ferrari, MD is Associate Professor of Cardiology and Head of the Cardiology Fellowship Program at the University of Pavia, Italy and cardiologist at the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, where he acts as head of the Cardiac Intensive Care Unit and director of The Cardiovascular Clinical Research Center.

Dr De Ferrari graduated in medicine and became a specialist in cardiology and in statistics at the University of Milano. Since graduation he has been involved in the neural control of the cardiovascular system, most notably on the relationship between the autonomic nervous system and the risk of sudden cardiac death in the setting of myocardial ischemia and infarction. He contributed to the concept of autonomic modulation as a potential therapy for patients with heart failure, has been co-Principal Investigator of the two first human studies on the role of chronic vagal stimulation in patients with advanced heart failure and is involved in the further development of this approach- He has worked extensively of post-myocardial infarction risk stratification and on secondary prevention after acute coronary syndrome, with both lipid-lowering agents and antithrombotics.

He has a considerable experience on multicenter clinical trials, having served as member of the Steering Committee for trials such as PROVE IT-TIMI22, ALPHA, SEPIA-ACS TIMI42, TRA2P TIMI-50, IMPROVE-IT, CardioFit VS, NECTAR-HF, RAFFAELLO, FOURIER and as country coordinator for several more trials. .

He is Author of more of 100 papers in peer-reviewed journals, has an H index of 41 and is member of the editorial Board of the American Journal of Cardiology, the Journal of Cardiovascular Translational Research, the Journal of Cardiovascular Medicine.

ABSTRACT

How can we manage dose-response and dose finding? Is preclinical testing sufficient?

It is well known that most pharmacological interventions show a dose– response curve (with some doses ineffective or even detrimental). It is very likely that the same concept applies to electrical stimulation in the bioelectronic field. Analyzing the case of vagus nerve stimulation for patients with heart failure as a paradigm, it is well possible that a considerable part of the divergent results from different clinical studies derives from a different “dose” of stimulation used.

However the concept itself of dose is challenging for bioelectronic medicine. A list of more than 10 parameters that can be varied for vagus nerve stimulation is mentioned below (from Ref 1)

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1. Right vs left vs bilateral stimulation
2. Electrode and waveform configuration
3. Bidirectional efferent and afferent (technically easier), preferential efferent or preferential afferent stimulation (technically more complex)
4. Continuous stimulation versus pulse-synchronous stimulation
5. With pulse-synchronous stimulation: delay from the R wave (or other trigger) and number of pulses per cycle
6. With continuous stimulation: frequency of stimulation
7. Current amplitude, titration protocols, and maximum current
8. Target: heart rate reduction vs low-intensity vagal stimulation without heart rate target
9. Duration of the ON/OFF cycles
10. Presence or absence of long stimulation pauses
11. Heart-rate-dependent stimulation intensity and limits for stimulation withdrawal (e.g., low heart rate)

Only very recently, some partial dose-finding studies have been performed in pre-clinical models with the added problem of selecting a surrogate marker of parasympathetic activation that may correlate with the improvement in heart failure in the clinical setting.

A step forward may only come from a very tight collaboration between careful preclinical evaluations in clinically relevant animal models and clinical evaluations performed by investigators with a thorough knowledge of the pathophysiology of the autonomic nervous system.

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Pieter de Graeff (EMA, NED)

Pieter de Graeff, PhD, MD, was born in 1950. Following medical training at the University of Groningen, he graduated in 1975. Following his military service, he fulfilled a yearlong internship in internal medicine in the US in Youngstown, Ohio.

In October 1977 he started his training as an intern at the department of Internal Medicine, University Hospital, Groningen. In January 1983 he was registered as an internist, practicing up to 2015.

Subsequently, he became a clinical advisor for the Dutch Medicines Evaluation Board, keeping a position as associate professor at the depts of Internal Medicine and Pharmacology/Clinical Pharmacology.

In 1989 he finished his thesis, titled "Effects of captopril on the heart. Mechanisms and Therapeutic Potentials." In 1994 he was co-registered as a clinical pharmacologist. In 1996 he became professor in pharmacotherapeutics. In 2003 he was elected as "teacher of the year".

He maintained a part-time position as senior clinical adviser of the MEB and as head of the cardiovascular subdivision until 2007. In 2007 he became an alternate member of the CHMP and in 2013 a full member. He has fulfilled a number of positions at various organisations, among which the cardiovascular subgroup WP of the EMA (since 1999), which he is currently chairing. He (co-) authored more than 120 publications in peer-reviewed journals with a focus on cardiovascular pharmacology and regulatory science.

He has been involved in writing a number of regulatory cardiovascular guidelines, including those on antihypertensive, lipid-lowering, heart failure and anti-arrhythmic agents.

James de Lemos (Boston, USA)

Dr de Lemos, MD is Professor of Medicine at UT Southwestern Medical Center and holds the Sweetheart Ball-Kern Wildenthal, MD, PhD Distinguished Chair in Cardiology. He has previously served as the Cardiology Service Chief at Parkland Memorial Hospital, and the director of the Cardiology Fellowship at UT Southwestern from 2005-2011. He is a senior investigator with the Dallas Heart Study, and also serves as the Medical Director for this study. His primary research interests are in early detection, risk assessment and management of cardiovascular disease, with a particular focus on the role of cardiovascular biomarkers. His research has evaluated existing biomarkers such as B-type natriuretic peptide, C-reactive protein and cardiac troponins as well as novel biomarkers reflecting biological pathways of disease. He was the lead author of the Z phase of the A to Z trial, an international trial investigating different cholesterol lowering strategies in patients with acute coronary syndromes. He has served on multiple committees of the AHA and ACC, including the STEMI Guideline Committee, and as current Chair of the Research and Publications Committee for the NCDR ACTION-GWTG registry. He has authored or coauthored over 300 manuscripts or book chapters and won several teaching awards.

ABSTRACT

Would a biomarker risk score help to identify high-risk subjects for randomized clinical trials?

Biomarkers play an increasingly important role in contemporary cardiovascular medicine, with established importance in diagnosis, risk assessment, and therapeutic selection. Within cardiovascular clinical trials, biomarkers may serve as surrogate endpoints in early-phase drug discovery programs. Biomarkers also play an important role as an entry criterion for clinical trials; for example, troponin elevation is often required for enrollment in trials testing novel therapies for acute coronary syndromes. Biomarkers can help to refine phenotypes to ensure selection of patients most suitable for a particular therapy. Also, requiring deviation of selected markers may help to ensure an adequate endpoint rate, allowing testing of efficacy with smaller sample sizes. Biomarker data are more objective than history and exam features and thus will help "even the playing field" across enrolling centers and countries. The TOPCAT trial provides a particularly important lesson in this regard. We will explore the potential value of panels of biomarkers, with each included biomarker reflecting non-redundant components of cardiovascular risk. We propose that such panels will provide more accurate estimation of risk than standard clinical trial entry criteria, which otherwise result in enrollment of subjects with widely varying CVD risk.

David DeMets (Madison, USA)

David L. DeMets, PhD is currently the Max Halperin Professor of Biostatistics and former Chair of the Department of Biostatistics and Medical Informatics at the University of Wisconsin – Madison. He has co-authored numerous papers on statistical methods, collaborative research and four texts on clinical trials, two specifically on data monitoring. He has served on many NIH and industry-sponsored data monitoring committees for clinical trials in diverse disciplines. He served on the Board of Directors of the American Statistical Association, as well as having been President of the Society for Clinical Trials and President of the Eastern North American Region (ENAR) of the Biometric Society. In addition he was Elected Fellow of the International Statistics Institute, the American Statistical Association, the Association for the Advancement of Science, the Society for Clinical Trials and the American Medical Informatics Association. In 2013, he was elected as a member of the Institute of Medicine.

ABSTRACT

The 2015 IOM Report: responsible sharing of clinical trial data

In 2014, the Institute of Medicine (IOM) commissioned a Panel to review the current practice of sharing of completed clinical trial data and to make recommendations regarding data sharing. There are several compelling reasons for sharing data including making it feasible for other investigators to reproduce initial published findings, to carry out additional analyses, to strengthen and increase scientific knowledge, and to stimulate new ideas for research. There are also some serious challenges to address, including the need to protect participant privacy and honor their consent, to safeguard legitimate economic interests of sponsors (e.g. Intellectual Property), to allow the academic investigators adequate time to publish secondary results, gaining their academic credit. In addition, there are several key stakeholders in the process of data sharing. These include the trial participants, the investigators, the institutions, funders and sponsors, research ethics groups such as Institutional Review Boards (IRBs), medical journals, professional societies and patient advocacy groups.

In sharing clinical trial data, it is necessary to define what data is to be shared. First, there is the raw patient level data which may take the form of case report forms (CRFs) with individual patient data, laboratory data as well as quality of life questionnaires and textual clinician notes. For data to have any meaning, there must be meta data. For data to be analyzable, it needs to be converted into numerical metrics at a participant level. There will be an analyzed participant level data set that corresponds to each publication or report. Finally, there are brief summaries of the analyzed data that appear in publications or in regulatory submissions.

The IOM Report on Responsible Data Sharing contains four basic recommendations. The first IOM recommendation is that the stakeholders in a clinical trial should foster a culture in which data sharing is the expected norm and be committed to a responsible strategy for this process.

A second recommendation is that sponsors and investigators should share the various types of clinical trial data no later than the following timelines (when & what) as described: Before the trial is initiated, it should be registered with clintrials.gov, or the equivalent in other countries.

Within 12 months of study completion in participant follow-up (e.g. last patient last visit or LPLV), a summary level of results should be provided as in clintrials.gov as well as a lay or public level presentation. Within 6 months of publication in a medical or scientific journal, the patient level analyzed and de-identified data used in the paper should be made available. Within 18 months of trial completion (last patient, last visit), the full analyzable de-identified data set should be made available. For trials which are submitted to regulatory agencies for produce approval, the full analyzable de-identified data set.

Recommendation 4 relates to the remaining data sharing challenges. In particular, sponsors and investigators must address over the next several months including infrastructure, technology, workforce & sustainability.

References

IOM Report, Sharing Clinical Trial Data, Maximizing Benefits and Minimizing Risk, January 2015
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Peter DiBattiste (Janssen, USA)

Peter M. DiBattiste, MD, FACC, FAHA, is the Global Development Head, Cardiovascular at Janssen Research and Development. In this role, he is responsible for establishing the strategy and overseeing the execution of the development programs for all cardiovascular products in development.
After decade in clinical practice as an interventional cardiologist, Pete entered the pharmaceutical industry in 1997. He joined Johnson & Johnson in 2005 as Vice President, Cardiology and assembled and led a clinical

team of physicians and scientists who have focused on the development of the oral anticoagulant, rivaroxaban. During Pete's tenure as Development Head, he led two of the largest clinical trials in the company's history – ATLAS and ROCKET AF – collectively enrolling more than 30,000 patients. Pete is focused on the continued development of Xarelto, and on the continued exploration and development of novel antithrombotics.
Peter obtained his MD at Harvard Medical School.
He completed his internal medicine residency at the University of Texas Southwestern, and his fellowship in cardiovascular disease at the University of Pennsylvania.

Jun Dong (FDA, USA)

Dr Jun Dong is a Medical Officer/Clinical Reviewer at the Center for Devices and Radiological Health, US Food and Drug Administration.

A significant part of his work is to review protocols and results of clinical trials that support marketing approval of ablation devices for the treatment of atrial fibrillation and other arrhythmias. Dr Dong is also an Adjunct Assistant Professor in Medicine at the Johns Hopkins Medicine/Cardiology where he participates in complex ablation procedures.
After graduating from medical school, Dr Dong completed his clinical trainings in Internal Medicine and Cardiology at the Second Teaching Hospital of Chongqing University of Medical Sciences in China. He received further training in clinical cardiac electrophysiology at the German Heart Center Munich and received a doctorate degree from the Technische Universtät München (Munich University of Technology) in Germany.
Dr Dong then completed a postdoctoral clinical research fellowship in cardiac electrophysiology with particular emphasis on catheter ablation of atrial fibrillation and image-guided catheter ablation of complex arrhythmias at the Johns Hopkins Electrophysiology where he later joined the faculty.

ABSTRACT

Atrial fibrillation prevention and treatment trials - Regulatory perspective

Atrial fibrillation (AF) ablation is subject to continuous technological innovations with a goal of improving effectiveness, safety and procedural efficiency. This presentation will discuss the challenges FDA is facing in the evaluation of rapid technological innovations in AF ablation and factors to consider in designing clinical trials to meet regulatory requirements for these innovations.

Kristina Dunder (EMA, SWE)

Dr Dunder graduated from Uppsala University (School of Medicine) in 1988. She specialized in internal medicine and endocrinology/diabetology and served as a medical doctor at the Uppsala Academic Hospital until 2005.
In 2004 she defended a thesis with the title "Clinical manifestations of coronary heart disease and the metabolic syndrome".
Since 2005 Dr Dunder holds a position as a clinical assessor and senior expert at the Medical Product Agency in Uppsala, Sweden. She is also the Swedish member of the CHMP (Committee of Human Medical Products) at the EMA (European Medicine Agency) in London, GBR since 2012 and a member of the Cardiovascular Working Party.

Dr Dunder was one of the Rapporteurs for the update of the guideline Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus which became effective November 2012, and is currently coordinating the ongoing update of the Guideline of medical products used in weight control as well as the Reflection paper on assessment of the cardiovascular safety profile of medicinal products for the treatment of cardiovascular and metabolic diseases.

Amany El-Gazayerly (EMA, NED)

Amany El-Gazayerly is a senior clinical assessor in the Dutch Medicines Evaluation Board, the Netherlands. She obtained her Bachelor in Medicine and Surgery degree from Cairo University, Egypt. She worked as a researcher in the research institute of Ophthalmology in Cairo. Then she obtained a Master and PhD degrees in Pharmacology from Cairo University.

She then followed an academic career and worked as a lecturer and assistant professor in pharmacology in Cairo University.
Since 2005 she pursued a career in the regulatory field, working as a cardiovascular assessor in the Dutch agency. She is also a member of the Scientific advice group of the European Medicines Agency EMA, and a member of the Cardiovascular working group in EMA. This is the group responsible for drafting and updating EU regulatory guidelines. Her main fields of interests are pulmonary arterial hypertension, anticoagulants, and antiarrhythmics.

Mads Engelmann (Novo Nordisk, DEN)

Dr Engelmann (B.Sc, MD, PhD.) joined Novo Nordisk A/S as International Medical Vice President in 2013 and is a senior cardiovascular (CV) expert to Novo Nordisk responsible for providing strategic CV expert input on complex medical issues arising during preclinical and clinical development including execution of trials, in particular design, conducting and reporting in CV outcomes trials and thorough QT studies.

Prior to joining Novo Nordisk, Dr Engelmann has held several positions in the pharmaceutical industry with focus on diabetes and cardiovascular complications.

Dr Engelmann has headed up Medical Affairs for GSK and AstraZeneca in Denmark, been responsible for diabetes medical activities in Scandinavia for Eli Lilly and as Global Medical Director responsible for launch and post-launch activities as well as phase 3 and 4 development for Eli Lilly in Europe.

Dr Engelmann holds a BSc in Chemical Engineering from the Technical University in Denmark, MD and PhD degrees from University of Copenhagen and is board certified in Cardiology and Internal Medicine.

Murray Epstein (Miami, USA)

Dr Murray Epstein is Professor of Medicine at the University Of Miami Miller School Of Medicine. He was a recipient of the 1990 Distinguished Scientist Award of the National Kidney Foundation. In May 2011, he was awarded the American Society of Hypertension's prestigious Marvin Moser Award for Clinical Hypertension. Dr Epstein was also awarded an Investigatorship of the Howard Hughes Medical Institute.He is also a member of many prestigious professional societies including the American Society for Clinical Investigation.

Dr Epstein served as a member of the National High Blood Pressure Education Program Coordinating Committee and is a contributor to the 6th Report of the Joint National Committee. Dr Epstein is listed in Who's who in America (59th, 60th and 61st edition) and Who's Who in Medicine.

Dr Epstein has authored over 440 journal articles and book chapters. He served as the Editor of four editions of The Kidney in Liver Disease, and three editions of Calcium Antagonists in Clinical Medicine. Many of Dr Epstein's publications have related to 1) the pathogenesis and management of hypertension, 2) renal function in diseases characterized by abnormal volume regulation, and 3) the role of the renin angiotensin aldosterone system, and 4) the evolving role of mineralocorticoid antagonist therapy as a means of retarding progression of chronic kidney disease and abrogating cardiovascular events in CKD patients. Dr Epstein has also written extensively on head out water immersion, a unique clinical investigational model that he has defined and applied to the study of a wide range of disease states. The unique attributes of this clinical investigative model include a prompt redistribution of circulating blood volume with a consequent relative central hypervolemia, in the absence of concomitant changes in plasma composition. Dr Epstein has successfully applied the immersion model as a clinical investigative tool to characterize the determinants of deranged volume homeostasis and renin-aldosterone, eicosanoid, kallikrein, vasopressin and ANF responsiveness in diverse edematous disorders including advanced liver diseases, chronic renal failure and hypertension

Most recently Dr Epstein's major investigative interests focus is on the role of mineralocorticoid receptor signaling as a determinant of cardiovascular complications in CHF and CKD, and mineralocorticoid receptor blockade as an intervention to abrogate both cardiovascular hard endpoints, as well as progressive kidney disease, and as therapy to confer cardiovascular and renal benefits, in patients with chronic kidney disease. He has recently extended these studies to ESRD patients who are being treated by hemodialysis. As a corollary of this investigative focus, at present Dr Epstein is actively involved in the clinical development of newer drugs to manage hyperkalemia, including patiromer, highlighting their role as "enablers' to facilitate sustained RAASI therapy while obviating down-titration or discontinuation of RAASI. A member of multiple editorial boards, Dr Epstein also serves as a reviewer for numerous prominent journals and for study sections for granting agencies.

ABSTRACT

The substantial gap between the recommendations in treatment guidelines and the real-world prescribing patterns for RAAS inhibitors: a "call to action" to develop newer treatment modalities to achieve and sustain normokalemia on a long-term basis

Recently several observational and retrospective studies have reported a large gap between the forceful and assertive recommendations in the promulgated and mandated guidelines for the treatment of CHF and CKD with RAAS inhibitor therapies and real-world practice.. A retrospective analysis of data from the American Heart Association's "Get With the Guidelines - Coronary Artery Disease" database reported that less than 10% of eligible HF patients hospitalized for myocardial infarction were prescribed an aldosterone agonist at discharge 1). Additional data derives from the ESC-HF Long-Term Registry, a prospective, observational study conducted in 211 Cardiology Centers of 21 European and Mediterranean countries, members of the European Society of Cardiology

(ESC) 2). Studies Applying Big Data Analytics to Delineating the Role of RAASI-induced Hyperkalemia in Disrupting Utilization of Guideline-mandated RAASI Treatment

In order to better elucidate this apparent treatment gap, we recently undertook a "Big Data Analytics" Approach - a comprehensive analysis of a large database of electronic medical records (>7million patients) to evaluate three pivotal questions: (1) whether RAAS inhibitors are being prescribed according to treatment guidelines, (2) what happens to RAAS inhibitor prescriptions after hyperkalemia events, and (3) what the clinical outcomes are in patients whose RAAS inhibitors are discontinued or prescribed at doses lower than recommended in guidelines 3).

De-identified medical records (2007-2012) for patients with at least 2 potassium readings were obtained from Humedica, a large U.S. database of electronic health records (www.humedica.com). Study patients were persons receiving care from providers in integrated health delivery networks across the U.S. Inclusion criteria required at least 1 outpatient RAAS inhibitor prescription and 12 months data prior to July 1, 2009 (the index date). RAAS inhibitors included ACE inhibitors, ARBs, direct renin inhibitors and select MRAs. To ensure continuity, inclusion also required evidence that patient engagement with the healthcare provider began at least 12 months prior to the index date and continued up to the index date. The response to hyperkalemia events was evaluated for each hyperkalemia event in the data (2007-2012) without restriction by patient comorbidity status.

RAAS inhibitor prescriptions were classified by dose level using the following dose categories: 'supramaximum' was defined as any RAAS inhibitor dose above the labeled dose, 'maximum' was defined as the labeled dose, 'submaximum' dose defined as any RAAS inhibitor dose lower than the labeled dose, or 'discontinued' defined as the absence of RAAS inhibitor prescriptions for a period > 390 days subsequent to prior prescription.

Determining RAAS inhibitor Dose Subsequent to Hyperkalemia Event

An event-level analysis was used to examine RAAS inhibitor dose changes following the occurrence of hyperkalemia. Hyperkalemia was defined as any serum potassium measurement above 5.0 mEq/L. All laboratory-reported events of serum potassium ≥ 5.1 mEq/L were classified by severity (mild, 5.1-5.4 mEq/L; moderate-to-severe, ≥ 5.5 mEq/L). RAAS inhibitor prescription status was assessed before and after each hyperkalemia event, with a 390-day follow-up period for assessing RAAS inhibitor dose following hyperkalemia. (390 days corresponds to the time period required to identify discontinued RAAS inhibitor prescriptions) Post-hyperkalemia event dosing was compared to the last pre-hyperkalemia dose (or prescription expiration) before the hyperkalemia event. Outcomes were described as the percent of hyperkalemia events for which the next RAAS inhibitor dose represented maintaining, down titrating or discontinuation. Results were segmented by RAAS inhibitor dose category (submaximum or maximum) at the time of the hyperkalemia event and severity of the hyperkalemia event (mild or moderate-to-severe). In this patient-level analysis, differences in clinical outcomes between patients with submaximum or discontinued RAAS inhibitor vs. those remaining on maximum doses were evaluated in the total study population as well as within disease categories (CKD 3-5, HF, or DM). Adverse outcomes evaluated were CKD progression and progression to ESRD (by eGFR laboratory value, diagnosis code, or chronic dialysis by procedure code); stroke and acute myocardial infarction (by diagnosis code during inpatient hospitalization); and coronary artery bypass and percutaneous coronary intervention (by procedure code); or all-cause mortality.

RAAS inhibitor dosing subsequent to hyperkalemia events

Laboratory records included 218,813 hyperkalemia events (144,800 mild and 74,013 moderate-to-severe) in 66,862 patients. Analysis of RAAS inhibitor dosing before and after these hyperkalemia events revealed that a substantial proportion of patients had changes in their dose following elevated serum potassium, with dose changes occurring more frequently after moderate-to-severe hyperkalemia events.

Cardiorenal outcomes and mortality by RAAS inhibitor dose

Patients on submaximum or discontinued RAAS inhibitor dose levels showed consistently worse outcomes compared to patients on maximum dose irrespective of comorbidity status or patient age. Over 50% of patients with CKD stages 3-4 who were discontinued from RAAS inhibitor experienced an adverse outcome or died compared with 47.4% of patients on submaximum dose and 42.6% of patients on maximum dose. Nearly 60% of patients with HF who were discontinued from RAAS inhibitor experienced an adverse outcome or mortality compared with 52.3% of patients on submaximum dose and 44.3% of patients on maximum dose had consistently worse outcomes compared to patients on maximum dose regardless of age group, with the exception of patients with DM who were <65 years in whom maximum and submaximum RAAS inhibitor doses were associated with similar levels of adverse outcomes or mortality (20.5% and 19.8% respectively).

The association between discontinuation of RAAS inhibitors and mortality was striking. Patients on submaximum dose or who discontinued RAAS inhibitors died twice as frequently as patients on maximum dose irrespective of comorbidity status. Among patients with HF, mortality was recorded for 13.7% of patients on maximum dose RAAS inhibitor compared to 27.7% on submaximum dose and 30.1% of patients who discontinued.

What insights and lessons can we derive from this comprehensive "Big Data Analytics" study delineating the Role of RAASI-induced Hyperkalemia in Disrupting Utilization of Guideline-mandated RAASI Treatment? Overall, the results of these analyses clearly indicate that there is a substantial gap between the recommendations in treatment guidelines and the real-world prescribing patterns for RAAS inhibitors. Among patients with cardiorenal comorbidities for which RAAS inhibitors are recommended by the guidelines, this retrospective analysis showed that more than half were prescribed lower than recommend doses, and

approximately 14-16% had been discontinued from RAAS inhibitor therapy.. Our results suggest that the prescribing patterns for RAAS inhibitors may be altered by the development of hyperkalemia. Moderate-to-severe hyperkalemia events (serum potassium ≥ 5.5 mEq/L) were followed by down titration or discontinuation of RAAS inhibitor therapy in nearly half of all patients on maximal dose and discontinuation in nearly one-third of patients on submaximal dose. An extremely important observation of this study is that patients on submaximum doses or who discontinued RAAS inhibitors had worse cardiorenal outcomes and higher mortality than patients on maximum doses. Taken together, these results highlight the extraordinary challenge behind RAAS inhibitor prescribing decisions, attempting to balance the risk of provoking hyperkalemia with the benefits to cardiorenal morbidity and mortality. A great irony is the fact that those patients who are known to derive the most benefit from these drugs (CKD patients with concomitant diabetes or HF) are the same patients who are at highest risk of developing hyperkalemia.

In concert these observations constitute a "call to action" to develop newer treatment modalities to lower serum potassium and to achieve, and even more importantly, to sustain nornokalemia on a long-term basis. Such an approach will function as an "enabler", obviating down-titration or discontinuation of RAASi therapies.

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Murray Esler (Melbourne, AUS)

Murray Esler is a cardiologist and medical scientist, based in Melbourne. He is a Senior Director of the Baker IDI Heart and Diabetes Institute, Melbourne, an Adjunct Professor of Medicine of Monash University, and a Fellow of the Australian Academy of Science. His research interests are stress and its effects on the heart and blood pressure, the causes and treatment of high blood pressure and heart failure, and the neurotransmitters of the human brain. He is the author of more than 400 papers on these topics. Prof Esler's principal research contribution has been the development of isotope dilution methodology to study the human sympathetic nervous system, and the application of this tool in the investigation of the sympathetic neural physiology of circulatory control, aging, exercise and mental stress responses, and the neural pathophysiology of cardiac failure and essential hypertension. His demonstration of a high level of chronic activation of the cardiac sympathetic outflow in patients with heart failure provided the theoretical backdrop for the evaluation of beta-adrenergic blockers in this condition. More recently, his demonstration of activation of the renal sympathetic outflow in essential hypertension was a stimulus for the development of radio-frequency ablation of the renal sympathetic nerves for resistant hypertension. He is chief investigator of a trial describing the successes achieved with this new treatment published in the Lancet (2010;376:1903-1909) and Circulation (2012;126:2976-2982). For his research in these fields Prof Esler was a recipient of the Merck Sharpe & Dohme Award of the International Society of Hypertension, a Centenary Medal of the Government of Australia, the Hamdan Award for Medical Research Excellence of the United Arab Emirates, the Order of Australia, the Bjorn Folkow Award of the European Society of Hypertension, and the Excellence Award of the Council for High Blood Pressure Research of the AHA. He was the 2014 Louis F Bishop Keynote Lecturer of the American College of Cardiology, and the 2014 American Society of Hypertension Keynote Lecturer.

ABSTRACT

Autonomic modulation readouts for patient selection, dose-finding and/or response prediction/monitoring: any simple test?

Therapeutic device modification of the sympathetic nervous system has been evaluated primarily in the treatment of resistant hypertension, with less testing in the treatment of heart failure and cardiac arrhythmias. The principal techniques used have been catheter-based ablation of the renal sympathetic nerves, and central sympathetic inhibition with an implanted arterial baroreceptor device.

As not all resistant hypertensive patients have material blood pressure lowering with renal nerve ablation, pre-selection of likely responders is clinically important, but difficult. There are some clinical pointers, such as the fact that those with isolated systolic hypertension have a lesser response, but pre-selection needs to move beyond this. The usual expectation is that those with neurogenic essential hypertension (sympathetic nervous system activation) will respond best to renal denervation, and arterial barostimulation. This may be so, but has not been proven, and contrary to this some non-neurogenic experimental models of hypertension do have BP-lowering with surgical renal denervation. Many patients with resis-

tant essential hypertension do have marked activation of the renal sympathetic outflow, and might be expected to respond well to device reduction of sympathetic activity, but no simple test can detect these patients. Isotope dilution measurement of renal norepinephrine spillover is required.

The field of renal denervation treatment of hypertension has been plagued by the absence of a readily accessible test of achieved renal sympathetic denervation. With arterial barostimulation this is less of an issue. A test of renal denervation which can be performed in the catheter laboratory, and which can guide the procedure is not yet available, despite active investigation. The efficacy of the renal denervation procedure can be evaluated retrospectively with renal norepinephrine spillover measurements; the results are unsettling – achieved denervation with current methodology lies in the range of 0% to 90%. Experimental studies in pigs and dogs explain this. The sympathetic nerves are some distance from the renal artery proximally, where RF energy is typically delivered (most notably in Symplicity HTN-3). Energy delivery in the distal renal artery and renal artery divisions produces more complete and uniform denervation. This knowledge clearly must inform clinical procedures in the future. At present, the prediction of BP fall with the renal denervation procedure from the neural pathophysiology of the hypertension, even if neural mechanisms could be delineated accurately, would be confounded by uncertainty concerning the adequacy of denervation.
How can responses be best monitored? Clinical BP lowering is best assessed with 24-hour ambulatory blood pressure measurement. Measuring the sympathetic modification with the procedure is complex. Sympathetic nerve recording with microneurography quantifies central sympathetic inhibition with arterial barostimulation, and that due to ablation of afferent renal nerves (which project to the CNS to cause sympathetic excitation in resistant hypertension) with renal nerve ablation devices. Are any "simple" tests of the sympathetic nervous system available, and of use in this context? A hierarchy of available human sympathetic nervous system tests can be constructed, ranging from most, to least precise and specific. Best are microneurography and measurement of regional, organ-specific norepinephrine spillover, measurement of whole body norepinephrine spillover ranks next, followed by plasma norepinephrine measurements, and urinary norepinephrine measurements, in order. Measurements of heart rate variability and heart rate low frequency spectral power are not reliable measurements of sympathetic activity (heart rate variability is a useful test of the cardiac vagus). There are no simple and fully reliable measures of sympathetic activity in the context of device sympathetic inhibition, or in fact in any other setting.

In cardiac failure and cardiac arrhythmias, sympathetic activation is commonly present, and a potential therapeutic target, but less tested with device sympathetic inhibition than in hypertension. In heart failure activation of the cardiac and renal sympathetic outflows is present; there is a well-documented quantitative link of the degree of both cardiac and renal sympathetic activation to prognosis. Device trials in these areas, to-date, are preliminary. The value of beta-adrenergic blockade in heart failure, however, suggests probable benefit.

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Derek Exner (Calgary, CAN)

After finishing medical school at the University of Saskatchewan, Derek (MD, MPH, FRCPC, FACC, FAHA, FHRS) completed his post-graduate training at the University of Western Ontario and the University of Calgary. Following that he completed his MPH at Johns Hopkins and a research Fellowship at the National Heart, Lung and Blood Institute. Dr Exner is the Associate Dean, Clinical Trials at the Cumming School of Medicine, Canada Research Chair in Cardiovascular Clinical Trials and is a Professor of Cardiac Sciences and Community Health Sciences at the University of Calgary. Derek is leading multiple large international trials, is a world authority on arrhythmias, has over 300 peer-reviewed publications and abstracts and multiple patents related to using ECG signals to evaluate cardiac structure and the risk of serious arrhythmias. He is actively engaged in research with multiple small and

large biotech companies in Canada and beyond and has obtained over $50 million in funding from peer-reviewed and industry sources over the past two decades. The Canadian Institutes of Health Research, the Heart and Stroke Foundation and Alberta Innovates Health Solutions all support Dr Exner's research.

ABSTRACT

Risk estimation following infarction noninvasive evaluation – ICD efficacy (REFINE ICD)

Study purpose:
To test whether an ICD reduces mortality in a group of 1,400 patients with a left ventricular ejection fraction (LVEF) of 36% to 50% plus abnormal T-Wave Alternans (TWA) and impaired Heart Rate Turbulence (HRT) measured 2 to 60 months after an index myocardial infarction (MI).

Background:
Sudden death prematurely ends the lives of over 1,500,000 people worldwide each year. Reliable identification of those at risk of sudden death has remained elusive. Relying on a low LVEF to select patients for preventive therapies such as an implantable cardioverter defibrillator (ICD) is hampered by poor sensitivity and low positive accuracy. The REFINE study (Exner et al., JACC 2007) found that abnormal TWA plus impaired HRT reliably identifies patients at risk of sudden death early after MI.

Objectives:
Primary - An ICD, in additional to usual care, versus usual care will increase the probability of survival in subjects with LVEFs 36% to 50%, impaired HRT and abnormal TWA measured 2 to 60 months after MI.
Secondary - Compare temporal patterns of health-related quality of life in ICD vs. control subjects.

Subject selection:
Inclusion
18-80 years old, clinically appropriate ICD candidate, LVEF 36% to 50% measured 2 to 60 months post-MI and > 3 months after angioplasty or bypass surgery and < 6 months of the screening visit, revascularization where clinically indicated, appropriate medical therapy, sinus rhythm in the 2 weeks prior to the Holter assessment, and abnormal HRT and TWA on the Holter assessment performed 2 to 60 months after MI.
Exclusion
No informed consent, inability to complete the screening Holter, use of antiarrhythmic drugs, persistent or permanent atrial fibrillation, indication for bradycardia pacing, indication for an ICD or resynchronization ICD, poor 12-month survival, chronic renal failure, participation in another trial that may interfere with the results, pregnancy, or an inability to comply with follow-up.

Design:
Parallel-design, prospective, multicenter, international, randomized controlled trial in which subjects will be randomized 1:1 to treatment (ICD) vs. control therapy. Subjects with LVEF values 36% to 50%, abnormal TWA, and impaired HRT measured 2 to 60 months post-MI will be randomized to ICD vs. no ICD.

Statistical aspects:
This trial will provide 90% power to address the primary hypothesis. Clinical events and ICD events committees will independently adjudicate outcomes. Standard methods of statistical analysis and reporting will be used. One event-driven interim analysis is planned.

Study management:
The Libin Cardiovascular Institute at the University of Calgary is the Clinical Coordinating Centre (CCC) and the Montreal Heart Institute is the Data Coordinating Centre (DCC). An international Executive Committee of recognized leaders in arrhythmia clinical trials have designed this study and will oversee trial conduct. An independent Data and Safety Monitoring Committee will provide additional, independent oversight of the trial.

Present status:
To date there are over active clinical 80 sites worldwide. Approximately 25% of the study population has been enrolled. The REFINE ICD trial is expected to complete enrolment in 2019.

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Andrew Farb (FDA, USA

Andrew Farb, MD is a medical officer and senior reviewer in the Division of Cardiovascular Devices at FDA's Center for Devices and Radiological Health (CDRH). He is a graduate of Dartmouth College (B.A.) and Cornell University Medical College (MD). He completed an internship and residency in internal medicine, a one-year residency in anatomic pathology, and a fellowship in clinical cardiology at The New York Hospital – Cornell Medical Center. Following a fellowship in cardiovascular pathology at The Armed Forces Institute of Pathology (AFIP), he served as a staff cardiovascular pathologist at AFIP with research interests in and publications on coronary atherosclerosis and mechanisms of thrombosis, coronary artery interventions, and structural heart disease.

He joined the FDA in 2004, where he has concentrated on clinical study development for interventional cardiology, structural heart, and peripheral vascular devices as well as providing guidance on pre-clinical animal testing. His most recent work at the Agency has focused on early feasibility and first-in-human studies. He co-authored FDA's Guidance document entitled "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies," and he is the Co-Leader of CDRH's Early Feasibility Study Program. In addition to his position at FDA, he provides cardiovascular pathology consultations and engages in direct patient care as an attending physician in clinical cardiology.

Michael Felker (Durham, USA)

Michael Felker, MD, MHS, is Professor of Medicine with tenure in the Division of Cardiology at Duke University Medical Center. He is Chief of the Heart Failure Section at Duke University School of Medicine, Director of the Heart Center Clinical Research Unit, and 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 190 peer reviewed articles and book chapters in the field of heart failure. He has served on the Executive and Steering Committees 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,* the leading heart failure textbook. His researches focus in on clinical trials in acute and chronic heart failure and the use of biomarkers as diagnostics, prognostic, and therapeutic tools in heart failure.

Valentin Fuster (New York, USA)

Dr Valentin Fuster, MD, PhD, serves The Mount Sinai Medical Hospital as Physician-in-Chief, as well as Director of Mount Sinai Heart, the Zena and Michael A. Wiener Cardiovascular Institute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health. He is also the Richard Gorlin, MD/Heart Research Foundation Professor, Icahn School of Medicine at Mount Sinai. Dr Fuster was the President of Science and is now the General Director of the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) in Madrid, Spain and also and Chairman of the SHE Foundation (Science for Health and Education).

The innumerable positions he has held include those of President of the American Heart Association, President of the World Heart Federation, member of the US National Academy of Sciences (where he chaired the Committee for the document on "Promotion of Cardiovascular Health Worldwide"), member of the US National Heart, Lung and Blood Institute and President of the Training Program of the American College of Cardiology.

After qualifying in medicine at the University of Barcelona, Valentin Fuster continued his studies in the USA. He was Professor in Medicine and Cardiovascular Diseases at the Mayo Medical School, Minnesota and the Medical School of Mount Sinai Hospital, New York, and from 1991 to 1994 Professor of Medicine at Harvard Medical School and Chief of Cardiology at the Massachusetts General Hospital, Boston. In 1994, he was named director of the Cardiovascular Institute at Mount Sinai a post he has combined since 2012 with that of Physi-

cian-in-Chief of the Hospital. Dr Fuster has been named Doctor Honoris Causa by Thirty-three universities around the world, and has three of the most important awards from US National Institute of Health. He is an author on more than 900 scientific articles in international medical journals, and has published as lead Editor of two leading books on clinical cardiology and research, "The Heart and Atherothrombosis and Coronary Artery Disease" and "Hurst's The Heart". He was also named Editor-in-Chief of the prestigious journal Nature Reviews in Cardiology. His contributions to cardiovascular medicine have had an enormous impact on the treatment of patients with heart disease.

His research into the origin of cardiovascular events, which have contributed to improved treatment of heart attack patients, was recognized in 1996 by the award of Prince of Asturias Award for Technical and Scientific Research. Among his many achievements, it is noteworthy that Dr Fuster is the only cardiologist to have received the highest awards for research from the four leading cardiovascular organizations the American Heart Association, the American College of Cardiology, the European Society of Cardiology and the Interamerican Society of Cardiology.

In 2008, Dr Fuster received the Kurt Polzer from the European Academy of Science and Arts. In 2009, he received the prestigious international Arrigo Recordati prize for his contribution to advances in the area of cardiovascular imaging. In June 2011 he was awarded the Grand Prix Scientifique of the Institute of France, considered the most prestigious award in cardiology, for his translational research into atherothrombotic disease.

Other accolades include the Gold Heart Award, the Lewis A. Conner Memorial and the James B. Eric Achievement Award from the American Heart Association, the Distinguished Service Award and the Distinguished Teacher Award from the American College of Cardiology, the Gold Medals of the American and European Cardiology Societies, also the highest award for Medicine from Erasmus University (Rotterdam). In 2012, Dr Fuster was named by the American College of Cardiology as one of the Living Legends in Cardiology Medicine, and was awarded the Research Achievement Award, the highest award given by the American Heart Association. In 2013, Dr Fuster was awarded the Ron Haddock International Impact Award by the American Heart Association and the American Stroke Association in recognition of his global leadership.

In addition, in 2014, Dr Fuster was appointed Editor-in-Chief of the Journal of the American College of Cardiology, the ACC's flagship publication and the main American source of clinical information on cardiovascular medicine. In May 2014, King Juan Carlos I of Spain granted Dr Fuster with the title of Marquis for his "outstanding and unceasing research efforts and his educational outreach work".

Dr Fuster, in addition to his dedication to research, is strongly committed to his responsibility to communicate to the public. This commitment has in the last four years produced six books, which have been very positively received and topped the sales lists. This vocation and the clear need to promote healthy lifestyle habits recently led to Dr Fuster launching the Science, Health and Education Foundation (SHE), which is directed at improving public health, especially in the young.

Elizabeth Galle (CVRx, USA)

Liz Galle is the senior director of Clinical Research at CVRx in Minneapolis where she oversees clinical studies seeking global regulatory approval. Prior to CVRx, she was at Boston Scientific for 10 years leading statistical and clinical research groups for both pre and post market purposes. She was also involved in the analysis of large public health trials such as the Women's Health Initiative, a collaboration between NHLB Institute and industry. Her interests and experience include cardiovascular clinical trials, improving the participation of women in clinical studies and research, and improving the efficiency of clinical trials.

ABSTRACT

Autonomic modulation device therapy - should we rethink the clinical trial?

Industry, regulatory agencies, patients, clinicians and reimbursement entities all share the common goal of getting patients access to new, safe and effective treatments as soon as possible.

Clinical trials for autonomic modulation device therapies are particularly challenging to design and execute, and the time to rethink the clinical strategy for improving access to these therapies is now.

Critical to successfully providing adequate safety and efficacy evidence is to have some understanding of the mechanism of action. Although these mechanisms of action can be complex and difficult to measure, a better understanding will help identify which patients should be eligible for the clinical trial and what endpoints are appropriate.

The threshold for regulatory approval constantly evolves, and depends on many factors such as the severity of disease and the applicability of surrogate and other endpoints. More recently, the clinical trial strategy must provide evidence to support many demands, such as regulatory approval, reimbursement, adoption and patient preference. This increasing burden of evidence has resulted in longer, more complex and expensive clinical trial strategies.

Lastly, these devices may involve an implant procedure that is invasive, and the decision on whether to include a sham in the trial design should be critically evaluated, and should consider factors such as duration of trial and endpoint selection.

Wendy Gattis Stough (Cary, USA)

Wendy Gattis Stough, PharmD, is Owner of Expert Medical Communications and Consulting, LLC, in Cary, North Carolina.

She also maintains an active faculty appointment as an Adjunct Professor of Clinical Research and Pharmacy Practice at Campbell University College of Pharmacy and Health Sciences in North Carolina. Dr Stough received her doctor of pharmacy degree magna cum laude from Campbell University School of Pharmacy and completed residency and fellowship training at Duke University Medical Center.

She spent 10 years in full-time academics at Duke University Medical Center, where she established a clinical practice in the management of patients with heart failure as a member of the multidisciplinary heart failure team. She also served as a principal investigator, co-principal investigator, and project leader for numerous multicenter Phase II-IV clinical trials at the Duke Clinical Research Institute.

In 2005, Dr Stough established Expert Medical Communications and Consulting, LLC. Dr Stough has been an active contributor to many (>20) publications from CVCT meetings. Dr Stough has worked with other leading professional cardiology organizations including European Society of Cardiology (ESC), Heart Failure Society of America (HFSA), Heart Failure Association (HFA) of the ESC, and the American College of Cardiology (ACC).

Dr Stough has authored or co-authored over 100 papers in peer reviewed medical journals including *JAMA, European Heart Journal, Journal of the American College of Cardiology, Circulation, European Journal of Heart Failure, Archives of Internal Medicine, American Journal of Cardiology,* among others.

ABSTRACT

Medical writing, publication ethics viewpoint

The medical literature is a key tool in the dissemination of information to practicing clinicians and researchers. Thus, ensuring the integrity of the medical literature is of critical importance. Scientific writers may assist academicians or industry sponsors with writing or editorial support on many types of manuscript, ranging from design papers, primary or secondary analyses, reviews, consensus documents, or other publication materials. Scientific writers can perform this role with integrity and transparency, but some reports of unethical practices (i.e. “ghost writing”) have raised concerns about involving scientific writers in medical publications.

Transparency is a crucial element to achieve high ethical standards for scientific writers. Before the project begins, specific processes should be developed for preparation of drafts, communication between the writer and all authors, mechanisms for author review and incorporating input, provision of drafts, and time allotted for review. Interim drafts should be maintained reflecting author input and contributions.
Ideally, scientific writers should report to academic investigators or a publication committee, or a group of co-authors.

The scientific writer’s role should be clearly identified in the acknowledgment or as a co-author, consistent with the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.
CVCT has an extensive history of publishing quality reviews, controversies, or viewpoints in high impact journals. Substantial knowledge is generated by discussions at CVCT meetings, involving all stakeholder groups.

Summarizing and quickly disseminating this information can influence future trials or policy, but the experts involved in these discussions have limited time to coordinate such consensus papers and engage the participants in the process.
Scientific writers have helped facilitate the development and publication of many CVCT papers, with transparency and integrity. Over 35 CVCT papers have been published and are well cited in the literature.

A wealth of data exists from clinical trials and other datasets that are slowly or never disseminated, often because of time constraints on clinical investigators who have many professional responsibilities (e.g., patient care, research, administrative duties). Often after primary results are released, interest wanes in conducting additional analyses, investigators advance to new projects, or sponsors withdraw analytic support.

However, dissemination of secondary data is important because if analyzed appropriately, it can inform planning of subsequent trials, generate new hypotheses, or contribute knowledge to the field. Scientific writers, with the oversight of academic clinical investigators, may be useful to help move such projects forward especially when investigators have limited time to devote to writing such papers.

Regarding open access data, scientific writers involved in such projects should obtain original protocols and all available information pertaining to the trial to ensure details about the study that could influence data interpretation are understood. Communication between the team analyzing the open-access data and the original study team should be encouraged if possible, and the scientific writer should be involved in relevant discussions.

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Konstantinos Gatzoulis (Athens, GRE)

Konstantinos Gatzoulis is Associate Professor of Cardiology at the University of Athens and Director of the Electrophysiology Laboratory at the First University Division of Cardiology at Hippokration Hospital, Athnes, Greece.

Dr Gatzoulis obtained his MD degree from the Aristotelian University of Thessaloniki, Thessaloniki, Greece, in 1980. He subsequently completed a residency program in Internal Medicine at Cleveland General Metropolitan Hospital at Case Western Reserve University (CWRU), Cleveland, Ohio (1984 1987). From 1987 to 1989 he completed a Fellowship program in Cardiology at university hospitals of CWRU, Cleveland, Ohio, where he was also trained as an Electrophysiology Fellow for two another two years (1989-1991) under Professor Albert Waldo.

He is a diplomate of the American Boards in Internal Medicine and Cardiology, while, after returning to Athens, Greece, he joined the Hippokration Cardiology team at the University of Athens, initially as a scientific associate and subsequently as a lecturer, assistant and, for the last four years, associate Professor of Cardiology. He has been directing an extremely busy non-invasive and invasive EP Laboratory for the last 11 years, with 1706 invasive and 2400 non-invasive procedures at a yearly basis, including EP studies, device implantations and endocardial ablations. He has written 215 papers (both in English and in Greek) focused on various aspects of Clinical Cardiac Electrophysiology.

His current research activities include ongoing projects mainly in the field of prevention of sudden cardiac death with emphasis on risk stratification strategies among CAD and cardiomyopathy patients, especially at early stages of heart failure; management of electrical storm, EP guided approach of syncope, role of non-invasive electrocardiographic assessment of syncope, and the broader role of invasive electrophysiological study in the arrhythmia field, including both ventricular and common supraventricular arrhythmias.

ABSTRACT

Identifying the arrhythmic risk in post-myocardial infarction patients with preserved ejection fraction: positive non-invasive indices percentage predicting an inducible programmed ventricular stimulation before an icd implantation. Preliminary results from the PRESERVE-EF study – risk stratification in patients with preserved ejection fraction (PRESERVEEF)

Gatzoulis KA, Tsiachris D, Arsenos P, Mendrinos D, Trahanas K, Vlachos K, Xenogiannis I, Vernardros M, Tsimos K, Triantafyllou K

Introduction: Although current clinical practice is focused in post Myocardial Infarction (MI) patients with an impaired Left Ventricular Ejection Fraction (LVEF) for ICD prophylaxis, there is evidence for the presence of increased arrhythmic risk and Sudden Cardiac Death (SCD) in some patients with preserved LVEF>35% as well.

Purpose: To detect among the post-MI revascularized patients with preserved systolic function and LVEF>40%, those, at increased risk for Arrhythmic SCD.

Methods: We introduced a combined Non-Invasive and Invasive Risk Stratification Approach in post-MI patients 40 days after revascularization who had a LVEF≥40% (Hellenic J Cardiol 2014;55:361-368 and clinicaltrials.gov NCT02124018). Patients with one positive out of the following seven Non-Invasive Criteria of: ≥30 premature ventricular complexes (PVCs)/hour, ≥1 non-sustained VT (NSVT) episode(s)/24 hour, 2/3 positive criteria for late potentials (LPs), QTc≥440 ms (♂) or QTc≥450ms (♀), Ambulatory T wave alternans (TWA) ≥65 μV, SDNN from Heart Rate Variability ≤75 ms, Deceleration Capacity of Heart Rate ≤4.5 ms and Heart Rate Turbulence (HRT) Onset ≥0% and HRT slope ≤2.5 ms were considered of increased arrhythmic risk and they were referred for Programmed Ventricular Stimulation (PVS).

Results: From the first two hundred eighty three (283) patients who were screened non-invasively, 77 patients (27%) had at least one positive non invasive marker and were referred for PVS. Fourteen (14) out of these 77 patients (18%) had inducible Sustained Ventricular Tachycardia on PVS and 13 received an ICD while one denied the implantation. The percentage of the presence of the Non Invasive indices in these 14 patients with positive PVS was as follows: NSVT: 85% (n=12), LPs 64% (n=9), VPCs 57% (n=8), QTc 29% (n=4), combined DC/HRT 26% (n=4), TWA 14% (n=2), SDNN 7% (n=1).

Conclusions: Preliminary data suggest that multifactorial non invasive risk screening may detect a subpopulation of post-MI patients with preserved LVEF under risk for Inducible Ventricular Tachycardia. Prospective follow up is expected to clarify the extent of ICD activations in this population.

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Etienne Gayat (Paris, FRA)

Etienne Gayat is an associate professor of medicine at the University Paris Diderot School of Medicine. Dr Gayat obtained his MD degree from the University Paris Diderot in France in 2010. He subsequently did a fellowship in anesthesiology and critical care medicine at the Saint Louis – Lariboisière University Hospital and remained on the faculty there until now. His two principal areas of interest are biostatistics/methodology and research on biomarkers for acutely ill patients. He obtained a PhD degree in biostatistics in 2013. He is a member of the research unit 942 at french medical research institute INSERM, focusing on biomarkers for acute conditions. He published more than 80 articles in peer reviewed journals. He is co-investigator of the FROG-ICU study and co-chairman of the HELP-MOM study, both involving patients in acute conditions and collection of biological samples. He is a member of the board of statistician of Intensive Care Medicine.

ABSTRACT

Are there alternative biomarkers to NPs to judge of congestion in heart failure?

Acutely decompensated heart failure (ADHF) is a common presentation to the Emergency Department (ED) and is associated with both poor short- and long-term outcomes. Because clinical presentation may not be sufficiently discriminating in an acute setting, biomarkers have been proposed to aid in diagnosis and risk stratification. The Natriuretic peptides (NPs), brain natriuretic peptide (BNP) and its inactive amino-terminal fragment (NT-proNP) are recommended by many guidelines for this purpose.

In ADHF, it exists a congestive cascade, which often begins several days or weeks before symptom onset and includes a sub-clinical increase of ventricular filling pressures (“hemodynamic congestion”) which may further lead to redistribution of fluids within the lungs and visceral organs (“organ congestion”) and finally to overt signs and symptoms of volume overload (“clinical congestion”). Several strategies for early detection of sub-clinical organ congestion have been proposed (e.g. daily body weight measurement, or more recently, intrathoracic impedance monitoring).

However, there is still an unmet need for reliable and non-invasive detection of congestion at an early (hemodyanamic) stage in order to, hopefully, reduce hospitalizations and improve outcome. The use of biomarkers, in particular natriuretic peptides (NPs), was advocated for this purpose. However, levels of circulating NPs are influenced by myocardial stretch and cell necrosis and may therefore not accurately reflect systemic congestion.

A new biomarker with potential interest to monitor congestion in ADHF has recently been described, this is the soluble form of CD146 (sCD146). CD146 is a component of the endothelial junction primarily expressed in endothelial cells and involved in the control of cell and tissue architecture, in cell signaling and as more recently described in angiogenesis. The potential interest of sCD146 in ADHF has been suggested by an unbiased proteomics approach.

In a large observational prospective multicenter study, it has been shown that sCD146 has similar discriminative power to detect the cardiac origin of an acute dyspnea than NT-proBNP. Moreover, plasma sCD146 added a discriminative power in patients lying in the “gray zone” of NT-proBNP. In this subgroup of patients, adding sCD146 to NT-proBNP further improved the diagnostic performance of NT-proBNP alone. In particular, sCD146 indicated to be helpful to rule-out the diagnosis of ADHF for those patients.

More importantly, both clinical and experimental data suggest that the trigger for the release of sCD146 is congestion. However, although promising, the potential

of sCD146 to guide decongestive therapy in HF should be validated in larger, multi-center, prospective cohorts.

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Nancy Geller (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), the ongoing Ranolazine ICD trial (RAID), and a recently published trial of surgical ablation of atrial fibrillation (versus no ablation) during mitral valve surgery.

She has published over 200 papers in the statistical and medical literature. She is an Associate Editor of Biometrics and 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.

ABSTRACT

Autonomic modulation device therapy: should we rethink the clinical trial strategy? Placebo effects, regression to the mean and the need for blinding

We will discuss the difficulties of designing clinical trials to establish that autonomic modulation devices are efficacious. In the case of renal denervation, subjects willing to undergo the procedure are likely at their sickest (e.g. very high blood pressure which appears to be treatment resistant), and are likely to have lower blood pressure readings after treatment (no matter what the treatment).

The fact that subjects undergo a procedure which is supposed to help them may induce a placebo effect or make them more compliant to other treatments (such as drug therapy or weight loss). This argues the need for double blind trials to avoid these problems.

Jeffrey Goldberger (Chicago, USA)

Jeffrey Goldberger is professor of medicine and Chief of Cardiology at the University of Miami Miller School of Medicine. Dr Goldberger obtained his MD degree from the Albert Einstein College of Medicine in 1984.

He subsequently did a fellowship in cardiology at the University of California, San Francisco. He joined the faculty at Northwestern University in 1990 where he held various administrative positions including the Director of Cardiac Electrophysiology.

He has been involved in leading a number of clinical trials including: DETERMINE and OBTAIN. He has served on events committees and DSMBs for various trials. Dr Goldberger has been a member of several medical journal editorial boards.

He has authored over 200 articles. He leads a national/international think tank on risk stratification for sudden cardiac death.

The trial roadmap for risk guided icd therapy

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Robert Golub (JAMA, USA)

Robert M. Golub, MD, is Deputy Editor, JAMA. His roles include oversight of the JAMA scientific content and managing the peer review process; he is also responsible for directing JAMA educational activities.

He is Associate Professor of Medicine at the Feinberg School of Medicine at Northwestern University, with academic appointments in the Division of General Internal Medicine and the Department of Preventive Medicine. Dr Golub developed the Northwestern University medical school curriculum on medical decision making, which began in 1992, and received the Society of General Internal Medicine National Clinician-Educator Award for Teaching Innovation. He served as chair of the Northwestern University Medical School Curriculum Committee.

Areas of research are in medical decision making (decision analysis, cost-effectiveness analysis, psychology of decision making, and assessing patient preferences). He has served on the Board of Trustees for the Society for Medical Decision Making and as visiting faculty for the Stanford University Faculty Development Program and the University of Buenos Aires Program in Clinical Effectiveness. Dr Golub received his undergraduate degree from Princeton University, and his MD from Columbia University College of Physicians and Surgeons.

He completed his internship and residency at Northwestern University School of Medicine/ Northwestern Memorial Hospital, where he also served as chief resident. He is board certified in internal medicine.

Antonio Gómez-Outes (EMA, ESP)

Antonio Gómez-Outes is medical assessor for cardiovascular and respiratory drugs at the Spanish Medicines Agency (AEMPS) and member of the Cardiovascular Working Party (CVSWP) of the European Medicines Agency (EMA). He is specialist in Clinical Pharmacology at the Spanish Ministry of Health, Doctor of Philosophy in Medicine at the Complutense University of Madrid and Master in Pharmacoeconomics and Market Access at the Carlos III University of Madrid.

Dr Gómez-Outes has participated as clinical assessor of in a number of relevant centralised registration procedures within the European Union in the cardiovascular field, including the market authorisation application for new antiplatelet drugs, new anticoagulants, lipid-modifying agents and new drugs for pulmonary hypertension. As member of the CVSWP, he has been involved in writing/revising a number of regulatory cardiovascular guidelines, including those for prevention and treatment of thrombotic diseases.

Jean-Marc Guettier (FDA, USA)

Jean-Marc Guettier, MD, is Director of the Division of Metabolism and Endocrinology Products at the Food and Drug Administration. The Division of Metabolism and Endocrinology Products provides regulatory oversight for investigational studies involving new drugs for endocrine and metabolic conditions including new therapies for patients with type-2 diabetes mellitus. In addition, the Division reviews applications for new drugs and biologicals for endocrine and metabolic conditions and makes decisions on the marketing approval of these products. Finally, the Division monitors the safety of products already marketed for endocrine and metabolic conditions. Dr Guettier received his medical degree from McGill University, completed his internal medicine residency at the University

of Minnesota and trained in endocrinology and metabolism at the National Institutes of Health.
Dr Guettier joined FDA and the Division of Metabolism and Endocrinology Products in January 2009 as a Medical Officer in the Diabetes Team, was team leader of the Diabetes Team from in 2011 to 2013, and has been Division Director since 2013.

Diabetes CV outcome trials : Regulatory perspective

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Michael Hanna (BMS, USA)

Dr Michael S. Hanna is an Executive Medical Director in Global Clinical Research (Cardiovascular) at Bristol-Myers Squibb, in Princeton, New Jersey (USA).
Dr Hanna received his A.B. from Dartmouth and his MD from the University of Connecticut. He served as a resident in internal medicine at the Columbia-Presbyterian Medical Center in New York, followed by an NIH post-doctoral fellowship in cellular cardiac electrophysiology in Dr Andrew Wit's laboratory at the College of Physicians and Surgeons.
Following his EP fellowship at the University of Pennsylvania, Dr Hanna joined the faculty at Penn serving as a clinical cardiac electrophysiologist with research interests in reentrant atrial and ventricular arrhythmias. He collaborated with Drs. Wit, Josephson, Frame and Allessie using advanced computerized mapping systems to characterize mechanisms of arrythmogenesis in both animals and humans.
He was director of the fellowship program in cardiac electrophysiology at Penn and head of the EP laboratory at the Presbyterian Medical Center.
In 2004, Dr Hanna moved from academia to industry taking a position in cardiovascular global clinical research at Bristol-Myers Squibb.
For the past decade his research interests have focused on thrombosis, novel mechanisms of anticoagulation and antiplatelet action, and cardiovascular outcome trials. He led the Apixaban in Atrial Fibrillation program, and has also worked in heart failure and antiarrhythmic drug development as well as cardiac safety.

ABSTRACT

Cardiovascular outcome trials in CKD patients Industry viewpoint

Patients with chronic kidney disease (CKD) are at increased risk for vascular disease, atrial fibrillation and heart failure. These illnesses increase their risk of adverse cardiovascular outcomes such as myocardial infarction, stroke and death.
Prevention of such outcomes is CKD patients is challenging for a number of reasons. First, existing therapies have been studied in patients with normal renal function, and to a lesser degree in those with mild–moderate renal impairment. Studies in patients with severe renal disease are sparse, often observational in design and yield conflicting results. Second, pharmacokinetic studies done in CKD patients may yield important information about exposure, but offer limited insights into the benefit/risk in this population. Third, while biomarkers offer important insights into the mechanism and progression of disease states, they are less helpful in informing the evidence base for clinical decisions or the regulatory bar for indication approval. Fourth, the CKD patient population is heterogeneous, and often dynamic, and the risks and benefits of drug therapies may differ depending on the severity renal impairment and the underlying cause.
Atrial fibrillation (AF) patients with CKD illustrate these challenges. AF is more prevalent in CKD patients than in those without CKD, and it is a marker of poor outcome. Thromboembolic events such as stroke, are associated with AF and are also more common in CKD patients, but prevention of such outcomes remains difficult.
Warfarin and other vitamin K antagonists have been shown to be highly effective in reducing stroke in AF patients, but such therapy is associated with significant liabilities, especially bleeding. In CKD patients, the role of warfarin is controversial.
Such patients are at increased risk of significant bleeding complications for a variety of reasons. Observational studies utilizing warfarin for stroke prevention in CKD patients with AF have yielded conflicting results of benefit or of harm, which may reflect differing populations, confounding or selection bias.
In addition, INR control, necessary for the safe and effective use of warfarin, is challenging in this population. Finally, warfarin has been linked to calcific uremic arteriopathy (calciphylaxis) and to aortic valve calcification in patients with severe CKD.
The liabilities of warfarin in CKD patients with AF creates a large unmet need for safer, effective therapy to prevent stroke in this population. Recently, novel oral anticoagulants such as apixaban (a direct factor Xa inhibitor) and dabigatran (a direct thrombin inhibitor) have been studied and approved for the prevention of stroke in patients with nonvalvular atrial fibrillation. In the case of apixaban, the registrational studies that led to approval included patients with mild–moderate renal impairment, but not with severe or end–stage renal disease.
The role of further studies in such patients, including PK and outcome trials, will be discussed.

Kevin Heist (Boston, USA)

Kevin Heist MD PhD is an associate professor of medicine at Harvard Medical School, and an associate physician in the Cardiac Arrhythmia Service at Massachusetts General Hospital. Dr Heist obtained his MD and PhD degrees at Stanford University in 1998. He then did residency in internal medicine at UC San Francisco (1998-2000), and fellowship in cardiovascular disease (2000-2003) and then clinical cardiac electrophysiology (2003-2004) at Massachusetts General Hospital. He has been on the cardiac electrophysiology faculty at Massachusetts General Hospital since 2004, where he has a busy clinical and procedural EP practice. He is active in clinical investigation, and has over 140 publications in peer reviewed journals. He has numerous ongoing clinical trials, and recently served as the steering committee chairman and first author on the primary publication of the DEFEAT-PE clinical study. Dr Heist is on several editoral boards, and is an author related to atrial fibrillation in Up to Date. He is currently on the governance committee of the Heart Rhythm Society, and is the immediate past president of the New England EP Society.

The challenge of continuous technological innovations: how might the results of the ongoing trials apply to novel ablation technologies?

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Adrian Hernandez (Durham, USA)

Dr Hernandez, MD, MHS, FAHA, is a cardiologist with extensive experience in clinical research ranging from clinical trials to outcomes and health services research. He is the Faculty Associate Director of the Duke Clinical Research Institute and Director of the Health Services and Outcomes Research Domain.

He has led several research grants funded to address issues in clinical care, health policy, quality of care, and outcomes. He is the PI of multiple large studies including the NHLBI's Heart Failure Research Network, PCORI funded study, PROSPER, on comparative effectiveness in stroke and AHA's Get With the Guidelines Registry.

He is also the Coordinating Center PI for PCORI's PCORNet and the NIH's Collaboratory, both of which aim to transform clinical research using electronic health records and health system data. He is the PI of the coordinating center for several large clinical trials including ASCEND-HF (nesiritide/heart failure), EXSCEL (exenatide/diabetes) and HARMONY-Outcomes (albiglutide/diabetes).

Dr Hernandez has over 300 published articles in high-tier journals on cardiovascular outcomes including the New England Journal of Medicine, Journal of the American Medical Association, and Lancet. He serves on the leadership of several national committees such as AHA's Scientific Sessions, AHA's Heart Failure Committee, ACCF Task Force on Clinical Expert Consensus Committee, and HFSA Guidelines Committee.

He has been recognized for his research through numerous awards and was elected to the American Society of Clinical Investigation in 2012. He has mentored over 25 students, residents, fellows and faculty and has and a recipient of the Robert M. Califf Mentorship Award.

Charles Herzog (Minneapolis, USA)

Dr Charles Herzog, MD, FACC, FAHA, is a professor of medicine, University of Minnesota, and cardiologist at Hennepin County Medical Center (HCMC) in Minneapolis, Minnesota for 31 years. He founded the program in interventional cardiology at HCMC and served as the cardiac catheterization laboratory director from 1985 to 1991, and the cardiac ultrasound laboratory director from 1997 through 2012. He was an investigator at the United States Renal Data System (USRDS) Coordinating Center

and director of the USRDS Cardiovascular Special Studies Center from 1999-2014. He participated in the development of the National Kidney Foundation's K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients and the workgroup for the KDIGO Clinical Practice Guidelines on Acute Kidney Injury, and contributed to the AHA 2015 Scientific Statement on Pharmacotherapy in Chronic Kidney Patients Presenting with Acute Coronary Syndrome. He helped plan the American Heart Association Cardio-renal Connection Symposium (2010), and co-chaired the 2010 KDIGO Controversies Conference, "Cardiovascular Disease in CKD: What is it and What Can We Do About It?" He was an Executive Committee member of the Evaluation Of Cinacalcet Therapy to Lower CardioVascular Events (EVOLVE) Trial, the largest randomized clinical trial enrolling dialysis patients. He chairs the Renal Committee of the ISCHEMIA-CKD Trial (ClinicalTrials.gov identifier: NCT01985360), an international NHLBI/NIH-sponsored clinical trial comparing a conservative to an invasive strategy in the treatment of stable ischemic heart disease in patients with severe chronic kidney disease, including dialysis.

He is the Co-PI for the WED-HED (Wearable Cardioverter Defibrillator in Hemodialysis Patients) Study (ClinicalTrials.gov identifier: NCT02481206), a randomized clinical trial testing the efficacy of wearable defibrillators for the prevention of sudden cardiac death in incident hemodialysis patients. He serves on the DSMB of the SONAR androxadust at phase 3 clinical trials.

He has authored or co-authored more than 170 published papers, reviews, and editorials. He has served on the Editorial Boards of the American Heart Journal, the Journal of Nephrology, Clinical Journal of the American Society of Nephrology, and liaison editor for Nephrology, Dialysis and Transplantation. His special interests include cardiac disease and CKD, and echocardiography.

ABSTRACT

Cardiovascular outcome trials in CKD patients (nephrocardiology)

Investigator viewpoint

Outline:

1. Where we've been in the past
2. Where we are going
3. Where we need to go: KDIGO Redux

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Joseph Hill (Dallas, USA)

Dr Hill, MD, PhD, is a cardiologist-scientist whose research focuses on molecular mechanisms of remodeling in the stressed myocardium. He graduated with an MD, PhD from Duke University. Next, he pursued postdoctoral scientific training at the Institut Pasteur in Paris, followed by clinical training in Internal Medicine and Cardiology at the Brigham and Women's Hospital, Harvard Medical School. Dr Hill served on the faculty of the University of Iowa for 5 years before moving in 2002 to the University of Texas Southwestern Medical Center to assume the role of Chief of Cardiology and Director of the Harry S. Moss Heart Center.

Dr Hill's research group strives to decipher mechanisms of structural, functional, and electrical remodeling in heart disease with an eye toward therapeutic intervention. Dr Hill serves on numerous committees, boards, and study sections, and he lectures widely. In addition, he serves on several editorial boards, including Circulation, Circulation Research, Journal of Biological Chemistry, and American Journal of Cardiology. He serves as editor-in-chief of a recently published textbook entitled Muscle: Fundamental Biology and Mechanisms of Disease.

He has received numerous recognitions and awards, including election to the Association of American Professors; he recently served as President of the Association of University Cardiologists and chair of the Academic Council of the American College of Cardiology. He was recently named the next Editor-in-Chief of Circulation. Dr Hill maintains an active clinical practice focusing on general cardiology, hypertension, and heart failure.

ABSTRACT

Trial publications: point and counterpoint with major journal editors

The design, implementation, and analysis of clinical trials is evolving rapidly. This includes novel approaches to subject enrollment, follow-up, and statistical analysis. In parallel, the publishing space is evolving swiftly.

New journals are emerging ever more frequently; the role of the printed page has diminished; the role of peer review has declined in some venues; and documents have come "alive" such that they can be regularly updated and revised. Where do these two worlds meet?

How do we converge these evolving fields to facilitate achievement of our mutual goals? Where is the optimal point in the handling of a paper to fulfill the conflicting objectives of timely dissemination of vital information and the critical requirement for rigorous peer review?

How we deal with flawed publications that are serially rejected and yet which appear ultimately in publication format, leading some to infer validity of the report? In an age of accelerating discovery, burgeoning cardiovascular need, and constrained resources, these questions are of particular relevance.

Phenotyping heart failure – is precision medicine the way forward?

Heart failure (HF) is one of only a handful of cardiovascular disorders which are increasing in incidence and prevalence. Already the number one discharge diagnosis in Medicare, a distinction held for some years, HF is responsible for a huge burden to individuals and society[1].

However, despite the enormity of the challenge, new therapies with clinical relevance have been lacking for many years (although two exciting exceptions have emerged recently). It is important to remember that HF is a syndrome, the culmination of a wide range of distinct disease processes: ischemic disease, hypertension, genetic disorders, and many more[2].

Nevertheless, we lump these processes together and treat them the same way. Worse, for the cases in which the ejection fraction on echocardiography is preserved (HFpEF), we have no evidence-based therapies whatsoever. Clearly, a much more individualized ("precision") approach is needed. However, this objective poses numerous significant challenges[3]. For example, access to diseased tissue is not routinely accomplished in HF, whereas in other fields that have relied historically on individualization (e.g. infectious disease) or are beginning to do so (e.g. oncology), this is less of an obstacle.

We will discuss the challenges and opportunities we face in the fight against HF and the potential role of "precision medicine" therein.

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Elaine Hylek (Boston, USA)

Elaine Hylek, MD, MPH, is a Professor of Medicine at Boston University School of Medicine. She received her MD from the University of Pittsburgh School Of Medicine and a Masters in Public Health (quantitative methods) from Harvard University School of Public Health. She completed her residency training in internal medicine at Massachusetts General Hospital and Harvard Medical School in Boston, Massachusetts. Her research areas include arterial (stroke) and venous thrombosis, anticoagulant therapies, and atrial fibrillation.

She has served as PI on several NIH R01 grants, served on the Executive Steering Committees for international clinical trials and national registries, Event Adjudication Committees, and Data Safety Monitoring Boards. She has also served as the Late Breaking Clinical Trial Discussant for multiple international trials in the field of thrombosis.

Dr Hylek is a Section Editor for Thrombosis and Haemostasis, a member of the International Society of Thrombosis and Haemostasis Executive Committee for World Thrombosis Day, and the Director of the Thrombosis and Anticoagulation Service at Boston Medical Center. She is extensively published and designated a U.S. News Top Doctor and voted Best Doctors in America for the past decade.

ABSTRACT

Non-valvular atrial fibrillation and stroke trials: who should be treated?

The 30-day mortality of stroke related to atrial fibrillation is 24%. Despite advances in anticoagulant therapy, multiple challenges remain including persistent under-treatment, long-term nonadherence, and hemorrhagic complications, particularly among older adults prescribed concomitant antiplatelet therapy.

The burden of atrial fibrillation that warrants lifelong treatment is currently unknown as is the risk associated with subclinical atrial fibrillation. Aggressive lifestyle modification has been shown to decrease the burden of atrial fibrillation, but awaits validation in large randomized trials.

The role of inflammation and fibrosis in the propagation of atrial fibrillation and formation of thrombus needs to be further elucidated. Alternate pathways to disrupt thrombus formation without attendant bleeding risks need to be explored. Although left atrial appendage occlusion is an approved prophylactic option, its long-term efficacy and safety across the spectrum of highest risk patients is unknown.

James Januzzi (Boston, USA)

Dr James Januzzi is currently the Hutter Family Professor of Medicine at Harvard Medical School. He is also a faculty member at the Harvard Clinical Research Institute. He graduated as the top-ranked student in the Class of 1994 from New York Medical College and performed a residency in internal medicine at the Brigham and Women's Hospital, followed by a fellowship in cardiology and cardiac ultrasound at the Massachusetts General Hospital. He joined the staff at MGH in 2000, and is a clinician, teacher, and experienced clinical researcher and clinical trialist.

Dr Januzzi's work has contributed greatly to the understanding of cardiac biomarker testing, where his work with several markers has set international standards for use in diagnosis, prognosis, and management of patients suffering from acutely decompensated heart failure, chronic heart failure as well as those with acute coronary syndromes. He has published more than 450 manuscripts, book chapters, and review articles, and has edited two text books on cardiac biomarker testing as well as the Massachusetts General Hospital Cardiology Review Book. He is on the editorial board of numerous scientific journals, including current service as an Associate Editor at the Journal of the American College of Cardiology: Heart Failure. He was the chairman of the NT-proBNP and ST2 Consensus Panels, the lead author of the Heart Failure Section for the Universal Definition of MI Biomarker Task Force, and is on the planning committee for the 2015 Heart Failure Society of America meetings. He is currently the Chair of the ACC Task Force on Consensus Statements and was a section editor and member of the working group for the 2013 ACC/AHA Clinical Practice Guidelines for Heart Failure.

ABSTRACT

Opportunities and limitations of natriuretic peptides for use in clinical trials

The natriuretic peptides have grown from being a medical curiosity to now representing a commonly used tool in clinical trials: a recent CiteLine scan revealed biomarkers (largely the NPs) were used in 39% of HF clinical trials, including as an inclusion criterion, as an endpoint, or as a toxicity monitor. Some trials used BNP or NT-proBNP for more than one application. BNP and NT-proBNP also provide useful information to assist in understanding benefit of a therapeutic agent in clinical trials. Additionally, NT-proBNP is currently being scrutinized as a "guide" to heart failure therapy. While the natriuretic peptides are useful for a broad range of applications in clinical trials there are important caveats regarding their use; not all changes in BNP or NT-proBNP are associated with prognosis (examples: rise in BNP related to valsartan/sacubitril use; rise in both peptides related to neuregulin-1 use). Additionally, it remains unclear if the data from BNP or NT-proBNP are robust enough to be used as a "surrogate" endpoint in Phase III trials.

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John Jarcho (Boston, USA)

John Jarcho, MD, is a deputy editor at the New England Journal of Medicine, assistant professor of medicine at Harvard Medical School, and a member of the cardiovascular division at Brigham and Women's Hospital in Boston, Massachusetts.

Dr Jarcho received his MD degree from the University of Utah School of Medicine in Salt Lake City, Utah. He completed a residency in internal medicine and a fellowship in cardiovascular disease, both at Brigham and Women's Hospital in Boston.

He joined the faculty of Brigham and Women's Hospital in 1989. Dr Jarcho's professional career initially focused on basic research and led to the first identification of

a genetic locus for hypertrophic cardiomyopathy. He then shifted his focus to clinical medicine, becoming a member of the Brigham Cardiac Transplant Service and ultimately medical co-director of that service.
In 2002 his professional focus shifted again; he became cardiology deputy editor at the online medical reference UpToDate. Finally, in 2005, he joined the editorial staff of the New England Journal of Medicine, where he has served for the past 10 years as the principal editor responsible for the review, revision and editing of manuscripts in the field of cardiovascular disease. He has led efforts by the Journal to establish a capacity for expedited review and rapid online publication of practice-changing clinical trials.
He maintains a clinical role with the Brigham Advanced Heart Disease Service.

ABSTRACT

Fast track publication: advantages and dangers

Over the last decade, expedited publication of major clinical trials in cardiology (and in other fields) has become an increasingly common phenomenon. Fast-track publication has been made possible by the development of online journal publication and has been fostered by a number of factors, including the expectation that research funding will be used wisely, the desire to ensure that the clinical benefits of research are made available rapidly, and the interest of investigators and readers in having access to study data at the time of first presentation of the findings at a major medical meeting.

However, there are potential problems associated with expedited publication, including incomplete data, errors by the investigators or the editors, and insufficient consideration of the optimal interpretation of study results. The advantages and problems associated with fast-track publication will be discussed.

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David Kao (Aurora, USA)

David Kao is an Assistant Professor od Medicine at the University of Colorado School of Medicine. Dr Kao obtained his MD degree from the Johns Hopkins University in 2003. He subsequently completed his internal medicine residency and chief residency at Stanford in 2007. He then completed a fellowship in the Division of Biomedical Informatics Research at Stanford before completing his cardiology fellowship at the University of Colorado. His interests include applied clinical and biomedical informatics, personalized medicine, and real-world implementation of translational research results using the electronic health record. His current research activities include high-throughput cluster-based heart failure phenotyping, cardiovascular pharmocovigilance, regional hospital outcomes data, and phenotype-transcriptome-genotype associations. He is a clinical registry and ontology developer at the Children's Hospital of Colorado, and he is also lead physician informaticist for the Clinical Decision Support program and Chairman of the Clinical Decision Support Governance committee at UC Health.

ABSTRACT

Phenotyping heart failure: helpful new tools for patient selection in trials?

Patients with heart failure have heterogeneous phenotypes with significant variation in prognosis and treatment response. In heart failure with reduced ejection fraction (HFrEF), a significant proportion of patients recover left ventricular function with medical or cardiac resynchronization therapy, but we are currently unable to predict which patients will not. No therapies have proved effective in heart failure with preserved ejection fraction (HFpEF), possibly due to phenotypic variation and a high burden of comorbidities. It is likely that certain phenotypes of both HFpEF and HFrEF respond to specific therapies better than others based on underlying physiology. Clinical syndrome identification has historically relied on astute clinical observation over many years to recognize prevalent and relevant constellations of clinical findings. Emerging bioinformatics methods provide a quantitative approach to identifying prevalent clusters of clinical features. Analyses by multiple groups suggest that cluster-based phenotypes have prognostic significance beyond traditional regression models and may identify patient phenotypes with heightened treatment response, even in HFpEF. Increasingly, it is believed that robust clinical phenotyping can improve the efficiency of randomized clinical trials by selecting high-risk patients with an higher likelihood of demonstrating response to a given therapy. I will review contemporary results of complex

phenotying analyses and discuss their potential relevance for future clinical trial design.

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Wolfgang Koenig (Munich, GER)

Wolfgang Koenig, MD, PhD, FRCP, FESC, FACC, FAHA is a Professor of Medicine/Cardiology at the University of Ulm Medical School, Ulm, Germany. He is a Board certified Internist and interventional cardiologist, and also specialized in Intensive Care Medicine. In addition he has extensive experience in the molecular epidemiology of cardiovascular diseases. After different prestigious positions as a former Director of the WHO-MONICA Augsburg Myocardial Infarction Register, Deputy Director of the Departments of Medicine and Head of the Emergency Room, Director of the Intensive Care Unit, and Director of Cardiovascular Laboratories, he has been 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 until March 2015. In April 2015 he joined the Deutsches Herzzentrum München, Technische Universität München and became an established investigator of the Munich Heart Alliance within the DZHK (German Centre for Cardiovascular Research). Presently he serves also on the Steering Committee of various large international randomized clinical trials testing innovative targets in cardiovascular medicine.

Dr Koenig's research interests involve the molecular basis of atherothrombogenesis including genetics with particular interest in the interrelations between hemostasis, inflammation, and atherothrombotic complications/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 novel biomarkers for cardiometabolic diseases.
Dr Koenig has an impressive publication list including papers in first rank journals. He ranks number 6 of the most frequently cited German speaking researcher in cardiovascular disease between 2008 and 2012. In 2014 he received the Rudolf Schönheimer Award from the German Atherosclerosis Society.

ABSTRACT

Is targeting inflammation still an option in patients on very low LDL cholesterol levels? Ongoing trials (CIRT, CANTOS, COLCOT)

Substantial experimental and clinical evidence suggests that inflammatory processes are involved in atherosclerosis. Based on the accumulated evidence from a large number of statin trials during the last 20 years, the lower the LDL cholesterol (LDL-C), the better is the prognosis. So far, LDL-C has been down titrated to around 50 mg/dl in JUPITER, a primary prevention trial with rosuvastatin and IMPROVE-IT, a secondary prevention trial combining simvastatin with ezetimibe. Based on such studies and additional evidence from recent PCSK9 inhibitor trials there seems to be no safety signal even at values of 20 or 30 mg/dl LDL-C.
It has been well known from the Physicians' Health Study that aspirin, even in low doses seems to have anti-inflammatory effects besides platelet inhibition. This has been supported by experimental data in mice. In addition, statins also, besides their LDL-C lowering effect, might have anti-inflammatory properties. Such data have been gathered from clinical studies but also in experimental settings. Furthermore, there is consistent data from at least 10 statin trials showing that a dual target therapy concept consisting of an LDL-C < 70 mg/dl and a high sensitivity (hs) CRP < 2 mg/L, as an exquisite marker of inflammation, is superior to achieving either target alone in terms of reduction of clinical endpoints as well as regression of atherosclerosis. Going beyond these convincing data, suggesting indeed that reduction of inflammation in addition to lipid lowering is beneficial to patients, one needs to directly test the hypothesis by an intervention that purely focuses on inflammation and has no additional effects. Such data are still lacking and

thus the inflammatory hypothesis is still unproven. However, at least 3 major trials are under way and will be completed during the next few years. CIRT (Cardiovascular Inflammation Reduction Trial) will use low-dose methotrexat in stable post-MI patients on top of standard of care and will evaluate its effect compared to placebo on non-fatal MI, non-fatal stroke and cardiovascular death. The study is currently being carried out in the US and Canada and approximately 2,000 patients have been included. Secondly, the large CANTOS study comprising 10,000 stable post-MI patients again on standard of care with persistent elevation of hs-CRP ≥ 2 mg/L will test the efficacy and safety of an antibody against interleukin-1β (canakinumab) regarding various cardiovascular endpoints but focusing on a primay endpoint of non-fatal MI, non-fatal stroke and cardiovascular death. A number of secondary endpoints that may also be related inflammation, namely new onset diabetes, deep vein thrombosis, ventricular tachycardia, and others will be evaluated in addition. This study has been fully recruited and might be completed within the next 18 months. Finally, based on preliminary results of the LoDoCo trial using colchicine in secondary prevention of vascular events which showed a dramatic reduction of a combined cardiovascular endpoint with a hazard ratio of 0.33 (95% CI, 0.18 – 0.59) the better powered COLCOT trial will be carried out to confirm such initial data. In addition, a recently published small clinical trial in only 150 patients during acute MI has shown that anti-inflammatory treatment with colchicine is able to reduce infarct size as measured by various biomarkers and MRI with late Gadolinium enhancement. In a mouse model canakinumab dampened hematopoetic stem cell proliferation and thus attenuated inflammation post-MI. Such clinical trials targeting inflammation are running the same time when 3 large PCSK9 inhibitor programs are being carried out in approximately 70,000 patients worldwide, probably achieving LDL-C levels in the order of 30 mg/dl. Thus, the question arises, whether in the presence of such low LDL-C levels additional reduction in inflammation is still a valuable component of a comprehensive post-MI interventional strategy and in particular how will we have to triage patients after an acute event based on these promising options, provided that these trials will be positive.

Mikhail Kosiborod (Kansas City, USA)

Dr Kosiborod is a cardiologist and clinical researcher at Saint Luke's Mid America Heart Institute, and Professor of Medicine at the University of Missouri-Kansas City. Dr Kosiborod received training in clinical research, epidemiology and health policy through the Robert Wood Johnson Clinical Scholars Program, as well as clinical training in cardiovascular medicine at Yale University School of Medicine. Dr Kosiborod is an internationally recognized expert in the fields of diabetes and glucose control, electrolyte management, quality of care and outcomes in patients with cardiovascular disease. He has authored and co-authored over 100 peer-reviewed publications, including scientific statements and position documents. He is involved in clinical trials, both in the leadership role, as well as the investigator role at Saint Luke's Lipid and Diabetes Research Center. Dr Kosiborod is actively involved in the work of multiple committees for the American College of Cardiology and American Heart Association, and currently chairs the American Heart Association Diabetes Committee, and the ACC/ADA/ACP/Joslyn Diabetes Collaborative Registry Steering Committee, was a co-chair of the American Heart Association's Global Congress on Big Data in 2014, and is a chair of the American Heart Association's Quality of Care and Outcomes Research Conference. He serves on the editorial boards of several scientific journals, including Journal of the American College of Cardiology and Journal of Clinical Endocrinology and Metabolism. Dr Kosiborod is the training co-director of the NHLBI T-32 Outcomes Research Fellowship at St Luke's Mid America Heart Institute (MAHI), and is closely involved in mentoring many trainees – both locally and across other institutions nationally and internationally.

Peter Kowey (Wynnewood, USA)

Peter R. Kowey, MD, FACC, FHRS, FAHA, after his training, joined the faculty at the Medical College of Pennsylvania as Director of the CCU and Arrhythmia Program, and rose to the rank of full Professor. He went on to become Chief of the Division of Cardiovascular Diseases at the Lankenau Hospital Main Line Health System and President of the Main Line Health Heart Center and is the William Wikoff Smith Chair in Cardiovascular Research. He also is Professor of Medicine and Clinical Pharmacology at Jefferson Medical College. Dr Kowey is a Fellow of several professional organizations including the Clinical Council of the American Heart Association, the American College of Cardiology, the American College of Physicians, the College of Physicians of Philadelphia, the American College of Chest Physicians, and the American College of Clinical Pharmacology. He was a founding member of the Philadelphia Arrhythmia Group and a charter member of the North American Society of Pacing and Electrophysiology. He has served on numerous committees for each of these organizations including program and abstract review committees for national and international programs. He spent 9 years as a member of the Cardiorenal Drug Advisory Committee, 4 years on the Cardiovascular Devices Committee of the Food and Drug Administration, and was on the Expert Ad-

visory Panel of the US Pharmacopeial convention. Dr Kowey's principal area of interest has been cardiac rhythm disturbances. He has been the recipient of over 150 grants and has authored or co-authored over 400 papers and scientific reports. His group has participated in a large number of pivotal clinical trials, many directed by Dr Kowey himself. He is the co-editor of 3 textbooks regarding cardiac arrhythmia. He is a referee for manuscript review for 25 journals and sits on the editorial boards of the Heart Rhythm Journal and the Journal of Cardiovascular Electrophysiology. He has provided consultation to over 60 international pharmaceutical companies and chaired several data and safety monitoring boards for clinical trials. While working with industry, he has pioneered the development of many antiarrhythmic drugs and antitachycardia devices that are used around the world for the treatment of patients with life-threatening cardiac rhythm problems. Dr Kowey also maintains a busy consultative arrhythmia practice and has been recognized as a leader in his field in several international publications.

ABSTRACT

AF burden and the role of novel biosensors in AF trials

Dr Kowey will discuss endpoints that have been used for the assessment of the efficacy and safety of drugs used to suppress atrial fibrillation, including burden, defined as the amount of time spent in atrial fibrillation (AF) divided by the total time of monitoring. To this point, burden has been used principally in early phase trials for proof of concept (placebo-subtracted AF suppression) and for dose finding. The latter usage has been particularly successful since burden permits the inclusion of a smaller number of intensively studied patients followed for a relatively short period of time.
There are many facets to consider in constructing a burden experiment including the method of AF quantification (rhythm control devices versus external or internal recorders), processing and integration of data, and interpretation of clinical significance.

The latter is of particular importance since an increased duration of time in AF is expected to translate into a heightened stroke risk with implications for anticoagulant therapy. In addition, regulators have been particularly wary of assigning significance to asymptomatic AF suppression since it may not convey tangible patient benefit. Thus, using burden reduction in late phase clinical trials may be problematic, especially given prior regulator insistence on reduction of "hard endpoints" such as hospitalization and mortality.
AF detection methods may also be employed in situations in which there are reasons to believe this arrhythmia are caused by a drug being used for another purpose. Although such associations are not common and not necessarily causal, pragmatic drug development often mandates monitoring to dismiss the risk or at least to define susceptible individuals. How this is accomplished and what actually constitutes a signal in this regard has not been conclusively determined and represents another area of intense research interest.

Finally, Dr Kowey will discuss the potential use of therapies to PREVENT AF. Heretofore, this strategy has not proven effective, probably because we have not been able to define the highest risk patient populations who might derive greatest benefit. He will discuss the use of biomarkers in addition to other parameters to increase the yield, hopefully optimizing the chances of preventing AF, before it occurs, with its attendant complications.

Stuart Kupfer (Takeda, USA)

Stuart Kupfer, MD, is Vice President Clinical Science, Cardiovascular and Metabolic Diseases, at Takeda Pharmaceuticals and is based in Deerfield, IL, USA. Dr Kupfer's areas of research include heart failure, hypertension, peripheral arterial disease, thrombosis, diabetes, obesity, chronic kidney disease, 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 MD at the University of Florida in Gainesville, FL, USA and completed 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.

Carolyn Lam (Singapore, SGP)

Dr Carolyn Lam is a Senior Consultant of the National Heart Centre, Singapore and Associate Professor of Duke-NUS Cardiovascular Academic Clinical Program, and Chairperson of the Asia Pacific Association of Women's Cardiovascular Disease. She graduated from the Faculty of Medicine, National University of Singapore, completed advanced specialty training in Cardiology in Singapore, and pursued her Research Fellowship at the Cardiorenal Laboratory, Heart Failure Fellowship at the Division of Cardiovascular Diseases, and Advanced Cardiology and Master of Biomedical Sciences at Mayo Clinic, Rochester MN. She further obtained training in clinical and genetic epidemiology

at the Framingham Heart Study in Boston, MA before returning to Singapore in 2010 on the National Medical Research Council's Clinician Scientist Award.

Dr Lam's clinical sub-specialty is heart failure, and she is recognized globally for her expertise in heart failure with preserved ejection fraction. She also has expertise in women's cardiovascular disease, hemodynamics, echocardiography, biomarkers and clinical trials. She started the first Heart Failure with Preserved Ejection Fraction Programme and Women's Heart Health Clinic in Singapore, was awarded the L'Oreal Women In Science Award (2012) for her work in women's cardiovascular disease, was named an InterAcademy Medical Panel Young Physician Leader at the World Health Summit in Berlin (2012), and won the award for the Junior Chamber International (JCI) Ten Outstanding Young Persons of the World for 2014 –Singapore (2014). She is the Programme Lead of the Asian neTwork for Translational Research and Cardiovascular Trials (ATTRaCT) – an A*STAR Biomedical Research Council-funded research platform; and principal investigator of an ongoing nation-wide heart failure study in Singapore (the Singapore Heart Failure Outcomes and Phenotypes [SHOP] study) and a multinational Asian study of patients with heart failure across 11 Asian countries (Asian Sudden Cardiac Death in Heart Failure [ASIAN-HF] study).

She is on the Executive Committees of several global heart failure trials, contributes to the editorial boards of top cardiovascular journals (JACC, European Heart Journal) and is an international member of the writing group of the Heart Failure Association/ European Society of Cardiology Consensus Document for the Diagnosis of Heart Failure with Preserved Ejection Fraction as well as International Consortium for Health Outcomes Measurement working group for Heart Failure Outcomes.

Cecilia Linde (Stockholm, SWE)

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

Brian Lindman (St Louis, USA)

Brian Lindman is an Assistant Professor of Medicine in the Cardiovascular Division at Washington University School of Medicine in St Louis, Missouri, where he is Co-Director of the Center for Valvular Heart Disease. His expertise is in valvular heart disease and echocardiography and his clinical and translational research centers on calcific aortic stenosis. His group uses sophisticated imaging techniques and a biobank of specimens to elucidate the pathobiology of aortic stenosis and the effects of pressure overload on the left ventricle and pulmonary vasculature. He has a particular interest in how diabetes affects these processes and aims to identify novel targets for adjunctive medical therapy to improve clinical outcomes in patients with aortic stenosis. He was the first to show that a single dose of a phosphodiesterase type 5 inhibitor (sildenafil) is safe in patients with severe aortic stenosis and provides favorable acute hemodynamic effects in the pulmonary and systemic circulations. The clinical effect of chronic administration of PDE5 inhibition is now being tested in patients with asymptomatic aortic stenosis. Many of his research questions and approaches are translatable to patients with heart failure with preserved ejection fraction. He is on the editorial board of JACC and is the recipient of an NIH K23 and Doris Duke Clinical Scientist Development Award.

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Klaus Lindpaintner (Newark, USA)

Klaus Lindpaintner, MD, MPH, FACP serves as Chief Scientific Officer at Thermo Fisher Scientific, the world's leading provider of analytical instru-ments, reagents, and services, where he is supporting efforts to drive innovation with regard to both content and process. Previously, he held senior posi-tions at Hoffman-La Roche, where he spearheaded the company's efforts in personalized health care and was responsible for the respective activities in translational research that have rebranded the company's image; at SDIX, a specialty-antibody-focused biotechnology company; and on the faculty of Harvard Medical School. Klaus has co-authored more than 250 scientific pa-pers, and holds honorary and adjunct professorships at several academic in-stitutions. He serves on numerous boards, working groups, and advisory panels for trade organizations, regulatory authorities, and non-governmental organizations on issues related to the successful imple-mentation and leverage of novel technologies in health care and industrial applications, as well as on the ethical and societal impact of these technologies. Klaus graduated from Innsbruck University Medical School with a degree in medicine, and from Harvard University with a degree in public health. He pur-sued post-graduate training and specialization in internal medicine, cardiology, and clinical and molecu-lar genetics in the US and Germany, and is a Diplomate of the Boards in these specialties.

Raj Madabushi (FDA, USA)

Rajanikanth (Raj) Madabushi, PhD., is a Team Leader for Cardio-Renal products in the Division of Clinical Pharmacology I of Office of Clinical Pharmacology, Center for Drug Evaluation and Research, FDA, Silver Springs, MD. Dr Madabushi received his PhD. degree in Pharmaceutical Sciences from Birla Institute of Technology and Sciences (BITS), Pilani, India. Following his PhD., he did a post-doctoral fellowship with Prof. Hartmut Derendorf at university of Florida, Gainesville. He joined the Pharmacometrics Group at FDA in 2005. As a pharmacometrics reviewer, he was predominantly involved in the application of quantitative clinical pharmacology approaches for regulatory decision making and addressing various drug development issues in the areas of Cardio-Renal, Hematology and Endocrinology drug products. In 2009, he became the Team Leader in the Division of Clinical Pharmacology I, specifically focusing the area of Cardiovascular, Renal and Hematology products. Since then, he has been involved in the drug development, regulation, research and policy from a clinical pharmacology perspective.

ABSTRACT

Dosing for non-vitamin K oral anticoagulants (NOACs) in patients with CKD: strengths and limitations of using PK data

The risk of cardiovascular morbidity and mortality increases dramatically in patients with CKD compared to those without CKD. It is also recognized that the risk for bleeding is significantly higher in CKD patients taking anticoagulants compared to patients without CKD. Despite this, there is a significant paucity of clinical information in patients with Chronic Kidney Disease (CKD), as they are either underrepresented or generally excluded by protocol in most Cardiovascular (CV) Outcome trials. Generally for subgroups that are not represented in phase 2/3 clinical trials but are expected to be recipients of treatment, dosing is derived based on matching of pharmacokinetics. In some instances, pharmacodynamics is also taken into account to derive dosing. This approach is routinely employed for deriving dose adjustments in patients with impaired organ function such as renal or hepatic function. This approach is also routinely applied to derive dose adjustments to mitigate drug interaction. However, this simple approach may not be applicable always and requires careful consideration specifically for antiplatelets and anticoagulants as the underlying hemostasis is altered by CKD. The talk will discuss the strengths and limitations of using PK/PD data for deriving dosing information for NOACs in patients with CKD.

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Felix Mahfoud (Hamburg, GER)

Dr Felix Mahfoud studied medicine at the Johann-Wolfgang-Goethe University, Frankfurt, Germany. He completed his residency at the Department of Internal Medicine and Cardiology, Angiology and Intensive Care Medicine, Saarland University Hospital, Homburg, Germany. Since 2014 he is associate professor and senior physician of Internal Medicine and Cardiology at Saarland University Hospital and Affiliate/Visiting Professor of the Harvard-MIT, Biomedical Engineering, Boston, MA. Dr Mahfoud is a recipient of multiple national and international awards. His special scientific interest includes pathophysiology, conservative and novel interventional therapies of heart failure and hypertension. He is member of several editorial boards and serves as board member of the European Society of Cardiology Council on Hypertension, Working Group Interventional Hypertension Treatment of the European Society of Hypertension, EuroPCR Board of Directors, Co-Chairmen of the Resistant Hypertension Course Berlin, TCT Associate Director, and program committee member of the ESC congress 2015 & 2016. Dr Mahfoud is involved as steering committee member in the design and execution of several pharmaceutical and interventional studies in hypertension treatment.

ABSTRACT

How important are center-related factors in device/procedure clinical trials, i.e. volume of patients and degree of experience with the procedure?

In the years since the first studies on RDN our view of the technique has significantly evolved. Far from being a simple procedure that could be performed with little training by any interventionist regardless of their subspecialty, it is now recognized as a complex, specialized therapy whose primary and secondary success depends on a large number of influencing factors and uncertainties that may not be filled by our current knowledge. Moreover, there are a number of different systems, methods and strategies currently employed in RDN (using uni- or bipolar radiofrequency energy, high-energy ultrasound and chemical ablation), which make it difficult to standardize treatment recommendations and compare different treatment modalities in patients. Several procedural aspects need to be considered for future clinical trials, as they would help to improve reliability and thereby efficacy of the denervation technique:

1. The optimal degree of contact against the renal artery wall and the depth, location, duration, and intensity of energy delivery to provide the best procedural results are still being investigated.
2. The application of radiofrequency energy post-bifurcation has been shown to reduce variability in treatment effects in pigs. It should be kept in mind that, if distal ablation may improve the effectiveness of RDN, it should also not increase the risk of the procedure.
3. Maximum procedural efficacy would also mean the achievement of ablation in all four quadrants, the whole circumference, of both renal arteries.
4. There appears to be a 'dose-response' dependency between the number of ablation attempts and the efficacy of renal nerve ablation in both post-hoc clinical and prospective preclinical investigations.
5. The feasibility, need and consequences of treating small renal arteries (<4 mm), accessory, polar or segment arteries remains to be clarified

The lack of reliable markers of procedural success to immediately establish on time whether denervation has been completely achieved in a specific patient remains the major unmet need.

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Fady Malik (Cytokinetics, USA)

Fady I. Malik, MD, PhD, FACC, is the Senior Vice President of Research and Development at Cytokinetics, a biotechnology company based in South San Francisco. Dr Malik has been with Cytokinetics since its inception in 1998, in a variety of roles, including Vice President, Biology and Therapeutics, all focused towards building the company's cardiovascular and muscle programs. Since 2000, Dr Malik has held an appointment in the Cardiology Division of the University of California, San Francisco, where he is currently an Associate Clinical Professor and an Attending Interventional Cardiologist at the San Francisco Veterans Administration Medical Center. Dr Malik received a BS in bioengineering from the University of California at Berkeley, and a MD/PhD from the University of California at San Francisco where he also completed an internal medicine residency and fellowship in cardiology.

Felipe Martinez (Cordoba, ARG)

Dr Felipe Martinez is Emeritus Professor of Medicine at Cordoba National University, Director at the Instituto Damic-Fundacion Rusculleda, President of the International Society of Cardiovascular Pharmacotherapy, Former President of the Argentinean Federation of Cardiology (2002-2003) and, Co-chairman of the Scientific Program at the World Congress of Cardiology (2008).
He has published more than 180 scientific articles, edited three books; the last one, Handbook of cardiovascular therapy, is sold out in its second edition. He has been Invited Speaker in more than 200 International meetings in 23 Countries. Dr Martinez has participated in 31 Steering Com and also has been a Member of Executive Com and Endpoint Com of International Clinical Trials. In many of those Studies the Institution directed by him, has participated as the Coordinating Group for Latinamerica.

Alexandre Mebazaa (Paris, FRA)

Alexandre Mebazaa, MD, PhD, FESC, is Professor of Anaesthesiology and Critical Care Medicine at the Hôpital Lariboisière, University Paris 7, France. His research interests include mechanisms of contractile impairment during acute heart failure and global studies on biomarkers in acute heart failure. He acted as member or Chair of several Steering Committees including SURVIVE, COMPOSE, TRUE-HF. He is also involved in several European and global registries on circulatory failure. He has authored or co-authored more than 200 papers and is Lead-Editor of the Acute Heart Failure textbook. Dr Mebazaa also serves as the Chair of Department of Anesthesiology and Critical Care in Paris.

Roxana Mehran (New York, USA)

Roxana Mehran, MD, FACC, FACP, FCCP, FESC, FAHA, FSCAI is Professor of Medicine (cardiology) and Health Evidence and Policy and Director of Interventional Cardiovascular Research and Clinical Trials at The Zena and Michael A. Weiner Cardiovascular Institute at The Icahn School of Medicine at Mount Sinai in NYC. She is also Chief Scientific Officer of the Cardiovascular Research Foundation (CRF). Dr Mehran is internationally recognized for her work in multicenter, multinational clinical trials specializing in complex data analyses and outcomes research.

Her research interests include mechanisms of restenosis, treatment and prevention of acute kidney injury (AKI) in cardiac patients, gender differences in cardiovascular disease (CVD), and pharmacologic and interventional treatments for acute coronary syndromes and acute myocardial infarction.
Dr Mehran possesses almost 20 years of experience working with regulatory agencies to design and conduct clinical trials and help shape health policy. She currently serves on the board of trustees of the Society

for Cardiovascular Angiography and Interventions (SCAI) and is a member of the Program Committee for the American Heart Association Scientific Sessions.
As an interventionalist, Dr Mehran is a highly-skilled clinician devoted to improving patient outcomes and also enjoys teaching and mentoring fellows in the hospital's cardiology program.

Michele Mercuri (Daiichi Sankyo, USA)

Michele Mercuri, MD, PhD, FAHA, is a Sr. VP, Head of Clinical Development for the Americas, and Chief Medical Advisor at Daiichi Sankyo in Edison, NJ. A graduate from the University of Perugia (Italy) received additional training in Internal and Geriatric Medicine at the Universities of Parma, and Modena.

Following Fellowships in Cerebrovascular Disease (J. Toole), and Vascular Ultrasound (G. Bond) at the Bowman Gray School of Medicine of Wake Forest University in Winston-Salem, NC, Michele served in the Faculty and as the co-Director of the Division of Vascular Ultrasound. Michele joined Merck in Rahway, NJ, in 1996 and worked in cardiometabolic drug development (J. Tobert and E. Stoner).

In 2003, Michele joined Novartis in East Hanover, NJ, to lead Cardiometabolic Disease and Atherosclerosis drug development (JJ Garaud) and then the Global Protocol Review Committee (G. Della Cioppa). Michele moved to Daiichi Sankyo in 2008 to design, execute and file the edoxaban Phase 3 program, a factor Xa inhibitor which subsequently filed and approved in the major regions of the world as LIXIANA® and SAVAYSA®.

Currently Michele looks after late stage development programs in the area of cardiovascular, metabolics, oncology and pain management.

Timothy Meyer (Boston Scientific, USA)

Timothy E. Meyer is Director of Electrophysiology, New Products and Biostatistics at Boston Scientific. Dr Meyer obtained his MS degree in Physiology from the University of North Dakota School of Medicine in 1995. He obtained his PhD in Movement Science from Washington University in St. Louis in 2005 and subsequently started his post-doctoral Fellowship at Washington University School of Medicine. He joined Boston Scientific in 2005 as a Sr. Scientist working on clinical trials and has held numerous positions within the Clinical department. His work has covered feasibility trials, IDE and CE-mark trials as well as mandated and non-mandated post-market clinical trials.

Dr Meyer manages a group of clinical trial managers and biostatisticians that are based in the US and Europe and manage and work on global clinical trials. In addition, he has over 25 articles in peer reviewed journals as well as numerous patents.

ABSTRACT

Atrial fibrillation prevention and treatment trials

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia. Not only is the prevalence of AF expected to rise but the global costs associated with this tachyarrhythmia are concerning.

Moreover, treating AF is not a simple problem as the mechanisms of AF are complex and associated with structural and electrical remodeling in the atria and ventricular myocardium.
From an industry perspective there is a balance between R&D investments of clinical trials and technology. This is due to the fact that we need to understand the AF substrate before pursuing different treatment technologies. Although there is a definite need for better tools to aid in the treatment of AF, knowledge gaps remain in the understanding of the substrate.
For example, catheter ablation has become a cornerstone for rhythm control in patients with atrial fibrillation. However, the results of randomized clinical trials using this procedure have shown mixed results.
Given that AF is driven by a multitude of risk factors, a very broad and strategic treatment approach is needed. Studies with sufficient sample sizes are needed to both phenotype patients as well as effectively determine whether catheter ablation versus other treatments will benefit certain patient subgroups more than others.
Individual companies and groups can tackle this disorder in isolation but collaborations and partnerships may be a more efficient and effective approach to tackle questions such as whether there are subgroups in which catheter ablation might best used as a first or second-line treatment.
Once AF is diagnosed, individual assessment should identify the modifiable risk factors in which lifestyle changes could help as well as understand the inherited predisposition to AF which cannot be modified.
The fact AF is a heterogeneous disease with respect to its aetiology, pathophysiology, mechanisms, clinical presentation, natural history, and outcomes indicates that patient-centric strategies need to be developed; ideally with partnerships between industry, government agencies and academic institutions.
Only then may precision-medicine play a role in the treatment of atrial fibrillation.

Peter Mol (EMA, NED)

Peter Mol is a principal assessor with a focus on cardiometabolic diseases at the Dutch Medicines Evaluation Board. He is a long-standing member of EMA's Scientific Advice Working Party and has coordinated over 100 European advices. He is also an assistant Professor at the University Medical Center Groningen at the Department of Clinical Pharmacy and Pharmacology. His research interest is in regulatory decision-making and knowledge transfer with a specific interest in risk communication and medication safety.

ABSTRACT

Cardiovascular outcome trials in CKD patients - Regulatory viewpoint

I will discuss surrogate endpoints for clinical trials in chronic kidney disease. I will emphasise the regulators' role in optimising the balance between early market access while safeguarding patient safety.

Zoë Mullan (London, GBR)

Zoë Mullan trained in Biochemistry at the University of Bath, GBR, before joining the publishing world in 1997 as a Scientific Information Officer with CAB International. She moved on to The Lancet in 1999, where she has worked since, variously as a technical editor, section editor, and presently Editor in Chief of the open access journal, The Lancet Global Health.

Should publications of trial results be made "open access"?

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Steven Nissen (Cleveland, USA)

Steven Nissen MD, MACC, is Chairman of Department Cardiovascular Medicine at Cleveland Clinic – 8 years. He served 9 years as vice-chairman and 5 years as medical director of the Cardiovascular Center (C5) that directs multicenter clinical trials. National leadership positions include term as President of the American College of Cardiology 2006–2007; serving the Food and Drug Administration as member of CardioRenal Advisory Panel 5 years and Chairman 1year; and continued service as Advisor to several FDA committees.

Steven Nissen is known for public policy discussions regarding drug safety, having testified in the Senate and House of Representatives on the need for FDA reform. Contributions to scientific literature include more than 400 peer reviewed journal articles and 60 book chapters. In 2014 he received Recognition of Excellence in Clinical Medicine by Thomson Reuters Highly Cited Researchers – Top 1% of the most cited articles of World's leading scholars in the Sciences and Social Sciences among authors indexed within the Web of Science, between 2002-2012, reported via www.ScienceWatch.com

Christina Nowack (Bayer, GER)

Christina Nowack is Global Clinical Leader at the Bayer Pharma AG in Wuppertal, Germany. Christina graduated from the Heinrich-Heine University of Duesseldorf, Germany in 2001 and obtained her MD degree in 2005. After working in hospital for several years, she joined FOCUS Clinical Drug Development GmbH in Neuss, Germany where she started a job as Study Physician/Investigator for Phase 1 international clinical trials. In January 2007, she moved to Grunenethal in Aachen, Germany where she took over a position as a Clinical Expert in Gynaecology and Pain.

After being promoted to an International Clinical Project

Leader, she also took over responsibilities as International Project Leader where she managed three international alliances. In October 2009, she joined Bayer Pharma AG in Wuppertal, Germany as Global Clinical Leader in the therapeutic area of Cardiovascular and Coagulation.

She was responsible for the clinical development of a product in acute decompensated heart failure in phase 2b which was terminated. Starting from pre D3 onwards she leads the clinical development of finerenone (BAY 94-8862), a next-generation, non-steroidal mineralocorticoid-receptor antagonist. After successful completion of the ARTS trial, she was responsible for starting ARTS-HF and ARTS-DN in worsening chronic heart failure and diabetic kidney disease (DKD). In April 2014, she concentrated on the clinical development of finerenone in DKD which is now in phase 3. In September 2017, the Phase III programme in DKD has started: FIGARO-DKD will investigate finerenone versus placebo in 6,400 patients while FIDELIO-DKD will investigate finerenone in comparison to placebo in 4,800 patients. Both studies will be conducted in about 40 countries including Europe, Japan, China and the US.

Christopher O'Connor (Washington, DC, USA)

Dr O'Connor is the CEO and Executive Director of the Inova Heart & Vascular Institute in Fairfax, VA. He previously served as director of the Duke Heart Center and chief of the Divisions of Cardiology and Clinical Pharmacology at Duke University Medical Center.

A Fellow of the American College of Cardiology (ACC), the American Heart Association, and the European Society of Cardiology, he has served on over 90 CEC and DSMC committees in 25 years and served as chair or co-chair on more than 15 of these committees. He has an extensive record of successful mentorship of trainees and has published over 500 manuscripts.

He has served as principal investigator (PI) or co-PI for over 20 national and international clinical trials with an extensive record of NIH/NHLBI and industry grants, including the NIH Heart Failure Network Core Skills Development Training Grant, focused on the training of future cardiovascular (CV) investigators. He was PI of the ASCEND-HF Trial, the largest acute heart failure trial ever conducted.

He has served as PI for a number of other CV trials, including the NHLBI sponsored HF-ACTION Trial, the largest prospective randomized trial examining the effects of lifestyle intervention on outcomes in heart failure patients. Dr O'Connor was also the lead investigator in the WIZARD Trial, a trial of antibiotic therapy in stable ischemic heart disease; SADHART, a randomized trial of antidepressant therapy in depressed post myocardial infarction patients; the ACTIV Trial, a randomized trial of vasopressin antagonists in moderate congestive heart failure; and RITZ 4, a trial of IV endothelin antagonists in acute heart failure. He is currently PI of the CAT-HF Trial, the largest trial in the US examining the treatment of sleep apnea in heart failure patients.

Dr O'Connor's research interests include: acute heart failure, co-morbidities in heart failure, clinical trials, biomarkers, and novel pharmacological and non-pharmacological approaches for the treatment of heart failure.

Dr O'Connor completed his undergraduate and medical school training at the University of Maryland. He completed his Internal Medicine residency and Cardiology Fellowships at Duke University Medical Center. He is a professor of medicine and associate professor in psychiatry and behavior sciences.

Patrick O'Malley (Bethesda, USA)

Patrick O'Malley is a professor of medicine at the Uniformed Services University of the Health Sciences (USU), and a Deputy Editor for JAMA – Internal Medicine. Dr O'Malley is a graduate of Williams College. He obtained his MD degree from the University of Rochester in New York in 1991, and his MPH degree from USU in 1998. He did residency and fellowship in internal medicine at Walter Reed Army Medical Center in Washington DC where he then served as director of the division of general internal medicine. He has been active in technology assessment research and primary care based implementation science. He was a co-PI of the Prospective Army Coronary Calcium project and has expertise in clinical epidemiology, synthesis research and meta-analysis.

He has over 120 articles in peer-reviewed journals and books. He has been editor at JAMA – Internal Medicine (previously Archives of Internal Medicine) since 2004. In his current role as Division Director for General Internal Medicine at USU, he has been active in curricular reform and serves as a director of the pre-clerkship curriculum. He is a longstanding member of the Society of General Internal Medicine and a Fellow of the American College of Physicians which awarded him the Crosby Award for Research in 2007.

ABSTRACT

Publication forum musings

Journals have an obligation to uphold the trust vested in them by safe-guarding the integrity of published scientific information. It is this science that serves as

the basis for life-changing decisions, and indeed underlies the trust that empowers the therapeutic relationship. This responsibility is part of upholding the social contract of our profession with society, which includes a basic tenet that we will police ourselves and assure our profession maintains the highest integrity. Business entities engaging in medical products do not explicitly abide by the traditional ethics of medicine, particularly as it relates to nonmaleficence and just allocation of resources.

This conflict creates a dilemma when business seeks to use the credibility of science journals for their products. How well science gets vetted and communicated depends on the integrity of the process and the credibility of the source. The process depends on the expertise of editors and reviewers, as well as the integrity of the researchers.

There is a great deal of trust within every step of this process; and it is indeed vulnerable to malfeasance and nefarious elements due to a lack of granular accountability. But it works fairly well. The credibility of the source is dependent on whether the entity is beholden to the same professional ethics consistent with the profession of medicine. When it is not, trust is eroded and impairs the willingness to publish data from such a source. Would industry abide by a business ethic that avowed the principle of nonmaleficence?

Fast-tracking of reports has clear appeal, but important trade-offs. In my view there is insufficient rationale for the rush; it is better to use a more deliberate process. The recent SPRINT trial is a great example of the many issues with early reporting without due process. There are many details that legitimately need to be reviewed to give the results the balanced presentation necessary to interpret results critically and fairly. Why is the urgency to report not commensurate with the urgency to fund the research question in the first place?

The benefits of more efficient publication of reports (whether through fast-tracking or open access) include the speed of publication and dissemination, increased researcher morale and productivity, and presumably the implementation of the new science into practice and therefore improved patient outcomes. This latter point though is an unknown, and an empiric question. There is reason to believe that there could be harm associated with premature publication and dissemination. The downsides include higher risk for error due to a less deliberate process and changed financial dynamics (eg, the payor has elevated power, and perhaps less incentive to be held accountable).

The wiki model of collaborative co-creation of intellectual products (which open access essentially allows) is perhaps reassuring that errors will get self-corrected, but clinical research is complicated and conclusions (especially if misrepresented in publicized reports) may not be so malleable.

Free access to publications is happening already for many publically funded studies. However, print advertising is diminishing and this puts the production cost burden on the publishing company. This could be built into the grant process to solve this. Open access to data is also already happening but can clearly be expanded (eg, Clinicaltrials.gov, CARDIA, MESA, Framingham). Improvements could include registering observational studies and registries, and making the data available earlier and with less restrictions.

Open access would certainly raise the bar on accountability of analyses and conclusions. Would industry be willing to collaborate?

There are clearly dysfunctional incentives for both authors and editors in the publishing of research that are not necessarily aligned for the good of medical science. It seems any solution to improve on this, without compromising on the ethics of publishing science, could range between enhancing the professional ethics of involved parties and stakeholders on the one hand, or to tighten accountability and regulation on the other.

Andrew Peacock (Glasgow, GBR)

Andrew Peacock, MPhil, MD, FRCP: Professor in Medicine at the University of Glasgow (Respiratory Medicine) and Director of the Scottish Pulmonary Vascular Unit, at the Golden Jubilee National Hospital in Clydebank, near Glasgow (one of the United Kingdom's seven designated specialist pulmonary units).

Dr Peacock is author of more than 200 papers, reviews, and chapters on pulmonary vascular disease. He is co-editor with Lew Rubin and Robert Naeije of Pulmonary Circulation: diseases and their treatments (4th Edition in press). In 2015 he was awarded the ERS Lifetime achievement award for his work in Pulmonary Hypertension

ABSTRACT

Endpoints in pulmonary arterial hypertension with special reference to the endothelium receptor antagonists

Pulmonary arterial hypertension is a rare disease and has to be distinguished from pulmonary hypertension due to a variety of causes, but usually either chronic lung disease or chronic heart disease.

Pulmonary arterial hypertension generally requires management by specialist units who are able to determine the level of pulmonary hypertension, pulmonary vascular and cardiac consequences and likely cause of pulmonary hypertension.

The initial treatment is always towards the cause and, if this is heart or lung disease, then these take priority. Where disease appears to be hereditary, idiopathic or related to connective tissue disease (Group I Pulmonary arterial hypertension), then the appropriate therapy is the use of 1 or more of 3 lines of treatment:

1. Prostcyclin or other agonist
2. Endothelin receptor antagonists
3. Phosphodiesterase 5 inhibitors

New treatments are being developed all the time, focusing particularly on the remodelling of pulmonary vessels that occurs with pulmonary hypertension rather than purely vasodilatation. By using these therapies, there has been a remarkable improvement in survival of patients with pulmonary arterial hypertension.

Appropriate measures for measuring the effects of drugs in a clinical drug remain controversial. Initial trials used 6 minute walk test and pulmonary haemodynamics and looked for improvement in 6 minute walk test with a drop in pulmonary artery pressure or pulmonary vascular resistance.

While these trials were successful and, undoubtedly, the survival of patients with pulmonary hypertension has improved with these 3 lines of therapy, there are a number of problems associated with these endpoints.
Firstly, pulmonary haemodynamics is not predictive of survival. Secondly, a change in 6 minute walk test, which is what was used in these trials, is also not predictive of survival.

This has generated a need for new endpoints, in particular, the composite endpoints of time to clinical worsening and time to clinical failure.
In this talk, I shall focus on the history of endpoints for the determination of success or failure in treatment of pulmonary arterial hypertension but I shall also examine cardiac endpoints.

In the past, right heart dysfunction and failure as a consequence of pulmonary arterial hypertension has been thought to be simply due to the high afterload causing impendence to right ventricular outflow.

While this is true, it has been surprising that patients with identical afterload seem to vary in response to treatment. In other words, some patients will do well with very high pressures and resistance and other patients will do badly with low pressure and resistance.

This has focused attention on the cardiac response to vasodilator and antiproliferative therapy and, in particular, whether some drugs, notably endothelin receptor antagonist, might have differential effects on the heart (negative inotropy), and the lung (vasodilatory).
This has raised the concept of “good for the lung but bad for the heart”.

This concept was extended by the use of anti-pulmonary hypertension drugs, notably the endothelin receptor antagonists and prostacyclin, to treat left heart failure. Both endothelin receptors and prostacyclin itself have been used to treat left heart failure and found to be harmful. This raises the question of whether these drugs could have direct effects on cardiac function and cardiac metabolism.
In this paper, I shall examine some of these problems and propose some solutions.

Vlado Perkovic (Sydney, AUS)

Professor Vlado Perkovic is Executive Director of The George Institute, Australia, Professor of Medicine at The University of Sydney and a Staff Specialist in Nephrology at the Royal North Shore Hospital. Vlado holds a Doctor of Philosophy from the University of Melbourne and completed his undergraduate training at The Royal Melbourne Hospital. Dr Perkovic’s research focus is in clinical trials and epidemiology across kidney disease, cardiovascular disease, blood pressure and the linkages between these conditions. He Chairs or Co-Chairs a number of steering committees, including the CREDENCE, CARMELINA, TESTING and ACTIVE-Dialysis trials, and is a member of several other major trial Steering Committees. He has also been central to the development of George Clinical, the clinical trial implementation arm of the George Institute with reach across the Asia-Pacific region. Vlado has been involved in developing Australian and global guidelines in kidney disease, cardiovascular risk assessment and blood pressure management. Vlado has published almost 200 peer-reviewed papers and is regularly invited to speak at major global conferences. He Chairs the International Society of Nephrology Association for Clinical Trials and is the immediate Past-Chair of the Scientific Committee of the Australasian Kidney Trials Network. Vlado has served on Australian Government taskforces focused on clinical trials, bioinformatics and biobanking.

Marc Pfeffer (Boston, USA)

Dr Marc Pfeffer, MD, PhD is the Dzau Professor of Medicine at Harvard Medical School, and Senior Physician in the Cardiovascular Division at the Brigham and Women’s Hospital in Boston. A noted researcher, Dr Pfeffer, along with his late wife, Dr Janice Pfeffer, and Eugene Braunwald MD, is credited with introducing the concept that angiotensin-converting enzyme inhibitors (ACEIs) could attenuate adverse ventricular remodelling following myocardial infarction and that this use would result in a prolongation of survival and other clinical benefits. Since this initial discovery, he has had a principal role in several practice-changing clinical trials such as SAVE, CARE, HEART, VALIANT, CHARM, PEACE, ARISE, TREAT, ALTITUDE, TOPCAT and ELIXA.

Dr Pfeffer is considered as a team builder and takes pride in academic advancement of trainees and junior faculty collaborating on the trials. He is known for his fairness in data sharing and assisting others in developing meaningful scholarly works from study databases. He sets high standards for relationships with the sponsors whether industry or NHLBI.

Dr Pfeffer is Senior Associate Editor of Circulation and

is a member of the Editorial Board of several other prominent journals. He serves on the Data Safety Monitoring Boards of major international trials. An internationally recognized expert in the field of cardiology, he was recognized by Science Watch as having the most 'Hot Papers' (highly cited) in all of clinical medicine. Dr Pfeffer was listed as one of the highly influential biomedical researchers of 1996-2011 in the European Journal of Clinical Investigation.

He is the recipient of the William Harvey Award of the American Society of Hypertension, the Okamoto Award from Japan's Vascular Disease Research Foundation, the Clinical Research Prize, the James B. Herrick Award as well as the Distinguished Scientist Award from the American Heart Association. Dr Pfeffer is an Honorary Fellow of the Royal College of Physicians and Surgeons of Glasgow and is the recipient of an Honorary Doctoral Degree from Sahlgrenska Academy, University of Gothenburg, Sweden.

Bertram Pitt (Ann Arbor, USA)

Bertram Pitt is a professor of medicine emeritus at the University of Michigan School of Medicine. Dr Pitt obtained his MD degree from the University of Basel in Switzerland in 1959. He subsequently did a fellowship in cardiology at the Johns Hopkins University School of Medicine and remained on the faculty there until 1977 when he left to direct the division of cardiology at the University of Michigan School of Medicine.

He has been chairman or co-chairman of a number of clinical trials in cardiology including: SOLVD; ELITE I and II; Prevent; Rales and Ephesus. He is currently chairman of the steering committee of the NHLBI TOPCAT trial examining the effect of spironolactone in patients with HF and preserved LV systolic function; co-chairman of the Emphasis-HF trial examining the role of eplerenone in patients with NYHA Class II HF; chairman of Break- DHF; co-chairman of STOP-CKD; co-chairman of Exceed; co-chairman of Escape-SHF and Escape-DH F; chairman of a study evaluating the role of an aldostereone synthase inhibitor in patients with HF and is a member of the executive committee of the Accomplish trial. In addition, he serves as the chairman of the DSMB for the NHLBI HF-Action trial and has over 500 articles in peer reviewed journals.

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

Stuart Pocock (London, GBR)

Stuart has been professor of medical statistics at the London School of Hygiene and Tropical Medicine since 1989. His main research interests concern randomised clinical trials, both in statistical methods for their design, monitoring, analysis and reporting, and also in collaborations on specific major trials especially in cardiovascular disease. He directs an experienced group of academic medical statisticians, who collaborate widely on clinical trials research, from planning to publication. A particular expertise is in data monitoring and as an independent statistical centre for industry-sponsored trials. Stuart and his group also research on epidemiology, especially pharmaco-epidemiology, meta-analyses, and journal reporting guidelines. Stuart's international collaborations are diverse, and include particular long-standing relationships with research institutes in Madrid and New York. He is a frequent lecturer/teacher at international conferences, workshops and short courses.

Krishna Prasad (EMA, GBR)

Krishna Prasad is a Group Manager at the UK Regulatory Agency with management responsibility for Cardiovascular-diabetes, anti-infective agents, oncology and musckuloskeletal therapy areas for the last 18 months. Dr Prasad's additional roles include Cardiology consultancy at St. Thomas' hospital, London. Dr Prasad qualified (MB BS) in 1987 obtaining his MD in 1989 and completing Certification in Cardiology subsequently. He has worked for MHRA, the UK regulatory agency since 2002 initially as reviewer progressing to lead the cardiology-diabetes areas and subsequently to the current post. Dr Prasad's areas of special interest in cardiology include heart failure, sudden death, cardiomyopathies and arrhythmias. He is a member of the Cardiovascular working party since 2008 as well the chair of the pharmacogenomic working party of CHMP assuming responsibility for coordinating European guidances on heart failure, lipid modifying agents and paediatric guidances in these areas as well authoring several reflection papers on pharmacogenomics and biomarkers. He is participated in many regulatory-scientific dialogues across the globe and has a keen interest in harmonisation of global approaches to both clinical trials and regulatory

guidance development. He is closely involved in the International Committee of harmonisation expert groups for E-14 and E-18 guidelines.

Jean-Claude Provost (GE Healthcare, GBR)

Jean-Claude Provost, MD, is the Global Head of Clinical Development of GE Healthcare – Life Sciences/ Core Imaging R&D. Jean-Claude has over 25 years of experience in the pharmaceutical and clinical trials industries, having occupied various positions in Clinical R&D and as well in managing businesses.

He graduated with a Doctorate in Medicine in 1990. He started his career in Clinical Pharmacology at Saint–Antoine University Hospital of Paris and then moved to Merck-Serono.

He then joined Bayer Pharmaceuticals and then was employed by Wyeth (now Pfizer) as Medical Director for immunology, cardiology & internal Medicine. He was involved as Sponsor in large cardiology trials like CIBIS, CIBIS II, INSIGHT, ACTION…In 2000, he joined a small imaging company (IoDP medical Imaging) that he transformed in an imaging core lab and sold it to Synarc Inc. in 2004.

He stayed with Synarc as VP for Cardiology and Neurology and in 2006 became CEO of CCBR (another company later on purchased by Synarc). In 2010 he co-founded SMO-Clinica for which he is still non-executive Chairman. He joined General Electric Healthcare in August 2014 to globally head the clinical development of imaging agents; he is based in Amersham, UK.

Henrik Rasmussen (ZS Pharma, USA)

Dr Henrik Rasmussen is the Chief Medical and Chief Scientific Officer at ZS Pharma. He received his MD and PhD from the University of Copenhagen, School of Medicine as well as his Certificate and Diploma in Professional Management and Business Administration at Milton Keynes Open University Business School.

Prior to joining ZS Pharma, Dr Rasmussen served as the Corporate Vice President and Head of Clinical Development, Medical and Regulatory Affairs for Novo Nordisk Inc. and held executive level positions at Nabi Pharmaceuticals, Genvec, British Biotech, and Pfizer Central Research. All told Dr Rasmussen has more than 25 years of experience in senior management in the biopharmaceutical industry.

In addition to his executive experience, Dr Rasmussen is a prolific author and has published over 150 full papers, reviews, book chapters, and abstracts in peer reviewed journals such as the Lancet, British Medical Journal, American Journal of Clinical Oncology, Kidney International, American Journal of Cardiology, and Archives of Internal Medicine.

Beyond being an expert in internal medicine, cardiology, and gastroenterology,

he is a member of the American Society of Clinical Oncology, the Society of Pharmaceutical Medicine, the American Academy of Pharmaceutical Physicians, and the American Association for the Advancement of Science.

Paul Reilly (Boehringer Ingelheim, USA)

Paul Reilly is Executive Director and Clinical Team Leader (Cardiology), Clinical Development and Medical Affairs at Boehringer Ingelheim.
He has been running cardiovascular clinical trials for 30 years. He worked for 10 years as global clinical team leader for the developmnet and apprvoal of Pradaxa for stroke prevention in patients with atrial fibrillation.
Most recently, he served for 3.5 years as global clinical team leader for the development of Praxbind (idarucizumab), the Pradaxa antidote, which was recently approved in the USA.

Drummond Rennie (San Francisco, USA)

Drummond Rennie, MD, MACP, FRCP, was educated at Cambridge University and Guy's Hospital Medical School, London, where he carried out research on the reasons for proteinuria in severe cyanotic congenital heart disease. This led to numerous investigations at very high altitudes on the pathophysiology of hypoxia. Having been Deputy Editor of the New England Journal of Medicine when at Harvard, he moved to the University of California, San Francisco as Deputy Editor of the Journal of the American Medical Association. With strong support from JAMA, he started and directed all seven 4-yearly International Congresses on Peer Re-

view in Biomedical Publication. He chaired a multi-journal group researching interventions in peer review and was co-director of the San Francisco Cochrane Center; served on the Proposal Review Advisory Team of the NSF, was president of the Council of Science Editors and president of the World Association of Medical Editors. He was a founder member of the CONSORT, QUOROM, MOOSE, STARD and STROBE initiatives to improve the reporting of clinical trials, meta-analyses and diagnostic tests. He was a member of the Commission on Research Integrity to the Public Health Service reporting to the US Congress. He introduced systems to link scientific authorship with accountability. He has been deeply involved with issues concerning distortion of the scientific record due to money and intimidation of researchers, the transparent reporting of clinical research, improving the validity of reported conclusions, trial registration, and evidence-based medicine. He received the 2009 AAAS Award for Scientific Freedom & Responsibility. He is a member of the Alpine Club, the American Alpine Club and the Tobogganing Club of St Moritz. See also his obituary: Rennie D. The living, structured auto-obituary. Lancet. 1996;348:875-6.

James Revkin (Pfizer, USA)

James H. Revkin, MD, FACC, FACP is a Senior Director, at Pfizer Inc., and an Associate Clinical Professor of Medicine at Yale University. Dr Revkin obtained his MD degree from Brown University in 1981. He subsequently completed a fellowship in cardiovascular (CV) medicine at the Yale University School of Medicine. He did Postdoctoral work at the Center for Bioengineering, University of Washington, Seattle, USA, in 1987, and joined its faculty as the Director of the Heart Failure Transplant Cardiology Program. He returned to Yale to do the same, until 1993.

He was Director of CV Medicine at Waterbury Hospital, one of Yale's affiliated Hospitals, supporting its Yale Primary Care Medicine trainees.

He joined Pfizer in 1999 as the protocol lead for the amlodipine pediatric hypertension study (PATH) and then moved to its torcetrapib/atorvastatin CETP inhibitor project, overseeing some of its Phase 2A studies and the design and execution of the project's Phase 3 vascular imaging studies (ILLUSTRATE, RADIANCE 1, and RADIANCE 2).
He joined Boehringer Ingelheim Pharmaceuticals Inc. in 2008, as its US Operating Unit Therapeutic Area Director for Cardiovascular Medicine and Metabolic Diseases. He contributed to the dabigatran regulatory filings for stroke prevention in atrial fibrillation and venous thrombo -embolic disease secondary prevention. He returned to Pfizer in 2012, as a Global Clinical Lead for the PCSK9 inhibitor bococizumab cardiovascular outcomes studies, SPIRE 1 and SPIRE 2.

Martin Rose (FDA, USA)

Martin Rose, MD, JD. Acting Team Leader, Division of Cardiovascular and Renal Products, U.S. FDA. Previously was in pharmaceutical industry for 22 years, with 17 years in leadership positions in drug development, regulatory affairs and medical affairs.

Past Chairman of the Regulatory Affairs Committee of BIO and the Government Affairs Committee of the American Society for Clinical Pharmacology and Therapeutics.

Yves Rosenberg (NHLBI, USA)

Dr Rosenberg, MD, MPH is Chief of the Atherothrombosis and Coronary Artery Disease Branch, Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute, National Institutes of Health, in-Bethesda, Maryland.
Dr Rosenberg obtained his MD from the University of Lyon, France, and is Board certified in Preventive Medicine. He also has an MPH from the Johns Hopkins School of Hygiene & Public Health, and a MS in Clinical Pharmacology. Dr Rosenberg's main research interests are the design and conduct of large multicenter phase III clinical trials; the methodology of trials of treatment strategies and comparative effectiveness trials.

As a Program Director at NHLBI for the last 20 years he has led and participated in the development, conduct, analysis and reporting of more than a dozen major international clinical trials, the results of which have usually been incorporated in clinical guidelines and are influencing today's practice of cardiovascular medicine in the United States and all over the world.

Dr Rosenberg is currently the lead NHLBI Project scientist for CABANA (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation), an international multicenter (125 sites, 2,200 participants) trial, and for ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) an 8,000 participants, 300 sites international trial. Dr Rosenberg served as a member of the Society for Clinical Trials Board of Directors.

Stephan Rosenkranz (Cologne, GER)

Stephan Rosenkranz is a professor of medicine at the Heart Center of the University of Cologne, Germany. Dr Rosenkranz obtained his MD degree from the Justus Liebig University of Giessen, Germany, in 1994. He subsequently did a fellowship in cardiology at the University of Cologne. Following his doctoral thesis, he undertook a post-doctoral fellowship at Harvard Medical School, USA, before returning to Cologne. He is currently head of the Center for Pulmonary Hypertension at the University of Cologne, and also serves as chairman of the Cologne Cardiovascular Research Center (CCRC). Furthermore, he is the head of a basic research group focussing on signal transduction and the biological importance of tyrosine kinases in cardiovascular disease. Dr Rosenkranz has published over 200 articles in peer reviewed journals. He is also a member of a number of medical organizations and has served as the chair of the working group on Pulmonary Hypertension of the German Cardiac Society (DGK), and is an elected Nucleus Member of the Working Group on the Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology (ESC). In addition, he is on the reviewing board of several research organizations including the Deutsche Forschungsgemeinschaft (DFG). Dr Rosenkranz has been involved in numerous clinical trials in cardiology, which – in the field of pulmonary hypertension – include: AMBITION; SERAPHIN; GRIPHON; PATENT; CHEST; LEPHT; DILATE; MELODY and SUPER. He is a Steering Committee member of current pulmonary hypertension trials, and also served as a member of several DSMBs. Dr Rosenkranz has received several scientific awards, including the Faculty Award of the University of Cologne, the Research Award „Prevention in Internal Medicine“, German Society of Internal Medicine (DGIM), and the Andreas-Grüntzig-Award (interventional Cardiology), German Cardiac Society (DGK).

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Robert Rosenson (New York, USA)

Robert S. Rosenson, MD, FACC, FACP, FAHA, FNLA, FACCP (inactive), is Professor of Medicine at the Icahn School of Medicine at Mount where he serves as Director of Cardiometabolic Disorders. He is a Fellow of the American Heart Association Council on Epidemiology and Prevention, Fellow of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology, Fellow of the National Lipid Association

and a past Fellow of the American College of Chest Physicians (inactive). He has been the recipient of a number of awards and honors, including the Ground-Breaking Doctors Award from Chicago magazine. In 2015, he received the Simon Dack award for his contributions to the Journal of the American College of Cardiology.

Dr Rosenson earned his medical degree from Tulane University in New Orleans, Louisiana where he conducted research on prostaglandin metabolism in coronary arteries. This work was recognized when he was awarded the Querens-Rives-Shore Award for best thesis in Cardiology. He then served his residency in medicine at Brigham and Women's Hospital in Boston, Massachusetts. He later completed a fellowship in cardiovascular medicine at the University of Chicago that was followed by an additional year of training as a Research Associate in lipoprotein metabolism.

Dr Rosenson is a Diplomate of the American Board of Internal Medicine, with a subspecialty in cardiovascular disease, the National Board of Medical Examiners, and National Lipid Association. He currently serves on a number of committees for professional societies.

He has served on nine committees for the American College of Cardiology, and he served as a member of the Expert Document Committee for the American College of Cardiology and ACCF Representative to the ADA Aspirin Therapy in Diabetes Position Statement. He has been extensively involved with the National Lipid Association where he serves a National Board Member and Northeast Lipid Association Board Member. Dr Rosenson served as Co-Chair for the task force on HDL biology, and he is the current Chair of the Statin Safety Expert Muscle Document Committee. Dr Rosenson led three international working groups on HDL that resulted in seminal articles on HDL nomenclature, HDL and macrophage cholesterol, and HDL functionality.

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. His laboratory was the first to demonstrate that statins reduce pro-inflammatory cytokine production. He has continued this work through mechanistic studies on inflammatory markers with studies on fenofibrate. Most recently, he has conducted research with selective inhibitors of inflammatory pathways such as lipoprotein-associated phospholipase A2, and secretory phospholipase A2.

He has made important contributions concerning the prognostic significance of lipoprotein subclasses in coronary atherosclerosis, cardiovascular events and prediction of type 2 diabetes. He has served as Principal Investigator on a number of NIH-funded research studies, pharmaceutical-sponsored drug trials, and multicenter studies. He served as Global Principal Investigator of the PLASMA I, PLASMA II and FRANCIS trials. He has authored 250 peer-review journal articles, and 800 book chapters, abstracts, and electronic publications for Up To Date Medicine.

ABSTRACT

Causes and consequences of the underutilization of high intensity statins in ACS patients

Among patients hospitalized for an acute coronary syndrome (ACS) and stable coronary heart disease (CHD), randomized controlled trials have demonstrated that high-dose/high-intensity atorvastatin therapy is more effective than either placebo, low-intensity therapy with pravastatin, moderate-intensity therapy with simvastatin or low-dose atorvastatin therapy in the reduction of recurrent cardiovascular disease (CVD) events (1). Thus, the recent American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Events in Adults recommends initiation of high-intensity statin therapy in CHD patients (2). This mandate for statin initiation is particularly relevant for ACS patients in whom initiation of this therapy is recommended before hospital discharge.

Data from registries suggest that over 80% of patients are prescribed statins following a myocardial infarction (MI) or coronary revascularization. However, few prior studies have reported the percentage of patients who filled high intensity statins following CHD events. In an analysis of Medicare beneficiaries, only 27% were prescribed high intensity statins after hospitalization for a coronary event (3). The principal factor associated with being filling high-intensity statin therapy following discharge was use of a high-intensity statin prior to hospitalization. Filling high-intensity statins following hospitalization was lower among patients who were not initially hospitalized for acute myocardial infarction. Underutilization of high-intensity statins post hospital discharge increases progressively during the ensuing years, such that another 24% of participants reduced their statin dosage or discontinued high-intensity statins.

The clinical implications of non-adherence to either high-intensity or low-intensity statin therapy were examined in the full Medicare population. Non-adherence to either high-intensity or low-intensity statin therapy was associated with higher rates of hospitalization for cardiovascular events, non-cardiovascular events and all-cause mortality. Lesser differences in adverse clinical outcomes were observed in CHD patients who had high adherence to either high-intensity or low-intensity statins.

Poor adherence to high intensity statin therapy is multifactorial and includes health system factors, provider behavior and patient behavior (6). Strategies to improve utilization of evidence-based therapy are the most important strategy to reduce the burden of cardiovascular disease.

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Heather Ross (Phoenix, USA)

Heather M. Ross, DNP, is an Instructor in the Doctor of Nursing Practice program at the College of Nursing and Health Innovation at Arizona State University. She is also a PhD Candidate in the Human and Social Dimensions of Science and Technology in the School for the Future of Innovation at Arizona State University, where she studies communication and complex sociotechnical knowledge systems related to biomedical technology innovation.

Dr Ross administers the graduate education component of Project HoneyBee in the Center for Sustainable Health at ASU's Biodesign Institute, focusing on the future of wearable technologies in healthcare. She is the principle investigator of two small multicenter clinical trials associated with Project HoneyBee, involving the use of patient-facing wearable devices in the chronic management of atrial fibrillation and heart failure, as well as a qualitative study examining the lived experience of conducting clinical and pre-clinical research involving wearable devices.

Dr Ross maintains an active clinical practice as a nurse practitioner in cardiac electrophysiology with Arizona Arrhythmia Consultants in Scottsdale, Arizona, USA.

ABSTRACT

AF prevention and treatment trials: patient-reported outcomes, symptoms, quality of life

Atrial fibrillation is increasingly understood to be a common manifestation of many independent and modifiable conditions that are dependent on individual behaviors, including obesity, hypertension, sleep disordered breathing, and vigorous exercise. In this light, it is critically important to understand patients' perceptions, perspectives, and engagement with any prescribed or recommended therapies. Atrial fibrillation therapies, whether catheter ablations, surgical interventions, or pharmacological therapies, will only be as effective as an individual's adherence to the protocol and maintenance of their anatomical and physiological substrate. In the case of atrial fibrillation, this substrate is in a constant state of flux and significantly impacted by patients' daily activities, behaviors, and choices. Therefore, clinical trials examining prevention or treatment of atrial fibrillation must incorporate patient-reported and patient-generated data in order to accurately assess the impact of the intervention being investigated.

Some of the tools that are commonly used to measure patients' outcomes and preferences include validated instruments for quality of life like the SF-36 and the AFEQT and the newer AFSymp tool. These instruments are certainly helpful in an effort to quantify the elusive construct of quality of life. However, it is well established that individuals' recall about quality of life is highly unreliable over time, limiting the usefulness of recall-based quantitative instruments. Moreover, quantified quality of life measurement instruments do not account for the daily lived experience that critically impacts the success or failure of a given therapy, including adherence to prescribed therapeutic regimens. Nor do intermittent recall-based or ambulatory monitoring measures accurately assess the burden of atrial fibrillation in terms of physiological recurrence. We do know that patients tend to underreport atrial fibrillation recurrences, with most patients actually experiencing significantly more atrial fibrillation than is acutely symptomatic or recorded with occasional monitoring approaches.

With the emergence of internet-based connectivity and patient-facing technologies, people are engaging in new types of monitoring and some patient populations are amending their daily behaviors because of these monitoring experiences. It is important to consider the differences between provider-facing monitoring such as with an implanted loop recorder, and patient-facing monitoring such as with a handheld device or smartphone app. For example, patient-facing devices allow for individual modulation of daily therapies and activities that directly impact atrial fibrillation compared to intermittent communication of provider-facing data. In addition, patient-facing data critically do not exert an additional tax on our already strained professional

workforce in cardiology to provide ubiquitous monitoring of ubiquitous data – whether for particular research endeavors or for usual care practices.

It is worth noting that few contemporary clinical trials in atrial fibrillation account for the patient's lived experience and behaviors that critically impact clinical outcomes for clinical trials and real-world therapies. We will discuss the range of existing tools for patient-reported data and recommendations for incorporating qualitative approaches, along with emerging opportunities to leverage connected health technologies in order for clinical research trials to represent and understand the relevant ecosystem for atrial fibrillation treatment and prevention.

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Patrick Rossignol (Nancy, FRA)

Patrick Rossignol, MD, PhD, is professor of Therapeutics, Nephrologist and Vascular medicine specialist, Deputy Director of Nancy Plurithematic Clinical Investigation center (CIC)-Inserm. He has participated/is participating in several EU FP6-7 programs (Ingenious Hypercare: Coord A; Zanchetti; MEDIA: Coord: W. Paulus; HOMAGE & FIBROTARGETS : Coord F. Zannad , Nancy CIC). He is coordinating a French network of excellence endorsed by F-CRIN (French Clinical research Infrastructure Network, the French affiliate of ECRIN/ERIC: Cardiovascular and Renal Clinical Trialists (INI-CRCT www.inicrct.org) since 2014. He is coordinating the University Hospital "French Government Investment for the Future" Fighting Heart Failure program (2016-2020). He is the PI of the ongoing largest double blind (spironolactone vs. placebo) academic cardiovascular outcome randomized controlled trial in hemodialysis (ALCHEMIST: ClinicalTrials.gov Identifier: NCT01848639) and steering committee member of several international randomized clinical trials. He is a EURECA-m (cardiorenal working group of ERA-EDTA: The European Nephrology Dialysis Transplantation Association) member since its creation in 2009 and got elected as board member for 6 years in 2013.

ABSTRACT

Cardiovascular endpoints in CKD and hemodialysis trials: are specific event definitions and adjudication needed?

Cardiovascular (CV) death is either the leading or one of the main causes of death in patients with chronic kidney disease (CKD).

A major methodological limitation of CKD trials is the difficulty of clearly defining clinical events such as acute coronary syndrome or heart failure within this specific population. An optimal and standardized definition of CV events as inclusion criteria and outcomes in patients with CKD would improve treatment effect measurement.

Moreover, subsets of patients with CKD have very different CV risk according to their characteristics and treatment modalities. Targeting the portion of the population at higher risk for CV events is likely to increase the impact of the tested cardiovascular therapeutic strategies. This better patient's selection process would both increase the probability of observing a meaningful beneficiary treatment effect in CKD randomized clinical trials and increase the statistical power of randomized clinical trials for a given number of patients.

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Prabir Roy-Chaudhury (Tuscon, USA)

Prabir Roy-Chaudhury MD, PhD, FRCP (Edin) is a Professor of Medicine and the Division Director for Nephrology at the University of Arizona. He is also the Director of the Arizona Kidney and Vascular Center. After graduating from the Armed Forces Medical College, Pune, India, he trained in Internal Medicine and Nephrology at the University of Aberdeen, Scotland and at the Beth Israel Hospital, Harvard Medical School, Boston, USA. In addition to being an active transplant nephrologist, DrRoy-Chaudhury's main research interest is in dialysis vascular access and uremic vascular disease and while at the University of Cincinnati (for over 15 years), he directed the Dialysis Vascular Access Research Program which was a comprehensive, integrated, multidisciplinary translational research program, which included basic science, clinical science and patient care components. This translational research program was funded through the National Institutes of Health, the Veterans Administration research program and through industry grants. DrRoy-Chaudhury has received national and international awards, has published over 150 peer reviewed manuscripts and is a sought after invited speaker, both nationally and internationally.

DrRoy-Chaudhury has also been actively involved in the public policy and administrative aspects of dialysis vascular access care and hemodialysis as a board member/councilor/committee chair for the American Society of Diagnostic and Interventional Nephrology, the Renal Network, the Interventional Nephrology Advisory Group of the American Society of Nephrology (ASN), the Cincinnati chapter of the National Kidney Foundation and the Medical Advisory Board of the Life Center (Ohio). He is a member of the ASN Board of Advisors and Capitol Hill advocacy team and a member of the ASN Postgraduation Education Committee. DrRoy-Chaudhury is also the American Society of Nephrology co-chair of the Kidney Health Initiative which is a public-private partnership between the ASN and the FDA which aims to bring together nephrologists, industry partners, patient advocacy groups and regulatory agencies; in an attempt to facilitate the passage of drugs, devices and biologics into the kidney disease space.

Stephen Ruble (Boston Scientific, USA)

Stephen Ruble is a fellow at Boston Scientific Corporation. He obtained his PhD from the University of Arkansas, and completed a post-doctor fellowship at the Medical College of Wisconsin and the VA Medical Center in the departments of anaesthesiology and physiology. His research focus has been on autonomic control and disease. Stephen spent 9 years on the faculty as a tenured professor at Samford University (Birmingham, AL) where he received the award for outstanding professor of the year. Since joining Boston Scientific in 2004, he has published more than 40 patents, and has received numerous awards for his innovative research efforts. Most recently, he served as the Chief Scientist for the NECTAR-HF trial. In his spare time, Stephen enjoys running, cross country skiing, music, and spending time with his family.

ABSTRACT

Autonomic modulation device therapy: should we rethink the clinical trial strategy?

In the past 18 months, there have been numerous failed trials exploring modulation of the autonomic nervous system as a therapeutic modality for treating cardiovascular disease. The reaction from industry can be swift and brutal, shutting down entire research programs in a matter of weeks. The ripple effect can be felt across numerous companies. The end result means less money being spent on important research and development efforts that could enable new therapies. This session will explore how these failed trials can inform future work, and how industry needs to adopt a new strategy to ensure the success of autonomic modulation device therapy.

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James Rusnak (Pfizer, USA)

James Rusnak, MD, PhD is the Therapeutic Area Clinical Head for Cardiovascular and Metabolics, Clinical Sciences in the Pfizer Global Innovative Pharmaceuticals Business Medicines Development Group. Previously, he was the Vice President, Clinical Research Head in the Cardiovascular and Metabolics Research Unit at Pfizer in Cambridge, MA. He received his B.Phil. in Chemistry and Neuroscience from the University of Pittsburgh.

He also received his MD and PhD in Pharmacology with dissertation in signal transduction pathways in oncology from the same institution. Following this training, he completed his Internship and Residency in Internal Medicine at Mayo Clinic, Rochester, MN. Jim first joined the pharmaceutical industry in 2000 at Bristol-Myers Squibb, Global Clinical Research, Cardiovascular and Metabolics. During his tenure in industry, he has led the development of multiple drugs at various stages in the development for cardiovascular, metabolic, renal, and immunology indications. Finally, he is the sole or co-inventor of a several patents in immunology and cardiovascular disease.

Joe Selby (PCORI, USA)

After obtaining his MD Degree from Northwestern, Dr Selby moved to Northern California for internship and a family medicine residency and eventually an MPH at UC Berkeley. His fellowship project concerned Behavioral Factors in Cardiovascular Disease.

He stayed in the bay area at Kaiser Permanente for 27 years, including 13 as Director of Research supervising up to 50 investigators and 500 staff members. He has had academic appointments at UC Berkeley, UCSF and Stanford. He has authored more than 200 peer reviewed articles on far ranging topics such as quality measurement and improvement, primary care delivery, colorectal cancer screening and many studies that could be classified under the heading of "comparative effectiveness" – largely in the areas of diabetes, HTN and cardiovascular disease. He has received honors from the Public Health Service, the American Epidemiological Society, Kaiser Permanente and in 2009 he was elected into the Institute of Medicine.

In July 2011 Dr Selby became the first Executive Director of the Patient-Centered Outcome Research Institute (PCORI). PCORI's mandate is to improve the quality and relevance of the evidence available in order to help patients, caregivers, employers, insurers and policy makers make informed healthcare decisions.

Patrick Serruys (Rotterdam, NED)

Pr W. Serruys with respected h-index – 118 is a professor of Interventional Cardiology at the Interuniversity Cardiological Institute of the Netherlands (1988-1998), and Erasmus MC. Since 1980 he was a Director of the Clinical Research Program of the Catheterization Laboratory, Thorax Center at Erasmus University, and till April 1st 2014 (retirement date) the Head of the Interventional Department, Thorax Center, Erasmus MC (University Medical Center Rotterdam), Rotterdam, The Netherlands.

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

In 1996 he received the TCT Career Achievement Award and in 1997 he was awarded the Wenkebach Prize of the Dutch Heart Foundation. In 2000 he was awarded the Gruentzig Award of the European Society of Cardiology. In 2001 he held the Paul Dudley White Lecture at the American Heart Association in the USA. In 2004 he received the Andreas Gruentzig Award of the Swiss Society of Cardiology.

In 2005 he held the 4th International Lecture at the AHA and Mikamo Lecture at the Japanese heart Association. In 2006 he received the highest award of the Clinical Council of the American Heart Association: the James Herrick Award. In 2007 he received the Arrigo Recordati International Prize (Italy) and the ICI Achievement Award (bestowed by the President of Israel – Shimon Perez). In 2008 he received the Einthoven Penning (Leiden). In 2009 he became Doctor Honoris Causa from the University of Athens.

In 2011 he received the Lifetime Achievement Award, bestowed by the American College of Cardiology, in recognition of many years of service and invaluable contributions to the ACC.

At the end of 2011 Prof. Serruys received the Ray C. Fish Award, bestowed by the Texas Heart Institute, for outstanding achievement and contribution to cardiovascular medicine. In 2012 he received a Golden Medal of the European Society of Cardiology. In 2013 he became Doctor Honoris Causa from the Complutense University of Madrid.

Monica Shah (NHLBI, USA)

Monica Shah, MD, MHS, MSJ, is the Deputy Chief of the Heart Failure and Arrhythmias Branch in the Division of Cardiovascular Sciences at NHLBI. She is also the NHLBI AIDS Coordinator and leads the NHLBI AIDS program team. Dr Shah is a board-certified heart failure and transplant cardiologist. She oversees a research portfolio that includes a number of large clinical trials and clinical trial networks, and has been extensively involved in all aspects of clinical research, with special focus on heart failure, mechanical circulatory support, cardiac transplantation, resuscitation, and HIV-related cardiovascular disease. Dr Shah has a special interest in the science of operationalizing clinical trials, strategies to streamline studies, and approaches to optimize enrollment, teamwork, and collaboration in clinical studies. Dr Shah is also clinically active and attends on the Advanced Heart Failure Service at the University of Maryland, where she is an Associate Clinical Professor of Medicine.

Dr Shah completed her undergraduate and medical education at Brown University. She then completed a residency in internal medicine at the Johns Hopkins Hospital, and a fellowship in cardiology at Duke University Medical Center, where she received specialized training in clinical research at the Duke Clinical Research Institute. Dr Shah also completed a fellowship in Heart Failure and Transplantation at the Brigham and Women's Hospital. Prior to joining the NHLBI, Dr Shah was an attending cardiologist and the Director of Heart Failure Research at the Washington Hospital Center. She was also an attending cardiologist at Columbia University Medical Center and Duke University Medical Center. In addition to her medical training, Dr Shah has a Masters in Health Sciences from Duke University and a Masters in Journalism from the Columbia School of Journalism.

Mitchell Shein (FDA/CDRH, USA)

Mitchell Shein MS, FHRS joined FDA's Center for Devices and Radiological Health in August, 1986, as a reviewer in the Division of Cardiovascular Devices. He is currently serving as an acting Deputy Director in that division and is responsible for all cardiac electrophysiological devices and patient monitoring equipment. His permanent position is Branch Chief for DCD's Implantable Electrophysiological Devices Branch. In addition to his FDA responsibilities, Mr Shein is active in the development of standards for cardiac pacemakers and defibrillators and chairs the ISO Joint Working Group for Active Implantable Devices – Cardiac Pacemakers and Defibrillators. His educational background includes a BS in Biomedical Engineering from Duke University and a MS in Physiology from Georgetown University.

Richard Simon (NCI, NIH, USA)

Dr Richard Simon is Associate Director of the Division of Cancer Treatment & Diagnosis and Chief of the Computational and Systems Biology Branch. He holds a doctoral degree in applied mathematics and computer science from Washington University in St Louis, Mo. He has published extensively on the methodology of clinical trials and author of Using Genomics in Clinical Trials and Predictive Medicine, published by Cambridge U. Press 2013. He is the recipient of the 2013 Karl Peace award of the American Statistical Association "for contributions that have played a pivotal role in bridging the gap among statistics, clinical research, and translational medicine to improve human health".

ABSTRACT

How best to design a personalized medicine trial? What can be learnt from oncology trialists?

Developments in biotechnology and tumor biology have established that cancers of many primary sites represent distinct sub-diseases which differ with regard to the DNA mutations which drive tumor invasion, their natural history and responsiveness to therapy. These findings have had a major impact on oncology drug development and clinical trial design which has resulted in improved treatments. Previously, phase III oncology clinical trials used broad eligibility based on the assumption that treatment effects might vary only quantitatively for subsets of patients. This assumption has been shown to be false for most traditional cancer diagnostic categories and treatments and the broad eligibility trials can lead to small average treatment effects, false negative results and approving drugs that require treating many patients for the few who benefit.

Most oncology drugs developed today are targeted to inhibit an oncogene constitutively activated by a genomic alteration. Phase III trials for such drugs are designed as targeted "enrichment" designs in which only patients whose tumors bear the relevant genomic alteration are eligible for randomization. Drugs have been generally approved with companion diagnostics for

measuring the alteration. Phase II studies are used to refine and analytically validate the test that will be used to screen patients in phase III trials. Prognostic gene expression signatures have less frequently served for guiding treatment except for identifying patients who have such good prognosis after standard therapy that they do not need additional treatment.
In some cases it is difficult to identify a predictive biomarker that identifies the patients most likely to benefit from a test treatment, for example with a drug whose mechanism of action is not well understood, an immunotherapy or an anti-angiogenic drug. Three strategies can be used in such cases. The most obvious is to conduct large phase II biomarker finding studies with patients' whose disease is extensively characterized prior to treatment. Secondly, to utilize a "run-in" or "randomized discontinuation" design in which randomization is delayed until one can assess which patients have a desirable pharmacodynamic or intermediate endpoint response to a short exposure on the test treatment. Finally, one can conduct an adaptive phase III design with broad eligibility of extensively characterized patients which evaluates both the overall treatment effect and identifies in a statistically valid way a subset of patients who have substantial benefit from the test treatment. All of these approaches will be discussed.

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Tabassome Simon (Paris, FRA)

Tabassome Simon, MD, PhD is Professor of Medecine and Clinical Pharmacology in the Department of Pharmacology, AP-HP, Saint-Antoine Hospital, Pierre and Marie Curie University (UPMC-Paris 06) in Paris, France. T. Simon is currently elected Chair of the European Association for Clinical Pharmacology and Therapeutics (EACPT).
Dr Simon is the Director of the Clinical Research platform of the East of Paris, including the Clinical Research Unit (URC-EST: http://www.urcest.chusa.upmc.fr/), the clinical Research Center, and the BioBank Research Center of UPMC-Paris 06 University. Currently, the clinical research platform coordinates several multicenter national and international studies throughout centers in France. In addition to teaching pharmacology for medical students, T. Simon is the Coordinator of Master Diploma of clinical research for physicians, the national coordinator of the university diploma for pharmacogenetics and personalized medicine, the university diploma for the formation of research nurses for clinical research and vigilance in France.

Dr Simon was the recipient of the Medal of Paris Saint Antoine University Hospital in 1992 and has received awards from the French Society of Cardiology, the French Society of Pharmacology, the French Society of Angiology, and the EACPT Scientific Award in 2011. One of her publications has been chosen by the editors of Circulation as Groundbreaking Studies in the Practice of Cardiovascular Medicine in 2009.

Her primary research interests are pharmacological cardiovascular prevention, pharmacogenetics, drug interactions and sex hormones. She has published more than 130 original articles in international peer-reviewed journals, including The New England Journal of Medecine, The Lancet, JAMA, Nature Med, Circulation, JACC, European Heart Journal, Hypertension, Atherosclerosis, Arterioscler Thromb Vasc Biol, Clinical Pharmacology and Therapeutics, Heart, J Clin Endocrinol Metab, etc.

Stuart Spencer (London, GBR)

Stuart joined The Lancet in 1999 and throughout his time there has led the Fast Track team that aims to select, review and publish prestigious manuscripts within 4 weeks of receipt. Although dealing with all areas of research, he deals with most of the cardiology submissions.

After graduating Stuart moved into research which started at the Brompton Hospital, London, looking at scoliosis in children before moving to the Veterinary School site at Bristol University. During this period he was invited to establish a research unit in The Netherlands. Later he set up a research team for a major pharmaceutical company in Switzerland for a year, and then spent 9 years as a senior researcher in New Zealand. He has also had two senior research fellowships at Leuven University, Belgium, and visiting professorships at King's College, London and Hong Kong University, and a doctorate of medicine from Umea University, Sweden. Stuart's research expertise includes such diverse topics as, growth, neuroendocrinology, immunology and fetal development. He also had a Senior Fellowship in bioethics for 5 years. This broad research base in front-line research has given a clear understanding of principles in research and publications applicable across disciplines.
Stuart is also a Trustee of the Scoliosis Association (GBR), is on the British Scoliosis Research Fund grants commit-

tee and the steering Committee of the Swedish National GP Research School.

ABSTRACT

Why bother with peer review?

The views expressed below are not necessarily the views of The Lancet or of the author.

Peer review is seen to have a long pedigree and to be the guardian of good science. There is a largely unquestioned acceptance that pre-publication peer review is scientifically sound, useful and essential. Unfortunately, there is very little evidence to support this belief. Indeed, peer review does not have a long tradition, is riddled with biases and errors, and is costly and inefficient. The problems with peer review begin with the fact that very few scientists are taught how to be effective at reviewing papers. While good peer review can improve the presentation of papers, it is less often able to remedy poor research design and represents a triumph of gloss over substance. If pre-publication peer review were really effective it would be much better at detecting fraud. Most cases of fraud are detected after publication. More thoughtful peer review might reduce the need for retractions. Although reviewers are expected to declare financial conflicts of interest (and some do), most do not declare personal, professional or philosophical conflicts. The weaknesses of pre-publication peer review are exemplified by the diametrically opposed recommendations often received by editors. Inevitably only a few views can be commissioned if publication is to move ahead at a reasonable pace; editors hope these are representative of the views of the wider readership of their journal. The number of letters criticising published papers that journals receive demonstrates that satisfying all the community is unlikely. Finally, the hidden cost of peer review is not insubstantial. At the very least, pre-publication peer review is inefficient, biased and in need of serious revision if it is to remain a bastion of scientific publishing in the digital age.

Christina Stahre (AstraZeneca, SWE)

Christina Stahre is an executive clinical director at AstraZeneca Cardiovascular & Metabolic Disease, Global Medicines Development. Dr Stahre obtained her MD degree from University of Linkoping, Sweden in 1987 and she did a fellowship in Anesthesia and Intensive Care at Sahlgrenska University Hospital and remained in Anesthesia positions until 2004. Main responsibilities were pre-hospital medicine, obstetric anesthesia, hyperbaric medicine and full scale anesthesia simulation. In 2004 she left the position as Head of Gynecology and Obstetric Anesthesia to join Patient Safety AstraZeneca R&D in Gothenburg. She has been involved in the development of new cardiovascular medicines from discovery to phase III - thrombin inhibitors, anti-platelets, antiarrhythmics, reflux inhibitors and for the last four years diabetes treatments. She was the AstraZeneca study physician for the SAVOR outcome trial from 2010 until 2014 and also an AZ responder at the FDA advisory committee meeting in April 2015.

Evan Stein (Cincinnati, USA)

Evan A Stein MD PhD FRCP(C) FCAP, is Director Emeritus, Metabolic & Atherosclerosis Research Center, Cincinnati, Ohio.

Dr Stein received his medical degree and PhD, from Witwatersrand University in Johannesburg, South Africa. He started the first lipid clinic in South Africa in 1972 and described the high gene frequency of Familial Hypercholesterolemia, especially in Afrikaners. He completed specialty training in Medical Biochemistry at McMaster University Medical Center, Canada and was on the full-time faculty at the University of Cincinnati, Ohio, for 11 years as tenured Professor of Pathology and Laboratory Medicine and Associate Professor of Internal Medicine and remained on faculty as Voluntary Professor until August of 2015.

During this time he was also the local trial director for the NIH Coronary Primary Prevention Trial (LRC-CPPT). In 1988 he relocated his clinical and laboratory groups and founded Medical Research Laboratories and the Metabolic and Atherosclerosis Research Center, where he still remains as Director Emeritus. Dr Stein has served appointments to the National Institutes of Health, including the General Clinical Research Centers Advisory Committee, NCEP Lipid Standardization Committee, Data and Safety Advisory Board of the NHLBI Program on Genetics in Hypertension from 1999-2003.

From 1993-2006 he was the PI of the central laboratory for the Women's Health Initiative (WHI) trial. He was appointed to the FDA Clinical Chemistry and Clinical Toxicology Advisory Panel from 2006-2010. His research focuses on diagnosis and treatment Familial Hypercholesterolemia, and he was one of the earliest investigators with statins, apheresis, ezetimibe, MTP inhibitors, squalene synthase inhibitors and most recently PCSK9 inhibitors. Dr Stein has authored or co-authored more than 280 publications in the area of lipid metabolism and laboratory medicine.

ABSTRACT

PCSK9 inhibitors: almost all said already? Just waiting for results of outcomes trials?

Since PCSK9 was identified in 2003, our understanding of its role in LDL metabolism has advanced rapidly. Studies in mice increasing and decreasing PCSK9 production demonstrated hepatic LDL receptor (LDLR) activity was concomitantly decreased or increased respectively.
Subsequent studies confirmed that people with low LDL-C levels had PCSK9 'loss-of-function' (LOF) mutations with significant reduction in lifetime risk of CVD, and no apparent adverse health effects. A key discovery in 2006 was that circulating PCSK9 bound to the LDLR, was internalized along with the receptor and LDL, resulting in LDLR degradation preventing its recycling. This was critical leading to the development of monoclonal antibodies (mAb) which bind to, and inhibit, PCSK9, increasing LDLR activity. Two fully human PCSK9 mAbs, alirocumab and evolocumab, entered human trials in 2010 and showed dramatic reductions in free PCSK9 and LDL-C.
Over the last 3 years clinical development has progressed very rapidly and these two agents have completed phase 3 studies, and received marketing approval by regulatory agencies in the USA and Europe. The trials have demonstrated dramatic reduction in LDL-C to a maximum of approximately 60% in HeFH and nonFH irrespective of background lipid lowering therapy. In HoFH the reduction with evolocumab is ~30% and is related to underlying genetic defect and residual LDLR activity. Increasing doses even 3 or 4 fold does not result in additional LDL-C reduction but does increase the duration of PCSK9 suppression and LDL-C lowering, thus reducing the frequency required for SC injections.
Concern that injections may lead to discontinuation and poor adherence to the therapy has not been substantiated. Serious and treatment adverse events have also been no different from those reported in placebo, comparator or control groups. No significant or sustained elevations of either liver function, muscle enzymes or other laboratory findings have been reported.

Two recent trials assessed CVD endpoints as exploratory or post hoc analysis as part of longer term safety trials and showed a significant reduction in major adverse CVD compared with either standard of care alone or placebo. While the total number of patients experiencing CVD events in both trials were relatively small the uniformity of results from the two studies bodes well for the outcome of the large longer term trials in progress. The first of a number of very large CVD outcome trials are expected in 2016 and if the reductions in CVD events seen in these early trials are sustained without new or serious side effects PCSK9 inhibitors will rapidly become incorporated into the routine standard of care.

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Ken Stein (Boston Scientific, USA)

Ken Stein, MD, FACC, FHRS, is currently Senior Vice President and Chief Medical Officer for Boston Scientific's Rhythm Management 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 Rhythm Management Group including the Cardiac Rhythm Management, Electrophysiology and Watchman Left Atrial Appendage Closure businesses.
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.

Theodore Steinman (Boston, USA)

Dr Steinman, MD is a Clinical Professor of Medicine, Harvard Medical School and a senior physician at Beth Israel Deaconess Medical Center and Brigham and Woman's Hospital, Boston. In 1971 he founded the Dialysis and Kidney Transplant programs at Beth Israel Hospital and served as the Director for 31 years. Polycystic kidney disease research has been his major focus for the past 25 years. Medical residency at Beth Israel Hospital, Boston and Nephrology Fellowship training was at Tufts New England Medical Center. Dr Steinman is past-president, Renal Physicians Association; past chairman, Scientific Advisory Committee Polycystic Kidney Foundation, past-president National Kidney Foundation Region I; past president and past chairman, National Kidney Foundation of Massachusetts and Rhode Island. He was a member of the Medical Advisory Board, Kidney Disease Outcome Quality Initiative (K/DOQI). Dr Steinman served as a Principal Investigator for both the NIH HALT PKD Study and the Otsuka Tolvaptan Study. Currently he is working on stem cell technology to grow new kidneys in patients with polycystic kidney disease. He is an author on 178 peer-reviewed publications, 32 book chapters 187 Proceedings and 144 abstracts.

Norman Stockbridge (FDA, USA)

Norman Stockbridge received his MD and PhD (Physiology) from Duke University. He did basic science research before joining the Division of Cardiovascular and Renal Products in FDA CDER in 1991. He has served as the Division Director since 2004.

Daniel Swerdlow (London, GBR)

Daniel Swerdlow is a clinician scientist in cardiovascular medicine and clinical pharmacology at Imperial College London, having completed his medical training and PhD in genetic epidemiology on the MDPhD programme at UCL. His research focusses on the use of genetics and other –omic technologies to validate therapeutic targets in cardiometabolic disease. He has published high impact papers using genetic methods to investigate drug targets related to inflammation and lipids, including demonstrating the likely utility of the interleukin-6 receptor as a therapeutic target in coronary heart disease, and confirming statin-induced diabetes as an on-target drug effect. He has won a number of international and UK prizes for his research and is regularly invited to speak on these and related topics, and to teach on undergraduate and postgraduate programmes in London and abroad.

ABSTRACT

Mendelian randomization studies

The development of new drug treatments for cardiovascular disease is a time-consuming, expensive and risky process, largely as a consequence of the propensity for new drugs to fail late in development. Failure often occurs at the phase III randomised trial stage either because of safety concerns or poor efficacy, by which time substantial human, time and financial costs have been incurred. Recent high-profile examples of late-stage failure include the CETP inhibitors torcetrapib and evacetrapib, and sPLA2 inhibitor, varespladib. Genetic studies using the Mendelian randomisation principle offer a source of 'randomised' data that can be used to validate the efficacy and safety of novel drug targets in advance of phase III intervention studies.

Such Mendelian randomisation studies use common variants in the gene encoding a protein drug target as unconfounded, unbiased proxies for pharmacological modulation of that target. In this way, observed associations of the genetic variants with biomarkers or disease risk can indicate the likely consequences of targeting the protein pharmacologically. Studies of this type have been used to investigate the off-target effects of the CETP inhibitor, torcetrapib, on blood pressure, to validate the interleukin-6 receptor as a promising target for coronary heart disease prevention, and to demonstrate that the increase in type 2 diabetes risk caused by statin treatment is an on-target effect of the drugs related to their effects on body weight. As the scope and availability of emerging –omics technologies increase and analytical techniques for Mendelian randomization are refined, the utility of this methodology continues to grow. Indeed, the approach is seeing widespread popularity in the industrial sector following its early development in academia. The technique certainly has limitations, but shows considerable promise as a robust, informative and efficient addition to the traditional drug development pipeline.

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Jean-Claude Tardif (Montreal, CAN)

Jean-Claude Tardif, CM, MD, FRCPC, FACC, FAHA, FCAHS, 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 Canada Research Chair (tier 1) in translational and personalized medicine and the University of Montreal endowed research chair in atherosclerosis. He founded the Montreal Health Innovations Coordinating Centre (MHICC) and is the 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 800 articles and abstracts in peer-reviewed publications including The New England Journal of Medicine, The Journal of the American Medical Association, The Lancet, Circulation, Circulation Cardiovascular Genetics, 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 and has edited several books. He has given 500 invited lectures around the world and trained 60 graduate students. His citation index (more than 12,450 citations) shows an h value of 52.

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.

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.

Dr Tardif has won multiple awards during his career, including the Research Achievement Award of the Canadian Cardiovascular Society, the Distinguished Lecturer Award of the Canadian Institutes for Health Research, 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) and recently inducted into the Order of Canada, the country's highest honor.

John Teerlink (San Francisco, USA)

Dr John R. Teerlink, FACC, FAHA, FESC, FRCP (GBR) is Director of Heart Failure and of the Echocardiography Laboratory at the San Francisco Veterans Affairs Medical Center and Professor of Medicine at the University of California San Francisco (UCSF, USA). He received a BA with Highest Honors from Swarthmore College (Comparative Religious Studies; Cellular Biology) and an MD from Harvard Medical School, completing Internal Medicine residency and Cardiology fellowship at UCSF, as well as post-doctoral research fellowships at Hoffman-La Roche (Basel, Switzerland) and UCSF (Howard Hughes), subsequently joining the faculty. Dr Teerlink is actively involved in the design and execution of many acute and chronic heart failure clinical trials, serving on endpoint, data safety monitoring, and steering committees. He was a permanent member of the FDA Cardiovascular and Renal Drugs Advisory Committee, and frequently serves as an ad hoc member of multiple other FDA advisory committees and panels for medical devices, diagnostics, biologics and drugs. Dr Teerlink is a clinical scholar presenting many lectures and publications, including a chapter on Acute Heart Failure in Braunwald's Heart Disease textbook, and was profiled in The Lancet as an internationally recognized leader in heart failure. He serves as a consultant on clinical development programs in all areas of cardiology, as well as in cardiovascular safety for multiple non-cardiovascular indications.

ABSTRACT

Cardiac myosin activation: phenotyping heart failure – is precision medicine the way forward?

Since the extraction of adrenaline in 1897, dozens of cardiotonic agents have been developed with the hope

of safely improving cardiac performance. Most currently available agents have a common mechanism of action whereby myocardial contractility is enhanced through cAMP-mediated increases in intracellular calcium. While these agents (e.g. dobutamine, milrinone) increase inotropy, serious adverse effects such as myocardial ischemia, arrhythmias and death are inherent to their mechanism of action, limiting their clinical utility to a narrow range of high risk patients for short-term or end-stage therapy.

Omecamtiv mecarbil (OM) is a novel small molecule that increases cardiac contractility by directly and very selectively activating the cardiac myosin heavy chain, the force-generating motor protein of the cardiac sarcomere. OM increases the transition rate of myosin into the strongly actin-bound state, increasing force-generation with a longer duration of contraction without associated increases in intracellular calcium transients in isolated cardiomyocytes. OM has no effect on phosphodiesterase III or cardiovascular receptors or channels. In animal studies, OM increased systolic ejection time associated with increased fractional shortening and stroke volume with no increase in LV dP/dt or heart rate, as well as improving left atrial pressure with stable myocardial oxygen consumption and coronary blood flow. These pre-clinical findings provided the basis for advancing into clinical studies.

OM has been investigated in nine Phase 1 and five completed Phase 2 clinical studies to-date in healthy volunteers and patients with chronic heart failure. These studies demonstrated that OM resulted in dose-dependent increases in systolic ejection time, Doppler-derived stroke volume, left ventricular ejection fraction (LVEF), and fractional shortening, with reductions in LV end-diastolic and end-systolic volumes. The dose-limiting toxicity in these studies occurred at excessive pharmacologic concentrations resulting in a syndrome of myocardial ischemia. These studies also demonstrated very predictable pharmacokinetics and pharmacodynamics.

The Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure (ATOMIC-AHF; NCT01300013) study evaluated the safety and tolerability, as well as the efficacy, of OM in 606 patients admitted for acute heart failure. Patients were randomized to either i.v. OM or placebo in an ascending dose, sequential cohort design. OM increased systolic ejection time, as well as decreased LV end-systolic dimensions, and in the high dose group may have improved dyspnea. The adverse event profile and tolerability of OM were similar to placebo without increases in ventricular or supraventricular tachyarrhythmias. Plasma troponin concentrations were slightly higher in OM-treated patients compared to placebo, but with no obvious relationship to OM concentration.

COSMIC-HF (Chronic Oral Study of Myosin activation to Increase Contractility in Heart Failure; NCT 01786512) is a two-part Phase 2 study in patients with chronic heart failure with reduced ejection fraction (HFrEF). In the initial dose escalation phase, 96 patients were enrolled to select one oral modified-release formulation for further evaluation in the expansion phase. The expansion phase evaluated 448 patients with chronic HFrEF who were dosed with the selected oral formulation for 20 weeks and followed for a total of 24 weeks. SEC-mandated reporting of topline results is available online, and as reported, data from the expansion phase showed improvements in several measures of cardiac function at 20 weeks following randomization. Adverse events, including serious adverse events and deaths, in patients on OM appeared comparable to those on placebo. A small increase in troponin was seen among subjects receiving OM. Events of increased troponin were independently adjudicated and none were determined to be myocardial ischemia or infarction.

Thus, results from the development program of the first selective cardiac myosin activator suggest that this targeted therapy may have a potential role in the future treatment of heart failure.

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Robert Temple (FDA, USA)

Dr Robert Temple has been Deputy Center Director for Clinical Science at FDA's Center for Drug Evaluation and Research since 2009, participating in the direction of the Center's operations.

He is also Acting Deputy Director of the Office of Drug

Evaluation I (ODE-I). ODE-I is responsible for the regulation of cardio-renal, neuropharmacologic, and psychopharmacologic drug products.
Dr Temple served as Director, Office of Medical Policy from 1999-2009. The Office of Medical Policy is responsible for regulation of promotion through the Office of Prescription Drug Products (formerly, Division of Drug Marketing, Advertising, and Communication) and for assessing quality of clinical trials.
Dr Temple has a long-standing interest in the design and conduct of clinical trials and has written extensively on this subject, especially on choice of control group in clinical trials, evaluation of active control and non-inferiority trials, trials to evaluate dose-response, and trials using "enrichment" designs.

Aliza Thompson (FDA, USA)

Dr Thompson is a Medical Officer and Clinical Team Leader in the Division of Cardiovascular and Renal Products, Center forh Drug Evaluation and Research (CDER), at the US Food and Drug Administration. She received her medical degree from Johns Hopkins Medical School and completed her Internal Medicine and Nephrology training at Columbia University/New York-Presbyterian Hospital.

She holds a Master of Science in Biostatistics/Patient Oriented Research Track from the Columbia University Mailman School of Public Health. Dr Thompson joined the Division of Cardiovascular and Renal Products in 2007. Her team focuses primarily on products being developed for renal-related indications and certain types of cardiac indications.

Gordon Tomaselli (Baltimore, USA)

Gordon Tomaselli, MD is the Michel Mirowski MD Professor of Cardiology at Johns Hopkins and is the Chief of the Division of Cardiology. He earned his undergraduate degree in biochemistry and chemistry in 1977 from the State University of New York at Buffalo and his medical degree in 1982 from Albert Einstein College of Medicine. He completed his medical training and residency at the University of California at San Francisco (UCSF) in 1985. Dr Tomaselli began his career in the UCSF Cardiovascular Research Institute as a research fellow before moving to the fellowship program at the Johns Hopkins School of Medicine in 1986 and joining the faculty three years later. Dr Tomaselli has been very active in professional organizations in cardiology and served as President of the American Heart Association in 2011-12.

He is a cardiac electrophysiologist and an expert on sudden cardiac death and heart rhythm disturbances. He has focused most of his research efforts on understanding the fundamental mechanisms of cardiac arrhythmias, including new therapies aimed at warding off the potentially fatal heart rhythm disturbances and improvements in the methods used to identify patients at greatest risk for this devastating outcome.

ABSTRACT

The roadmap for risk guided ICD therapy - Risk-guided strategy trials

Omics based risk stratification. PROSE-ICD

Primary prevention implantable cardioverter defibrillators (ICDs) reduce all-cause mortality but the benefits are heterogeneous.

Current risk stratification based on left ventricular ejection fraction has limited discrimination power. We hypothesize that genetic, transcriptomic, proteomic and metabolomic biomarkers in addition to clinical, electrocardiographic and imaging metrics may help to identify patients at risk who are most likely to benefit from ICD placement.
The Prospective Observational Study of Implantable Cardioverter Defibrillators (PROSe-ICD) enrolled 1,189 patients with systolic heart failure who have undergone ICD placement for primary prevention of sudden cardiac death. The primary endpoint is an ICD shock for adjudicated ventricular tachyarrhythmia. The secondary endpoint was all-cause mortality.
Follow up is ongoing, among 1,189 participants, there have been 391 deaths and 261 patients have experienced ICD shock over 6 years of follow up.
An additional 54 patients received heart transplantation or advanced hemodynamic support device implantation.
Of all patients receiving shocks, 155 (60%) had an appropriate ICD shock and 131 (40%) experienced inappropriate shocks, the majority due to rapid AF.
Interestingly, the annual mortality rate of 5.7% exceeds that of first appropriate shocks (3.0%/year).
In a post-hoc analysis of this cohort, we identified significant differences in mortality between African-American (~40% of the cohort) and white patients.
In fact, among 538 patients from PROSe-ICD who had at least 1 repeated EF assessments after ICD implantation, we found that the EF decreased in 13.0%, improved in 40.0%, and was unchanged in 47.0% of the patients over a mean follow-up of 4.9 years.
We have found a number of proteomic and amino acid derivative metabolomics metrics that identify patients at higher mortality risk but not increased risk for appropriate shocks.
Omic markers may be most useful in identifying patients at high competing risk of mortality. This study was registered on clinicaltrials.gov as NCT00733590.

Robert Toto (Dallas, USA)

Dr Robert Toto is Associate Dean for Clinical and Translational Research and Directs the Center for Translational Medicine at UT Southwestern Medical Center. He received his MD degree from the University of Illinois in Chicago in 1977 and did his Internal Medicine training at the University of Michigan in Ann Arbor and Baylor College of Medicine in Houston, Texas. He completed his nephrology training at University of Texas Southwestern Medical Center in Dallas in 1983 and joined the full-time faculty immediately thereafter.

Dr Toto is nationally and internationally known for clinical research and teaching. He has awarded numerous teaching awards from Medical Students and Residents at UT Southwestern Medical Center and is a regular speaker at National and International Nephrology meetings on a variety of topics in renal disease. Dr Toto has a broad background in the pathophysiology, diagnosis, treatment and prevention of chronic kidney disease, including published experience with biomarkers of kidney function, and an established research program focused on diabetic nephropathy. In addition, he has served on the editorial boards of Kidney International, Journal of American Society of Nephrology, the American Journal of Kidney Disease and Nephrology, American Journal of Nephrology, Nephrology Dialysis and Transplantation and Current Opinion in Nephrology and Hypertension.

ABSTRACT

New potassium binding agents: How do these work? Dose-effect relationship, other electrolyte effects: any concern with carry over, overshoot, rebound and other non K effects?

Hyperkalemia is a common electrolyte disorder among patients with chronic heart disease, chronic kidney disease as well as those with diabetes. Drugs that block the renin-angiotensin-aldosterone system (RAAS) are used throughout the world in such patients because they have been shown to improve both cardiac and renal outcomes. However, hyperkalemia can lead to discontinuation of RAAS blockade and prevent initiation of RAAS blockade in people who could otherwise benefit from their life-saving properties. Hyperkalemia can be difficult to treat and for the past 50 years sodium polystyrene sulfonate, an oral potassium binding resin, has been the only FDA approved drug for treatment of hyperkalemia. Recent short-term clinical trials in people with heart disease and kidney disease have demonstrated that oral administration of the potassium binding agents patiromer and zirconium cryosilicate are effective, safe and well tolerated by patients with heart disease, kidney disease and diabetes. This lecture will review these recent clinical trials emphasizing the benefits, risks and limitations of the use of these agents. While long-term efficacy and safety have not been established for these agents, they represent a breakthrough in the management of hyperkalemia. If these agents can be used long-term in conjunction with RAAS blockade more patients with heart disease and kidney disease can enjoy cardiovascular and renal protection afforded by RAAS blockade. Further, these agents may allow the design of new clinical trials combining RAAS blockers to improve outcomes in people with chronic kidney disease.

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Ellis Unger (FDA, USA)

Dr Ellis F. Unger, MD, is the Director, Office of Drug Evaluation-I, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), US FDA. His Office oversees the regulation of drugs for cardiovascular, renal, neurological, and psychiatric disorders.

Dr Unger obtained his medical degree from the University of Cincinnati, and received post-doctoral training in internal medicine at the Medical College of Virginia. He completed a fellowship in Cardiovascular Diseases at The Johns Hopkins Hospital. Dr Unger was a Senior Investigator in the Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, from 1983 to 1997 where he led efforts in translational science on experimental promotion of angiogenesis. From 1997 to 2003, Dr Unger served as a Medical Officer, Team Leader, and subsequently Branch Chief in the Center for Biologics Evaluation and Research, FDA. When regulatory authority for therapeutic biologics was transferred from CBER to CDER in 2003, Dr Unger joined the Division of Cardiovascular and Renal Products in CDER, and became Deputy Director of that Division. Dr Unger was promoted to Deputy Director, Office of Drug Evaluation-I, in July, 2009, and became its Director in July, 2012.

David Van Wagoner (Cleveland, USA)

David R. Van Wagoner, PhD, FHRS, FAHA, is a staff member of the Departments of Molecular Cardiology and Cardiovascular Medicine at the Cleveland Clinic, and an Associate Professor in the Department of Molecular Medicine of Case Western Reserve University. In 1985, Dr Van Wagoner earned a PhD from the Department of Pharmacology of Thomas Jefferson University (Philadelphia, PA), and did postdoctoral studies at the University of Pennsylvania and Case Western Reserve University. From a background in cardiovascular pharmacology, he has focused his research at the Cleveland Clinic on the mechanisms, treatment and prevention of atrial fibrillation (AF). With a background in cellular cardiac electrophysiology, Using surgical tissue specimens and animal models, Dr Van Wagoner has characterized the electrophysiologic and structural remodeling that occurs in patients with paroxysmal, persistent and long-standing persistent AF. His studies have linked systemic inflammation and oxidative stress pathways to the etiology of AF. His NIH funded research seeks to clarify the mechanisms linking genetic loci associated with risk of AF to their impact on atrial gene expression and on cellular pathophysiology. As chair of the Heart Rhythm Society Research Committee, Dr Van Wagoner has collaborated with other scientists, cardiologists and surgeons to identify clinical and translational research priorities that will help to advance our understanding of AF, facilitate efforts to improve its treatment and eventually lower its incidence. He is interested in the roles of genetics, diet, and lifestyle on risk of AF, and in studies that evaluate the impact of changes in diet and lifestyle of AF burden. He serves on the editorial board of 8 cardiovascular journals and is a frequent reviewer for NIH, the AHA and other funding organizations.

Atrial fibrillation prevention and treatment: clinical trials as part of the research agenda

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Freek Verheugt (Amsterdam, NED)

Professor Freek Verheugt is Emeritus Professor of Cardiology at the Heart-Lung Centre of the University Medical Centre of Nijmegen, The Netherlands, and was Chairman of the Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam, The Netherlands.

Prof 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 Medical Centre, University in Rotterdam. He has been a Professor at the University of Colorado Health Sciences Center in Denver, CO, USA, and at the Free University in Amsterdam. He was President of the Netherlands Society of Cardiology between 1999 and 2001. Prof Verheugt's main fields of scientific interest are pharmacological and interventional treatments of acute coronary syndromes and atrial fibrillation.

Prof Verheugt has published over 500 papers in peer-reviewed international journals including *The New England Journal of Medicine, The Lancet, Circulation, Journal* of the American College of Cardiology and European Heart Journal, of which he is an Editorial Board Member. He has over 24,000 citations, an H index of 63 and is also an editorial adviser of The Lancet, *The New England Journal of Medicine* and *Circulation.*

ABSTRACT

Antidote trials and how will reversal agents impact use of NOACs?

Non-vitamin K oral anticoagulants (NOACs) are superior in efficacy and safety for stroke prevention in atrial fibrillation, but lack an antidote in case of urgent surgery or sever bleeding. Several antidotes are currently under development and investigation.

The monoclonal antibody idarucizumab has been developed as a specific antidote to dabigatran[1]. It has been tested in healthy volunteers in a placebo-controlled trial.2 It proved safe and effective, in that diluted thrombin time was almost immediately corrected. Yet, the results may be different in bleeding patients, or those in a critical clinical condition where emergent or urgent surgery is indicated. An open-label phase-III trial (RE-VERSE-AD) which an interim analysis of the first 90 (out of 300 planned) patients had been published.[1,2] Dabigatran-treated patients were stratified for either bleeding requiring anticoagulant reversal or for urgent surgery. Dilute thrombin time (TT) and ecarin clotting time (ECT) normalized immediately in nearly all patients and was still normal at 24h after the antidote in about 80% of patients. Also haemostasis was restored at around 11 hours. Early (<72h) thrombosis occurred in a single patient in whom anticoagulants had not been restarted. Side-effects were not noted. Mortality was considerable in this very high risk population: 20%. Fatal bleeding was observed in 5 patients (6%). The agent has been approved for use in the US and Europe

Andexanet alfa (PRT 4445) is a specific antidote to Xa blockers and consists of a decoy Xa molecule (truncated form of enzymatically inactive Xa). It has been tested in animal models.4 The results of two clinical trials with the agent in humans on apixaban (ANNEXA-A, NCT02207725) and on rivaroxban (ANNEXA- R, NCT02220725) will be presented at AHA 2015.

Finally, a non-specific antidote to all NOACs (PER 977, Aripazine®) has been developed and has been tested in human plasma.[5]. In patients on edoxaban a single full-dose aripazine bolus decreased the whole blood clotting time within 10% above the baseline value in 10 minutes or less, whereas in patients receiving placebo the time to reach that level was much longer (approximately 12 to 15 hours).[6]

The question is how often and under which antidotes to NOACs will be used in clinical practice. Only well-performed prospective registries in patients on NOACs will give the answer.

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MACE components versus bleeding types across the various indications in ACS and thereafter

Significant advances in the management of acute coronary syndromes (ACS) have decreased morbidity and mortality rates over the last 30 years. Despite these improvements in outcome the burden of cardiovascular disease remains high: still 40% of patients will die in the 10 years after the diagnosis of ACS.[1] One of the major drawbacks of current ACS management is increased bleeding. Thus, there is considerable interest in developing novel therapies to further improve the outcomes in ACS where it both of treatment efficacy and safety is concerned.

Most can be learned from the results of clinical trials and registries. Where the results of randomized studies in ACS treatment are well known, the best registry of ACS is less often mentioned. The GRACE registry that included 100,000 patients with ACS contains numerous data on short- and long-term risk in ACS related to patients' baseline features and treatment.[2] Bleeding is associated with a worse short- and long term outcome.[3,4] Not that many patients bleed to death, but bleeding is probably a marker of a poor prognosis. Probably malignant diseases, gastrointestinal disorders, or kidney failure are responsible, but also discontinuation of life saving agents. At the moment of bleeding usually platelet inhibitors and/or anticoagulants are reduced in dose or stopped with potentially fatal consequences.[5] And patients with even minor or minimal bleeding stop all their medication including ACE-inhibitors, betablockers and/or statins.

Finally, ACS risk scores at admission like GRACE can accurately predict early and late outcome6, especially when bleeding risk like CRUSADE is also taken into account.[7]

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Nicolas Vodovar (Paris, FRA)

Nicolas Vodovar is a Senior Research Associate at Inserm UMR-S 942 in Paris, where he leads a research group on BNP biology and metabolism. Dr Vodovar obtained hi PhD degree from Paris 6 University on the genetic and genomic analysis of host-pathogen interactions. He did a first post-doc studying the intracellular trafficking of proteins using live in vivo imaging at Ecole Normale Supérieure in Paris, and a second in arbovirus-insect interactions at Pasteur Institute. Since 2013, Dr Vodovar has joined the laboratory of Alain Cohen Solal, which is focused on biomarkers in Heart Failure, in Paris where he studies human-specific aspects of BNP in Heart Failure. Dr Vodovar has authored numerous high impact factor articles.

ABSTRACT

LCZ696, NPs and neprilysin intercations

One of the landmarks of acute decompensated heart failure (ADHF) is the overproduction of natriuretic peptides (NPs) by stretched cardiomyocytes to mitigate cardiac overload. Various strategies have been developed to potentiate the beneficial effect of the NPs, including the recent use of neprilysin angiotensin receptor inhibitors (LCZ696-Entresto). However, contrary to rodents, human BNP is poorly sensitive to neprilysin degradation while retaining affinity to neprilysin. Furthermore when plasma BNP rose above 916 pg/mL, neprilysin activity was markedly reduced and stratified 95% of the population into two groups: BNP < 916 pg/mL/neprilysin activity ≥ 0.21 nmol/mL/min and BNP ≥ 916 pg/mL/neprilysin acti-

vity < 0.21 nmol/mL/min with very different prognoses. In vitro, BNP was responsible for neprilysin inhibition. Altogether, these data show that besides being an effector of the cardiac response to cardiomyocyte stretching in ADHF, elevated plasma BNP is also an endogenous neprilysin inhibitor. A biologically relevant BNP threshold discriminates two populations of HF patients with different vasoactive peptide profiles and outcome. If confirmed, this may identify an important threshold for managing HF patients, in particular in the context of the pharmacological inhibition of neprilysin. These findings will also be discussed as an attempt to explain the paradoxical natriuretic peptide profiles of patients treated with LCZ696.

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Daniel Weiner (Boston, USA)

ABSTRACT

Unmet need and challenges related to CV outcomes in CKD and dialysis patients: prevalence, epidemiology and the differing significance of biomarkers

Clinical trials are sparse in nephrology, and few studied interventions, particularly in dialysis patients, are associated with a benefit on hard clinical outcomes, like mortality. In all stages of CKD, cardiovascular disease is the leading cause of death, although, in advanced CKD, including dialysis, this may more reflect arterial stiffness and subsequent structural heart disease and arrhythmia rather than atherosclerosis based on results of statin trials. Similar to other advanced chronic diseases, in very advanced CKD, accepted cardiovascular disease risk factors like dyslipidemia, obesity and hypertension may either not be associated with adverse events or may associated with reduced overall risk, likely reflecting malnutrition and protein energy wasting. Additionally, cardiac injury biomarkers may be mildly to moderately elevated in advanced CKD, even in the absence of an acute heart failure or ischemic event. Lastly, the burden of comorbid disease in advanced CKD is so high that a potentially beneficial intervention may only address one threat to health, with competing outcomes occurring at a high enough frequency to make these potential benefits unapparent in targeted intervention trials.

These factors make studies in people with advanced CKD very challenging, likely contributing to the paucity of clinical trials in advanced CKD and, specifically, positive clinical trials in advanced CKD. They have resulted in trials that evaluate composite outcomes rather than hard outcomes, with elements of these composites focused on pathology felt to be on the causal pathway to cardiovascular death. One excellent example of this is the Frequent Hemodialysis Network (FHN) trial, which evaluated a composite outcome of death or change (from baseline to 12 months) in left ventricular mass, as assessed by cardiac magnetic resonance imaging. Whether composites like this result in a sufficient level of evidence to change clinical practice remains uncertain, and it is notable that the results of the FHN were not deemed impressive enough to result in a high level recommendation for more frequent hemodialysis in the recently published KDOQI 2015 Hemodialysis Adequacy Guideline Update. Ongoing major clinical trials in dialysis include ALCHEMIST, which is evaluating whether aldosterone is associated with a reduction in a cardiovascular disease composite, including nonfatal myocardial infarction and acute coronary syndrome, hospitalization for heart failure, nonfatal stroke or cardiovascular-induced death. ALCHEMIST poses interesting outcomes questions for the dia-

lysis population, including: 1) Should all-cause mortality be included as an outcome given tremendous competing risks; 2) How is heart failure hospitalization defined in dialysis patients, where fluid overload is the norm; and 3) Should there be a higher threshold for diagnosis of NSTEMI in this population given challenges with troponin levels? A second major ongoing trial in dialysis is the TiME trial, which takes a different approach to addressing outcomes in dialysis, relying on the assumption that nearly all dialysis outcomes are influenced by or directly caused by cardiovascular disease and therefore focusing on mortality outcomes in a large cluster randomized trial of dialysis session duration.

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William White (Farmington, USA)

Dr William White (MD, FACP, FAHA, FASH) is Professor of Medicine and Chief of the Division of Hypertension and Clinical Pharmacology in the Calhoun Cardiology Center at the University of Connecticut School of Medicine where he has worked for 37 years. In addition, he is lead physician for the Hypertension and Vascular Diseases faculty practice in the Cardiology Center at the John Dempsey Hospital in Farmington, Connecticut. Dr White is a Fellow of the American College of Physicians, a Fellow of the Council for High Blood Pressure Research of the American Heart Association, a Fellow of the International Society for Hypertension in Blacks and a charter member of the American Society of Hypertension. Dr White was the President of the American Society of Hypertension from 2012-2014.

Dr White has a longstanding interest in clinical hypertension and pharmacology, particularly in the areas of ambulatory blood pressure monitoring, clinical trials of antihypertensive drugs, and the impact of non-cardiac drugs (e.g., NSAIDs, neuropsychiatric agents, analgesics) in cardiovascular disorders. He is the author of over 450 original articles and 90 book chapters in the field of cardiovascular medicine and pharmacology. Dr White has published 6 medical textbooks, including Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics (Springer Science) and Hypertension and Related Disorders (CV Mosby Press). To support this work, Dr White has been the recepient of research funding from the National Institutes of Health, the American Heart Association, the Donaghue Research Foundation, and the pharmaceutical industry.

During the past 20 years, Dr White has been highly involved in major clinical trials in cardiovascular medicine, including as member of the Steering Committee of the CONVINCE trial which evaluated cardiovascular outcomes in at risk patients using chronotherapy, BLISS which evaluated the cardiovascular effects of low dose testosterone therapy in post-menopausal women, the CARES trial which is on going on evaluate the cardiovascular safety of gout therapies, EXAMINE , which assessed the impact of the DPP-4 inhibitor aloglitpin in patients with type 2 diabetes and acute coronary syndromes, and the EnLigHTN trials which is assessing the effects of renal denervation in patients with treatment resistant hypertension.

Janet Wittes (Washington, DC, USA)

Janet Wittes, PhD, is President of Statistics Collaborative, Inc. which she founded in 1990. One of Statistics Collaborative's main functions is to serve as the statistical reporting group for data monitoring committees. Previously, she was Chief, Biostatistics Research Branch, National Heart, Lung & Blood Institute (1983–89). Her 2006 monograph, "Statistical Monitoring of Clinical Trials – A Unified Approach" by Proschan, Lan, and Wittes, deals with sequential trials.

She has served on a variety of advisory committees and data monitoring committees for government (NIH and the VA) and industry. For the FDA, she has been a regular member of the Circulatory Devices Advisory Panel and has served as an ad hoc member of several other panels. Currently, she is a regular member of the Gene Therapy Advisory Committee. She was formerly Editor in Chief of Controlled Clinical Trials (1994-98). In 2015 she received the American Statistical Association's W. J. Dixon Award for Statistical Consulting. Her research has focused on design of randomized clinical trials, capture recapture methods in epidemiology, and sample size recalculation. She received her PhD in Statistics from Harvard University.

ABSTRACT

Point and counterpoint with major journal editors – statistical perspective

Clinical trials require the collaboration of many disciplines to ensure that the questions being addressed are important, that the design of the study is consistent with the questions being asked, that the study has been conducted in a way that ensures rigor, that the measurements are taken precisely and accurately, and the statistical methodology is valid and powerful. When the study is reported in a medical journal, the main paper is often limited to be so succinct that it cannot present full discussion of all the most important aspects of the trial. All too often (at least from the point of view of this statistician), the section on statistics has too little information on methodology to allow the reader to understand in sufficient detail what methods were used and how appropriate they were.
The main statistical methods are typically specified, but often what is lacking is information on such issues as what the protocol listed as primary and secondary outcomes, how missing data were handled, and what methods were used to deal with multiplicity. If the methodology is Bayesian, the word "Bayes" may be used, but not the specific model employed. If a model has many covariates, the method for selecting them is often not included. Sometimes, analyses that are based on non-randomized groups are not clearly distinguished from analyses based on randomized comparison.
Thus, when we as statisticians review a paper that summarizes the trial, we often cannot judge the validity of the methods used.
Of course, what we want would make papers much too long. Seeing a paper with complicated statistical methods but no statistician as an author raises in at least this statistician's mind questions about who did the analysis and did the statistician withdraw from authorship. The problem of not being able to judge the validity of the statistical methodology is somewhat alleviated by the increasingly common practice of including more statistical detail in on-line supplemental material.

Use and misuse of off-treatment analysis

It is a truth universally acknowledged that a bad event cannot have been caused by a drug not taken. Perhaps this realization is what leads to the call for "on-treatment" analyses in assessing whether a drug is a causative agent for adverse experiences; however, as is the case in so many situations, the details matter. In order to use "on-treatment" analyses to assess causation, the first step is to define what one means by "on-treatment". Often what is called "on-treatment" is the period while a person is taking the drug in question; sometimes it is the time while the patient is on the drug plus one week, or two weeks, or thirty days.
Sometimes "on-treatment" includes the period up to five half-lives of the drug. All these definitions assume that a drug cannot cause an event after it, or its important metabolites, are gone from the body. T
hese definitions have at least three important problems in randomized trials. First, these kinds of analyses do not respect the randomization; insofar as unbiased comparisons must respect randomization, such analyses are often fundamentally biased. Second, sometimes a drug may cause an event that leads the investigator to withdraw the drug.
If, however, the event begins a cascade of other events that occur after the defined "on-treatment" period, these other events do not "count" against the drug. Third, sometimes a participant experiences a serious adverse event and the investigator withdraws the drug even though the drug had nothing to do with the event.
"On-treatment" analysis will incorrectly count these events as drug-related. The talk will present some data from an actual cardiovascular outcome trial of an antidiabetic agent that shows when an on-treatment analysis of placebo demonstrates the same rate of adverse events as on-treatment analysis of the drug.

These arguments warn against on-treatment analysis. If, however, one looks only at the randomized treatment groups when a sizeable number of participants do not continue to the end of the study, non-compliance can attenuate adverse event rates. In conclusion, formulaic approaches to ferreting out likely causality, be they "on-treatment" or strict intent-to-treat, can either overestimate or underestimate true causal associations.

Tom Wong (London, GBR)

Tom Wong, MBChB, MD, FRCP, FESC, is a Consultant Cardiologist and Electrophysiologist at the Royal Brompton and Harefield Hospitals in London, Clinical Director of the cardiac catheterisation laboratories. He is also the Chief of one of the largest arrhythmia service in UK leading a team of over 40 clinicians. Dr Wong obtained his undergraduate medical degree from University of Aberdeen and further his training in cardiology in London, UK.

Dr Tom Wong's research interest in the area of the charaterisation and the interventional therapies of complex arrhythmia. He has led and completed the first randomised control trial showing the clinical benefit, in term cardiopulmonary exercise performance, in treating patients with persistent atrial fibrillation and heart failure by catheter ablation compared to drug therapy alone, ARC-HF trial (A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure).

The is the chief investigator CASA-AF trial (Catheter Ablation Versus Thoracoscopic Surgical Ablation in Long Standing Persistent Atrial Fibrillation) assess efficacy of ablation of long standing atrial fibrillation comparing the thoracoscopic approach and percutaneous catheter based approach ablation. CASA-AF trial is supported by the National Institute for Health Research of UK.

Faiez Zannad (Nancy, FRA)

Faiez Zannad, MD, PhD is Professor of Therapeutics at Université de Lorraine, Nancy, France. He obtained his MD and cardiology specialty in Université de Lorraine, France and his PhD in clinical pharmacology at Université de Lyon, France with fellowship at MRC unit, Oxford, UK. He is currently head of the Division of Heart Failure and Hypertension and Director of the Inserm Clinical Investigation Center at "Institut Lorrain du Coeur et des Vaisseaux" in the Centre Hospitalier et Universitaire of Nancy. He coordinates 2 EU FP7 grants: HOMAGE, on omics biomarkers for mechanistic phenotyping and prediction of drug response and FIBROTARGETS on fibrosis as a biotarget, both in heart failure.
As the primary investigator or member of oversight committees in major clinical trials, he made significant contributions to evidence based heart failure therapy, mainly with beta-blockers (CIBIS) and mineralocorticoid receptor antagonists (RALES, EPHESUS, EMPHASIS-HF). He has served as chairman of the French Society of Hypertension, chairman of the ESC Working Group on pharmacology and drug therapy and board member of the ESC Heart Failure Association. He is currently and since 2004, chairman and founder of the annual international meeting: Global CardioVascular Clinical Trialists (CVCT) Forum and Workshop, dedicated to the science of clinical trials, and of the International Workshop on Biomarkers in Heart Failure. As of October 2015, he has authored more than 500 scientific publications, totalling 66715 citations.

ABSTRACT

Acute and chronic hyperkalemia therapy future trials. Unmet needs and newer opportunities for potassium binding agents in chronic heart failure

Hyperkalemia is a common clinical problem especially in patients with heart failure, chronic kidney disease, and diabetes mellitus. Treatment with renin angiotension aldosterone system inhibitors (RAASi) often exacerbates the risk of hyperkalemia in these patient groups. Hyperkalemia often results in the failure to initiate, frequent discontinuation, or suboptimal dosing of life-saving RAASi in these patients. In this respect, new promising treatments for hyperkalemia in development may offer better efficacy, tolerability and safety profiles than do existing approved treatments. Moreover, these compounds might enable more eligible patients to receive RAASi therapy, or receive RAASi at target doses. The type of evidence needed to support a treatment claim (reduction in serum potassium) differs from that needed to support a prevention claim (preventing hyperkalemia to allow RAASi treatment). Thus, several issues related to clinical trial design and drug development need to be considered. Regulatory considerations, which differ for treatment and prevention claims, impact the design of clinical trials. The following aspects of trial design should be considered: choice of control group, duration of treatment and follow-up, data completeness, methodologies for handling missing data, and selection of endpoints. These should be tailored according to the sought indication. Three potential indications could have a significant impact on clinical practice: i) Treatment of hyperkalemia and maintenance of serum K reduction, ii) Prevention of hyperkalemia in patients at risk (e.g., on RAASi), iii) Enabling RAASi use and improved clinical outcome.
Patient populations with unmet need who may be prioritized in future trials are i)high degrees of renal impairment (e.g., eGFR <30 mL/min/1.73 m2), ii)Higher baseline serum K+ (i.e., > 5 mmol/L), iii)Emergency department/ICU setting, iv)HF with diuretic resistance and Resistant v)hypertension with CKD.

Autonomic modulation therapy. A critical appraisal of recent and ongoing trials in heart failure. Recommendations for future trials

Recent but little experience has accumulated with autonomic modulation therapy in heart failure as compared to hypertension, with most trials still ongoing. As these trials complete and data emerge, future research directions will become more evident. Ongoing studies are targeting patients with reduced ejection fraction and progressive, symptomatic, heart failure despite optimal guideline driven medical therapy. Enrolling patients with a substrate likely to benefit from decreased sympathetic activation and increased parasympathetic tone will be key to determining the efficacy of autonomic modulation in heart failure. For example, vagal stimulation has been shown to improve markers of myocardial remodeling and biomarker profiles in experimental and animal models, as well as in symptomatic heart failure patients. Thus, the NECTAR-HF and INOVATE-HF studies were designed to enroll patients with evidence of left ventricular remodeling, defined as left ventricular end-diastolic diameter (LVEDD) of >55 mm (NECTAR-HF) or between 50 and 80 mm (INOVATE-HF). LVEDD-based inclusion criteria were not specified in clinical trial registry databases for the other ongoing heart failure trials (SWAN-HF, SYMPLICITY-HF). The issue of optimization of the medical treatment and non-adherence to treatment should be assessed prior to applying these invasive therapies.
In the NECTAR-HF trial, an improvement in the primary efficacy endpoint, LVESD, was not seen when comparing the active to inactive groups at 6 months or when vagal nerve stimulation was activated in the control group (6 – 18 mo. within group change). The NECTAR-HF trial did however have a favorable adverse event profile and a survival rate at 18 months that was within the expected range compared to historical controls, thus meeting the pre-specified safety criteria. A NECTAR-HF study extension is now being started to test the feasibility of using alternative stimulation parameters.
INOVATE-HF has been designed to assess safety and efficacy of vagus nerve stimulation in symptomatic patients with heart failure on optimal medical therapy using the CardioFit System (BioControl Medical, Yehud,

Israel). The recruitment of up to 650 patients is now completed in a 3:2 ratio to receive active treatment or standard optimal medical therapy. Inclusion criteria include left ventricular systolic dysfunction, the presence of New York Heart Association Class III symptoms, sinus rhythm, and QRS width less than 120 milliseconds. The study is powered to detect differences in the primary efficacy end point of all-cause mortality and heart failure hospitalization and 2 safety end points.

The (BEAT-HF) Barostim neo - Baroreflex Activation Therapy for Heart Failure is an outcome trial being planned as a prospective, randomized trial in subjects with reduced ejection fraction heart failure. Subjects will be randomized to receive Barostim Activation Therapy with an implanted neo system in addition to medical management or to receive medical management alone (no device implant). The trial will be conducted at up to 90 investigational centers in the U.S. and up to 20 investigational centers outside the U.S. These centers will enroll up to 800 subjects to randomize approximately 480 subjects who meet the entry criteria.

Unlike hypertension trials, surrogate endpoints are generally not accepted as primary efficacy endpoints for pivotal heart failure trials. Remodeling endpoints may be appropriate for feasibility/proof-of-concept or phase II studies, but clinical outcome endpoints (e.g., all-cause and/or cardiovascular death, all-cause and/or cardiovascular or heart failure hospitalization) are typically more appropriate for pivotal heart failure studies. As with hypertension trials, measures of functional capacity, patient-reported outcomes, health-related quality of life, and cost-effectiveness endpoints are important to assess the totality of evidence with these interventions.

Because of the novel and emerging nature of autonomic modulation therapy for the treatment of heart failure, the potential safety issues are not fully realized. Adequate follow-up time should be planned to allow for robust assessments of safety. The primary safety objective should be to reasonably rule out an adverse effect on all-cause mortality and hospitalization rate. Studies to determine short and long-term interactions (if any) with other guideline-recommended devices such as implantable cardioverter defibrillators or cardiac resynchronization therapy devices are needed.

Common methodological issues need to be addressed, including but not limited to prediction of response to therapy, level of intensity of stimulation (dosing), validation of autonomic activity readouts which may serve in “dose-finding” preliminary studies, blinding issues and the possible use and approvability of extended composite endpoints and Bayesian approaches. Additionally, collecting detailed information on non-cardiovascular adverse effects (such as potential long-term effects on the laryngeal nerve after baroreceptor stimulator implantation) should be rigorously performed. Renal artery stenosis after renal denervation has not been reported frequently, but further research is needed to confirm true stenosis rates.

Running CV therapy trials specifically in patients with significant renal impairment, or including CKD patients in common CV therapy trials? Pros and Cons and Insight from recent and ongoing trials
Presented by Patrick Rossignol (Nancy, FRA)

Cardiovascular disease (CVD) occurs commonly in patients with chronic kidney disease (CKD) including those treated with hemodialysis (HD), and is associated with poor outcomes in this population. Pharmacologic management of hypertension, dyslipidemia, acute and chronic coronary artery disease, acute and chronic heart failure and atrial fibrillation in the general population is based on extrapolation of randomized, controlled clinical trials where CKD patients are little represented, if not excluded, and particularly for HD patients. Classical risk factors, such as blood pressure, LDL cholesterol and body weight bear an inverse paradoxical relationship with outcomes in HD patients. Statins do not improve outcomes in HD patients. Therefore, powering CV outcome trials to enroll large enough numbers of patients with different degrees of CKD, or, running specific CKD CV outcome trials, especially in HF patients is to be encouraged. Cardiologists and nephrologists should collaborate in order to achieve this aim. Nephrologists and HF specialists should prepare for and be trained to conducting large outcome trials. Disappointingly, looking in clinicaltrials.gov reveals a very low number of such trials. Insights from recent or ongoing trials in the diabetes (EMPAREG), NOACs, and hypertension (SPRINT, PATHWAY2, ESTIM-rHTN) settings will be discussed.

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The EMPA-REG outcome and cardiovascular safety diabetes trial: survival MACE and heart failure findings

The United States (US) Food and Drug Administration (FDA) issued an Industry Guidance in 2008 for evaluating the cardiovascular safety of new therapies for the treatment of patients with type 2 diabetes mellitus. The guidance was developed in response to concerns about the cardiovascular safety of these drugs, which originated with rosiglitazone. At the time the guidance was released, the consequences of these requirements on diabetes drug development were uncertain. Several clinical trials designed to meet this regulatory requirement have been reported.

It is likely that the relevance of drugs for the treatment of type 2 diabetes as triggers of worsening heart failure may have been underestimated in the past, while the weight of atherogenic and/or prothrombotic disease has been overemphasized. Few studies have pre-specified heart failure as a primary or secondary endpoint. Heart failure events occur with similar frequency as other major adverse cardiovascular events in clinical trials of patients with type 2 diabetes and elevated cardiovascular risk, occurring second to MI and at a greater frequency than stroke in the placebo arm of both SAVOR-TIMI-53, EXAMINE, and TECOS. When a cardiovascular safety trial is deemed necessary, depending on the safety signals detected in earlier phases of development, heart failure should be assessed; whether it should be a stand-alone co-primary endpoint, a component of the primary composite endpoint, or a key secondary endpoint depends on the study population, the drug's mechanism of action, and possibly other factors.

Since cardiovascular disease is the leading cause of death and disability in patients with type 2 diabetes, some now believe the appropriate emphasis and resources should be shifted to proving efficacy rather than ruling out harm. Only requiring cardiovascular outcome safety trials when there is suspicion or a signal of an adverse effect seems reasonable given the number of recent studies that have demonstrated non-inferiority and the resources and time involved in conducting these large-scale trials.

The EMPA REG OUTCOME trial is such a large-scale trial superiority trial, which has been able to show that empagliflozin was able to improve CV outcome, and mainly heart failure outcomes. The results are robust and mechanistically plausible, since this drug may act as a mild natriuretic agent, in addition to slightly lowering blood pressure and body weight, and it is likely that a large number of patients in the trial had undiagnosed heart failure with preserved ejection fraction. This is a syndrome with no proven therapy so far. This class of SGLT2 inhibitors is worth investigating in this indication.

On another hand, it remains doubtful that glucose lowering in itself can produce any macrovascular benefit.

The information currently available is considered sufficient to revisit the debate for new therapies to treat type 2 diabetes, where patients, industry, regulators, and academia can openly discuss what certainties are needed and how much uncertainty can be accepted.

Risk-guided strategy trials

ADMIRE-ICD an 123I-mIBG imaging risk stratification guided ICD therapy trial: study objectives and design

Current international guidelines recommend implantation of an ICD in patients with left ventricular ejection fraction (LVEF) ≤35% to reduce the risk of sudden cardiac death (SCD). However, only about half of all patients who meet the guideline criteria actually have a device implanted. Furthermore, during the first year of implantation, as few as 5% of patients who have a device implanted will actually experience an appropriate shock or pace termination of a fatal arrhythmia. Within the patients with low LVEF risk stratification may be improved using 123I-mIBG imaging. AdreView™ Myocardial Imaging for Risk Evaluation for ICD therapy (ADMIRE-ICD) is an event-driven Phase IIIb, multicentre, randomised strategy trial aiming to demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation in a population of NYHA II and III HF patients with 30%≤ LVEF ≤35%. This will be achieved by comparing the AdreView™-guided therapy group to that observed in patients receiving Standard of care (SC), as the medical care as recommended by internationally accepted HF guidelines, in whom no clinical decision will be made based upon AdreView™ scan results. The primary endpoint will be all-cause mortality. Key secondary endpoints include cardiovascular (CV) death (SCD, arrhythmic, HF, and other CV causes), CV hospitalization, all-cause hospitalization, resuscitated life-threatening ventricular tachycardia, unstable ventricular tachy-arrhythmias, ICD appropriate shocks and clinical and healthcare resource utilization. An ad hoc committee will adjudicate all events. The study will be conducted at 110 centers in the USA, Canada and Europe. At least 2607 patients will be screened (taking into account approximately 15% screen failure rate) in order to include at least 2216 patients in the study at approximately 130 centres. The primary efficacy analysis will take place after 247 instances of the primary efficacy endpoint have accrued. The primary efficacy endpoint will be analysed for non-inferiority with an non-inferiority margin of 1.20. If the lower bound of the confidence interval exceeds 1.0, superiority will be claimed/established. This analysis will be performed at a 1-sided alpha value of 0.025. The accrual time is expected to be 18 months, with a total study duration of 48 months. The study is sponsored by GE health care. First patient first visit is expected in Q4 2015 and study termination in Q4 2019. ADMIRE-ICD is set to be the first risk stratification guided ICD therapy trial, and among the first risk based precision medicine CV trials.

Bram Zuckerman (FDA/CDRH, USA)

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Posters

Patient-reported angina severity as a marker of procedural appropriateness

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PURPOSE: Revascularization of occluded coronary arteries using percutaneous coronary intervention (PCI) is one of the primary treatments for coronary disease. Selection of appropriate patients is important to ensure the maximum benefit is derived from this costly procedure. Current appropriateness guidelines endorsed by the ACC and AHA use the Canadian Cardiovascular Society (CCS) classification as the primary marker of angina severity, however this has been shown to be poorly predictive of outcomes. Patient-reported angina measures, such as the Seattle Angina Questionnaire (SAQ) have much greater predictive ability. We investigated the potential impact of using SAQ scores rather than CCS when classifying procedural appropriateness.

METHOD: Consecutive patients presenting to the cardiac catheterization lab during the first three quarters (Jan – Oct) at Massachusetts General Hospital for outpatient PCI procedures were entered into the cohort. Patients were excluded if they presented as inpatients, or if they did not have survey data available. The patients completed the SAQ-7 short-form patient reported outcome instrument, which has scales for overall disease severity, angina severity, physical limitation, and quality of life. The SAQ-7 is scored from 0 to 100, with lower scores representing more severe symptoms. The patients also completed the Rose Dyspnea Scale (RDS) as a measure of dyspnea severity). This scale is scored from 0 to 4, with lower scores representing more severe symptoms. Clinical variables and appropriateness classification were obtained from submissions to the National Cardiovascular Data Repository (NCDR) Cath PCI submissions. We determined the correlation between CCS and SAQ-7 classification using linear regression. We then assigned a cutoff for the SAQ-7 Summary and Angina Frequency classes based on the 75%-ile in the group of patients who were CCS class 3 (a key division in the appropriateness criteria).

RESULTS: 229 patients were eligible for inclusion in the cohort, however SAQ-7 responses were only available for 187 (81.7%). Of the 187 patients, 107 (57.2%) were Appropriate, 58 (31.0 %) were Sometimes Appropriate, and 7 (3.7%) were Rarely Appropriate. There were 15 (8.0%) patients that were not mappable due to missing data for one or more components of the AUC. Of the 7 rarely appropriate patients, 6 (85.7%) had CCS Class 1 or lower angina. There was only modest correlation between SAQ-7 scores and CCS class, with R-squared values ranging from 0.166 for physical limitation 0.270 for quality of life ($p<0.0001$ for all models). SAQ-7 scores also correlated with appropriateness class, with mean summary scores of 49.8 (45.2 -54.4) in the Appropriate group, 73.8 (67.5 – 80.1) in the Sometimes Appropriate group, and 71.3 (53.2 – 89.4) in the Rarely Appropriate group. The specified 75%-ile score cutoffs for SAQ-7 were found to be 66.4 for the summary score, and 80 for the angina frequency score. Using the summary scale cutoff, 57/160 (35.6%) of patients who had CCS ≥ 3 did not meet the cutoff, and 6/26 (23.1%) of patients with CCS <3 did meet the cutoff. Four of the seven patients classified as rarely appropriate would be reclassified as appropriate. Of the patients scored as appropriate, 28/107 (26.2%) did not meet the summary scale cutoff and were reclassified as sometimes or rarely appropriate. Using the angina frequency cutoff, 64/161 (39.8%) of patients with CCS ≥ 3 did not meet the cutoff, and 3/26 (11.5%) of patients with CCS <3 did meet the cutoff. No patients who were scored as rarely appropriate were reclassified. Of the patients scored as appropriate, 33/107 (30.8%) did not meet the angina frequency cutoff and were reclassified as sometimes or rarely appropriate.

CONCLUSION: Physician-reported angina severity does not correlate well with patient-reported angina severity, which has much greater prognostic utility. Use of patient-reported angina severity would be an important improvement to current appropriateness guidelines. The impact of using patient-reported measures of angina severity would likely be that more procedures are scored as sometimes or rarely appropriate, and less scored as clearly appropriate. Our study had several limitations. We used a relatively arbitrary cutoff, and our population size was small. Future research with larger population sizes and more clinical sites will be necessary prior to use of patient-reported angina severity for appropriateness classification.

Incidence and predictors of sudden cardiac death in patients with coronary disease and mild LV dysfunction: the PRE-DETERMINE study

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INTRODUCTION: Patients with coronary disease and mild left ventricular (LV) dysfunction (LV ejection fraction ≥ 35%) are at increased risk for sudden cardiac death (SCD). Risk stratification and eligibility for preventive therapies such as implantable cardioverter-defibrillators (ICD) in this population remain uncertain.

METHOD: The Pre-Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (PRE-DETERMINE) study is an ongoing multi-center prospective cohort of patients with coronary artery disease and mild-moderate LV dysfunction (LVEF ≥35%). Patients with a history of cardiac arrest, prior ICD placement, or anticipated life-expectancy <6 months were excluded. Mode of death was adjudicated using Hinkle-Thaler classification. Cox proportional hazards models with backwards selection was used to identify multivariable predictors of SCD.

RESULTS: Baseline characteristics of the study population (n=5,724; 68±11 years, 76% men, 89% white race, LVEF 52±10%) are described in Table 1. Over a median follow-up of 3[1.5] years, there were a total of 480 deaths (8.4% of study cohort). Of 364 deaths adjudicated thus far, the prevalence of cardiac death was 39% (n=143) of which nearly two-thirds was sudden and/or arrhythmic (n=82; 57%). Multivariable predictors of SCD included diabetes (hazard ratio [HR]: 2.30, 95% CI: 1.48-3.60, p<0.001), history of atrial fibrillation (HR: 2.37, 95% CI:1.47-3.80, p<0.001), never vigorous exercise (vs. 1-4 times/week; HR 1.92, 95% CI: 1.14-3.20, p=0.01), and depressed LV ejection fraction (vs. EF ≥50%: HR 2.28, 95% CI: 1.40-3.70 for EF 40-49%; 3.67, 95% CI: 1.95-6.87 for EF <40%; p<0.001 for both) (Table 2, Figure).

DISCUSSION: In this contemporary cohort of patients with coronary disease and mild-moderate LV dysfunction, the majority of cardiovascular death was sudden and/or arrhythmic. Diabetes, atrial fibrillation, absence of vigorous exercise, and moderate levels of LV dysfunction were predictive of SCD. Follow-up is ongoing and future work will integrate ECG and plasma biomarkers to help refine prediction of sudden death for this at-risk population.

Evaluating the role of cardiac resynchronization therapy in the setting of prolonged AV conduction in heart failure patients with non-LBBB and reduced ejection fraction - a clinical translational research proposal

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The incidence and prevalence of heart failure (HF) is increasing, associated with significant morbidity and mortality.1 Implantation of a cardiac resynchronization therapy (CRT) device in HF patients is an effective therapy to reduce HF hospitalizations and all-cause mortality,2 however a significant proportion of patients do not respond to this therapy, especially those without left bundle branch block (non-LBBB).3 We have previously suggested in a secondary analysis of the MADIT-CRT trial, that HF patients with non-LBBB and a prolonged AV-conduction derive significant clinical benefit from CRT with reductions in HF hospitalizations and mortality.4 The mechanism of action however has not yet been fully identified. Furthermore, it is unknown whether the beneficial effects of CRT to improve outcomes in patients with first-degree AV-block were present in a prospective cohort. Hence, there is a need to investigate the underlying mechanism of CRT benefit, and prospectively assess the impact of CRT in HF patients with non-LBBB, New York Heart Association (NYHA) class I, II, or III heart failure, EF<35%, and prolonged AV-conduction (PR ≥ 230 ms). We propose a 3-phase, clinical translational research project: 1) basic science study (animal model), 2) pilot clinical study (case series of 10 patients), 3) prospective, randomized, multicenter, clinical trial.

Our study will attempt to answer the research questions of revealing the pathomechanism of CRT benefit, and whether CRT is an effective therapy to improve outcomes in HF patients with non-LBBB, EF<35% and first degree AV-block (PR>200 ms).

We hypothesize that CRT has beneficial effects by restoring AV-sequence to improve contractility, and reduce volumes.

Specific Aim 1: To assess whether CRT is effective in immediately improving the contractility of the heart in an animal model of non-LBBB, EF<35%, and a prolonged AV-conduction.

This will be accomplished by creating a heart failure dog model, implementing CRT to restore the AV-conduction, and measuring the contractility of the heart.
Hypothesis: CRT immediately improves the contractility of the heart in a heart failure dog model with non-LBBB, EF<35%, and a prolonged AV-conduction.

Specific Aim 2: To assess whether CRT is effective to improve acute echocardiographic response in HF patients with non-LBBB, EF<35%, and a prolonged AV-conduction.

This will be investigated in a case series study by measuring echocardiography response immediately after CRT implantation.
Hypothesis: CRT is associated with immediate improvement in echocardiography response in HF patients with non-LBBB, EF<35%, and a prolonged AV-conduction. Valentina Kutyifa_10202015
2 February 15, 2015

Specific Aim 3: To prospectively assess the effects of CRT to improve clinical outcomes in HF patients with non-LBBB, EF<35%, and a prolonged AV-conduction in a prospective randomized clinical trial.

This will be tested by performing a prospective randomized clinical trial in non-LBBB patients with prolonged AV-conduction.
Hypothesis: CRT is associated with significant improvement in 6-month echocardiography response (left ventricular end-systolic volume reduction) in HF patients with non-LBBB, EF<35%, and a prolonged AV-conduction.

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Randomized control trial of multiple biomarkers in personalized management of heart failure

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PURPOSE: Use of biomarkers has been proven to be resourceful in the management of heart failure (HF) patients. The AHA 2013 guidelines have suggested four biomarkers for guideline-directed medical therapy and also specific recommendations on what classes to titrate in response to a particular marker. Our aim is to create a myocardial injury summary score (MISS) integrating the 4 specified biomarkers and compare the impact on MISS among patients randomized to tailored therapeutic management based on the biomarkers and those with traditional clinical management without the use of biomarkers. We hypothesize that personalized management with targeted therapy based on the biomarkers will lead to reduction in MISS scores.

METHODS: Prospective randomized, controlled, parallel-group trial: Arm 1- Biomarker-Guided Therapy (marker results given to clinical team at each bimonthly visit); Arm 2- Usual Care (blinded to marker results, keep bimonthly visits).
Ambulatory patients aged more than 18 with LVEF of <40% with NYHA Class II-IV heart failure and eGFR≥ 30 ml/min/1.73 m2 are to be included in the study. Patients with a planned cardiac transplantation or a recent hospitalization within 30 days are to be excluded.

MISS SCORE: The basic metric is the ratio of the peak value for a biomarker after treatment to the baseline value before treatment. Both the baseline and post-treatment values may represent single assay measurements, or a single value determined from multiple measurements with rules used to ensure robust assay estimates($\sum$ log10 [Biomarker(i)Peak / Biomarker(i)Baseline]/n, i = 1, n). Sample size: We plan to enroll 30 subjects in each arm which will have >80% power to detect a 25% reduction in the MISS score from baseline to 12 months or last observation carried forward at an alpha of 0.05.

OUTCOME: The primary outcome is the change in MISS between baseline and 12 months after follow-up with the treatment as the independent variable. We also intend to collect and compare data on re-hospitalization and mortality between the 2 different arms of treatment.

ANALYSIS: A one-way ANOVA with treatment as the independent variable and MISS as the dependent variable would be conducted.

ENROLLMENT DETAILS: We currently have 4 patients enrolled in this study (2 male and 2 female).

FUTURE RESEARCH: Large scale outcome trials can be considered if we could determine that personalized management can directionally influence reduction in MISS score. These future trials would propose that reduction in MISS score would benefit the patients in decreasing the events (re-hospitalization and mortality).

Dislodging sudden cardiac death

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Substantial evidence has accrued to suggest that inflammation, oxidative stress, and defective autophagy may play important role in neuronal and peripheral cell's susceptibility to cellular dysfunction, and ageing- associated conditions, including cancer, rheumatoid arthritis, cardiovascular, metabolic, and neurodegenerative disorders. Lesions in such chronic disorders such as cancer and cardiovascular disease have associated with them a variety of proteins known to be involved in inflammatory processes. This is particularly true in the case of cardiovascular disease, where inflammatory reactions are believed to be important contributors to tissue degeneration and loss. Proteins present include complement proteins, C-reactive proteins, and macrophage-derived proteins, such as human cartilage glycoprotein 39 (HC-gp39). Data collected from different pathologies indicate a correlation between HC-gp39 plasma levels and severity of disease progressions suggesting important role for HC-gp39 as a marker of pathology. On top of this, HC-gp39 has been shown to play important role in the pathogenesis of endothelial dysfunction, atheriosclerosis and abnormal angiogenesis, all are important hallmarks of cardiovascular disorders. In concord, JS Johansen, Kastrup J. and associates disclosed that HC-gp39 serum levels directly correlate with cardiovascular morbidity and mortality, and all-cause mortality, unstable angina, left ventricular dysfunction, propensity to diabetes, hypertension, obesity and several types of cancer, thereby, indicating that HC-gp39 is a powerful player in the genesis and clinical outcome of cardiovascular disease. This inevitably implies that understanding the mechanisms by which HC-gp39 exerts its biological effects should be instrumental for unraveling the mechanisms governing the pathogenesis of cardiovascular disorders. HC-gp39(also known as YKL-40) is an inflammation-responsive glycoprotein, and a C-lectin that binds heparin and chitin-like oligosacharides, It belongs to the family of chitinase-like protein, that are found in vertebrates and invertebrates. It is recently suggested that HC-gp39 may exert its biological effects through 8 mechanisms, whereby its ability to impact on autophagy machinery, induce the expression and up-regulation of angiogenesis, bind heparin, and exhibit hormetic-like biphasic dose response may represent the major components governing this process (Okom Ofodile). Because autophagy and apoptosis share the same signaling pathways and cellular receptors, and are modulated by common proteins, the emerging notion implicating HC-gp39 in modulating autophagy machinery (Okom Ofodile, Abstract: AJPP, 2010), buttresses the concept that HC.gp39 would be involved in the molecular choreography that dictates cell fate. Hence, untangling the signaling networks governing the mechanisms by which HC-gp39 exerts its biological effects will provide key insights into the genesis of a range of chronic disorders, and, thereby the circumstances linking autotoxicity, oxidative tissue damage, inflammation, autoimmunity, and defective autophagy in various disorders, including cardiovascular and metabolic conditions. In combination, given the compelling evidence associating HC-gp39 alterations with cardiovascular health, and the overwhelming evidence that complement inhibitors, antioxidants, chaperones and autophagy enhancers are cadioprotective against most common heart diseases, offers optimism that consequent enhancement of both short and long term health of the heart is attainable.

Temporal trends of digoxin use in patients hospitalized with heart failure: analysis from the american heart association get with the guidelines - heart failure registry

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BACKGROUND: Digoxin has Class IIa recommendations for treating HF with reduced ejection fraction (HFrEF) in U.S. Digoxin use, temporal trends, and clinical characteristics of HF patients associated with digoxin use in current clinical practice in the U.S. have not been well studied.
METHODS AND RESULTS: An observational analysis of 255,901 patients hospitalized with HF [117,761 HFrEF and 138,140 HF with preserved EF (HFpEF)] from 398 hospitals participating in the Get With The Guidelines–HF registry between January 2005 and June 2014 was conducted to assess the temporal trends and factors associated with digoxin use. Among 117,761 HFrEF patients, only 19.7% received digoxin at discharge. Digoxin prescription decreased from 33.1% in 2005 to 10.7% in 2014 (Ptrend <0.0001). Factors associated with digoxin use in HFrEF included atrial fibrillation (odds ratio [OR] 2.14, 95% confidence intervals [CI] 2.02-2.28), history of implantable cardioverter-defibrilator (ICD) use (OR 1.39, 95% CI 1.32-1.46), COPD (OR 1.13, 95% CI 1.08-1.18), diabetes mellitus (OR 1.10, 95% CI 1.06-1.14), younger age (OR 0.96, 95% CI 0.95-0.97), lower blood pressure (OR 0.96, 95% CI 0.96-0.97), and having no history of renal insufficiency (OR 0.91, 95% CI 0.85-0.97). Use of digoxin in patients with HFpEF (n=138,140) without atrial fibrillation was 9.8% in 2005, which decreased to 2.2% in 2014 (Ptrend <0.0001). CONCLUSION. One in five HFrEF patients received digoxin at discharge, with significant downward temporal trend in use over the study period. Use of digoxin in HFpEF patients without atrial fibrillation was very low and decreased over the study period.

Roxadustat, a novel inhibitor of hypoxia-inducible factors for the treatment of anemia in chronic kidney disease

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Hypoxia-inducible factors are the key cellular response elements to changes in oxygen levels. Acting as transcription factors, these elements not only regulate the physiological response to oxygen demand and delivery, but also have been implicated in cardiovascular disease and malignancies (1). In the kidneys hypoxia-inducible factors activate the expression of erythropoietin in response to hypoxemia. Hypoxia-Indicible-Factor-Prolyl-Hydroxilase enzymes (HIF-PH) regulates the activity of hypoxia-inducible factors through initiation of proteasome mediated degradation.
The kidneys are the site of erythropoietin generation, which I n turn provides the signal to the bone marrow for erythropoiesis. The diminished response of this pathway in patients with chronic kidney disease is the major cause of chronic and progressive anemia in this patient population. Erythropoetin stimulating agents were a major breakthrough in the treatment of anemia of chronic kidney disease. An improvement in quality of life, and decrease in blood transfusion led to wide spread use. The more recent recognition of adverse outcomes has let to the quest for alternative agents. The hypoxia-inducible factors, and the HIF-PH enzymes have been recognized as potential targets (2).
In March 2014, the first patients were enrolled into a phase 3 clinical trial for a first in class oral treatment for anemia in chronic kidney disease (3). Currently, 8 multicenter international clinical trials are registered to study the effects of this novel oral inhibitor of HIF-PH enzymes, Roxadustat. If non inferiority in the treatment of anemia is demonstrate, this novel therapeutic class could tremendously simplify, and improve the care of patients with chronic kidney disease.

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How does your favorite patient-reported outcome instrument measure up? Current patient-reported outcome instruments for chronic heart failure and the United States Food and Drug Administration guidance

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PURPOSE: Patient-reported outcomes (PROs), including symptoms and their associated functional limitations, contribute substantially to heart failure (HF) patient morbidity. PRO measurements capture the patient perspective and are valuable therapeutic targets. They are recommended by HF guidelines and can be systematically assessed with structured questionnaires. PRO instrument selection by researchers, regulators and clinicians is guided by their individual conceptual and measurement properties, however strict requirements have been set by the United States Food and Drug Administration (FDA) regarding the acceptability of standardized PRO measures as a basis for product label-claims. The aim of this study was to evaluate the characteristics of existing PRO instruments used with chronic HF patients and their potential to support an FDA-approved product label-claim.

METHOD: Extensive searches of Embase/MEDLINE, clinicaltrials.gov, the PROQOLID database, conference abstracts, and specialty guidelines identified PRO instruments used in patients with chronic HF from January 2006 through May 2015. Information on critical properties of development and validation recommended by the FDA guidance were systematically extracted and used to evaluate the selected PRO instruments. Collected properties included documented content validity, the tested populations, mode of administration, recall periods, reproducibility, internal consistency, construct validity, ability to detect change, and presence of responder definitions.

RESULTS: This search identified 19 PRO instruments used with chronic HF patients from 2,552 articles and 2,334 conference abstracts. Every PRO instrument was either initiated or completely developed prior to the release of the draft or finalized FDA guidance in 2006 and 2009, respectively. The Kansas City Cardiomyopathy Questionnaire (KCCQ) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) were the most extensively evaluated and validated in studies of this population. Judged by criteria listed in the FDA PRO guidance, most identified PRO tools had multiple deficiencies, and no existing PRO measure met all of the criteria to support a product label-claim in the United States. The most common deficiencies were to content validity (often due to lack of documentation of patient input), the use of a non-preferred recall period (interpreted as longer than 1 day for symptoms or 1 week for symptom-related impacts), and absence of a proven responder definition.

CONCLUSION: Currently available chronic HF PRO measures do not fulfill all the requirements advised by the FDA PRO guidance and are therefore unlikely to support an FDA-approved product label claim, even though some appear to be suitable for evaluation of patient status, appraisal of therapeutic efficacy, and prognostication of outcomes in clinical and research settings. Future investigations are merited to develop a new PRO measure for use in patients with chronic HF in accordance with the FDA guidance.

Prognostic value of serial changes of high-sensitivity cardiac troponin I and T using reference change values among hemodialysis patients

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INTRODUCTION: Measurement of the biological variation of cardiac troponin (cTn) allows determination of reference change values (RCVs) to use for interpreting serial testing.
Using plasma collected serially over 12-months from a stable outpatient hemodialysis (HD) population, our goals were two-fold. First, we calculated RCVs for hs-cTnI and hscTnT assays. Second, we determined outcomes based on hs-cTnI and hs-cTnT RCVs.

METHODS: hs-cTnI (Abbott) and hs-cTnT (Roche) were measured in 677 stable outpatient HD patients (enrolled May 2011-November 2012). Hazard ratios (HR), based on RCVs calculated for each hs-cTn assay, for 'all-cause', 'sudden cardiac death (SCD)' and 'infectious' mortality were determined with serial measurements obtained 3 months apart.
Results. Patient demographics were: mean age 59±14y; mean dialysis duration 5.2±4.2y; 53% male; 59% African American and 50% diabetic ESRD. 18.6% of patients died during a 3-year follow-up. RCVs were: hs-cTnI, +37% and -30%; hs-cTnT, +25% and -20%. Patients with serial hs-cTnI and hs-cTnT changes >RCV had all-cause mortality of 25.2% and 23.8% respectively, compared to 15.0% and 16.5% with ≤RCV (both $p<0.05$). Outcomes and adjusted HRs are shown in Table. Patients with serial hscTnI and hs-cTnT changes >RCV showed a greater risk of all-cause mortality compared
to ≤RCV (HR: 1.9 (95% CI: 1.4, 2.8), p=0.0003; and HR: 1.7 (95% CI: 1.2, 2.4), p=0.0066; respectively). However, only hs-cTnI changes >RCV were predictive of SCD (HR: 2.6 (95% CI: 1.3, 5.1), p=0.005).

CONCLUSION: Our findings are unique in two ways. First we determined the biological variation of hs-cTnI and hs-cTnT in a large HD population. Second, based on the RCV for each hs-assay, serial changes in hs cTnI and hs-cTnT >RCV identify patients at greater risk of all-cause mortality, with hs-cTnI also predictive of SCD. These findings support the use of serial changes >RCV for risk-stratification in HD patients..

High-Sensitivity (hs)-cTn Assays		**Abbott hs-cTnI**			**Roche hs-cTnT**		
	All n=677	**≤RCV** n=439 (64.8%)	**>RCV** n=238 (35.2%)	***p* value** <0.0001	**≤RCV** n=484 (71.5%)	**>RCV** n=193 (28.5%)	***p* value** <0.0001
Outcomes							
All-cause mortality, n (%)	126 (18)	66 (15)	60 (25)	0.0012	80 (16)	46 (23)	0.0275
Sudden Cardiac Death (SCD), n (%)	35 (5.2)	16 (3.6)	19 (8.0)	0.0149	23 (4.8)	12 (6.2)	0.4369
Infectious death, n (%)	7(1.0)	5 (1.1)	2 (0.8)	0.7138	6(1.2)	1(0.5)	0.4021
Hazard Ratios (HR) adjusted for age, gender, race and dialysis duration							
		≤RCV	**>RCV**				***p* value**
Abbott hs-cTnI							
Adjusted HR for all-cause mortality		1.0 (reference)	1.9 (95% CI: 1.4, 2.8)				0.0003
Adjusted HR for SCD		1.0	2.6 (95% CI: 1.3, 5.1)				0.005
Adjusted HR for infectious death		1.0	0.674 (95% CI: 0.126, 3.610)				0.6451
Roche hs-cTnT							
Adjusted HR for all-cause mortality		1.0 (reference)	1.7 (95% CI: 1.2, 2.4)				0.0066
Adjusted HR for SCD		1.0	1.4 (95% CI: 0.7, 2.9)				0.316
Adjusted HR for infectious death		1.0	0.442 (95% CI: 0.052, 3.753)				0.4545

Hypertension control program in Argentina (HCPIA)

Authors: Jiang He. Tulane (University Health Sciences Center)
Co-authors: Adolfo Rubinstein
Organization: : Institute for Clinical Effectiveness and Health Policy.

BACKGROUND: Although the efficacy and effectiveness of lifestyle modifications and antihypertensive pharmaceutical treatment for the prevention and control of hypertension and concomitant cardiovascular disease and premature death have been demonstrated in randomized controlled trials, this scientific knowledge has not been fully applied in the general population, especially in low and middle income countries.

OBJECTIVES: To test whether a comprehensive intervention program within a national public primary care system will improve hypertension control among uninsured hypertensive patients and their families in Argentina

DESIGN: Cluster randomized trial

STUDY PARTICIPANTS: 1,888 study participants from 16 primary care clinics within a public primary care network in Argentina will be recruited. Patients with hypertension from the participating clinics, their spouses, and their adult hypertensive family members will be enrolled.

INTERVENTION: Eight clinics with approximately 944 participants will be randomly assigned to the comprehensive intervention group and 8 clinics with similar participants to the usual care group. The comprehensive intervention, including health care provider education, a home-based intervention among patients and their families (lifestyle modification and home blood pressure [BP] monitoring) delivered by community health workers, and a mobile health intervention, will last for 18 months.

OUTCOMES: BP and other indicators will be measured at baseline and months 6, 12, and 18 during follow-up using standard methods. The primary outcome is a net change in systolic (SBP) and diastolic BP (DBP) from baseline to month 18 between the intervention and control groups among hypertensive study participants. The secondary outcomes are the proportion of hypertensive patients with adequate BP control (BP<140/90 mmHg or <130/80 mmHg if patient has diabetes or CKD), net BP changes in normotensive participants, and cost-effectiveness.

An educational intervention to improve physician effectiveness in the detection, treatment and control for patients with hypercholesterolemia and high cardiovascular disease (CVD) risk in low-resource settings in Argentina (EPRINA)

Author: Adolfo Rubinstein
Co-authors: Pablo Gulayin, Vilma Irazola
Organization: : Institute for Clinical Effectiveness and Health Policy.

In Argentina, the National Risk Factor Surveys conducted by the Ministry of Health (MoH) indicate that between 2005 and 2009 the prevalence of hypercholesterolemia increased from 27.9% to 29.1%, whereas the rate of non-optimal LDL-C,is 28.0%. The rate of high cholesterol awareness is 37.3 and the percentage of those who are under pharmacological treatment is dismally low: only 11.1%. Furthermore, only one of every four subjects with a self-reported diagnosis of CHD is taking statins and most individuals with coronary heart disease (CHD) who are on statins have sub-optimal LDL-C levels. Until now, the MoH has provided drugs free-of-charge for the treatment of different cardiovascular risk factors. Nevertheless, statins have not been included to date in the list of covered drugs. As of 2014, statins (simvastatin) will be incorporated into the package of drugs provided free-of-charge for patients with high cholesterol, according to CVD risk stratification. The goal of this study is to test whether a multifaceted educational intervention targeting physicians improves detection, treatment and control of hypercholesterolemia among uninsured patients with moderate-high cardiovascular risk in Argentina.
This randomized cluster trial will enroll 350 patients from 10 public primary care clinics who will be assigned to receive either the intervention or the usual standard of care. The intervention program will target the public primary care system through clinician education for implementation of a Clinical Practice Guideline (CPG) to improve management of dyslipidemias. This study, strongly supported by the Argentine Lipid Society and the MoH, is timely and necessary to address CHD risk in vulnerable populations in Argentina.

Non-cardiovascular death in patients with impaired fasting glucose-insights from the NAVIGATOR trial

Authors: Abhinav Sharma, Flávio de Souza Brito, Jie-Lena Sun, Laine Thomas, Steven M. Haffner, Rury Holman, Renato D. Lopes
Organization: Duke Clinical Research Institute

BACKGROUND: Patients with impaired glucose tolerance (IGT) are at higher risk of cardiovascular mortality. The burden of non-cardiovascular (non-CV) death and the risk factors for non-CV death in these patients are not well defined.
Objectives: Using data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, causes of non-CV death and risk factors for non-CV death compared with CV death among patients with IGT were assessed.

METHOD: The NAVIGATOR trial was a double-blind, multicenter, multinational, placebo-controlled trial involving patients with IGT and CV disease or CV risk factors.

The primary outcome was to evaluate whether the use of nateglinide and valsartan could reduce the risk of new-onset diabetes and CV events in this population. Patients were randomized to treatment with nateglinide or placebo and valsartan or placebo in a 2x2 factorial design.
Subjects also received instructions about lifestyle intervention aimed at reducing body weight and dietary fat intake. A total of 9306 participants from 40 countries were randomized and followed for a median of 6.4 years. Valsartan reduced the risk of development of diabetes (relative risk reduction 14%, $p<0.001$) but did not reduce the risk of CV outcomes.
Non-CV death was defined as any death not due to a CV cause. Non-CV deaths were divided into 2 subgroups: (1) malignant deaths, and (2) non-malignant deaths. Deaths resulting directly from cancer, a complication of cancer (e.g., infection, complication of surgery, chemotherapy, or radiotherapy), or withdrawal of other therapies because of concerns relating to poor prognosis associated with cancer were classified as malignant deaths. Deaths not attributable to a CV or non-CV cause were classified as undetermined.

As the adjudication process primarily differentiated CV from non-CV death, for this analysis, we combined non-CV death and undetermined causes of death for analysis. Fifty-four variables collected at baseline, including demographics, clinical measurements, medical history, laboratory results, and investigator-reported electrocardiogram were tested. Using data from adjudicated causes of death, Cox proportional hazards regression models were developed to identify the prognostic risk factors associated with CV and non-CV death (which included undetermined causes of death). Variables were selected for inclusion by forward selection with alpha<0.05. Covariates were tested for linearity and non-linear relationships were handled by fitting linear splines. The proportional assumption was satisfied for all covariates.
A sensitivity analysis was performed to assess model results if CV death and undetermined cause of death were combined compared with non-CV cause of death.

RESULTS: 9306 patients were randomized in the NAVIGATOR trial (median follow-up 6.4 years). A total of 622 subjects died during the NAVIGATOR trial follow-up. 244 (39.2%) were CV deaths, 322 (51.7%) were non-CV deaths, and 56 (9%) were of undetermined causes.
Patients who died were significantly older, male, and smokers. They also had more ECG alterations, renal dysfunction, chronic obstructive pulmonary disease, and atrial fibrillation/flutter when compared with survivors. Non-CV death comprised 52% of all-cause mortality.

Of these patients who died of non-CV causes, 190 (31% of all-cause mortality; 59% of non-CV mortality) were deemed to be associated with malignancy. Several risk factors were independently associated with non-CV death: body mass index (BMI) above 35 kg/m2 (HR 1.05; 95% CI 1.01–1.10), presence of non-melanoma skin cancer (HR 2.38; 95% CI 1.53–3.70), increased white blood cell count (per 1 unit above 5.0×109/L; HR 1.09; 95% CI 1.02–1.17), and increased potassium level (per 1mmol/L above any value; HR 1.59; 95% CI 1.26–2.0). Independent risk factors for CV death included: atrial fibrillation/flutter (HR 1.78; 95% CI 1.21–2.60); cerebrovascular (HR1.71; 95% CI 1.22–2.39), coronary (HR 2.09; 95% CI 1.57–2.79), and peripheral artery disease (HR 1.66; 95% CI 1.08–2.55); renal dysfunction (HR 1.88; 95% CI 1.03–3.41); and all regions (other than Asia, Europe, Latin American) versus North America (HR 2.23; 95% CI 1.17–4.25).

CONCLUSION: In patients with IGT and CV risk factors, non-CV etiologies are the most common causes of death. Among this group, malignancy was the most common cause of death. Future studies will have to identify strategies to risk stratify patients with IGT with regards to causes specific death in order to initiate appropriate medical screening and interventions.

Towards skeletal muscle and fat mass estimates as potential surrogate endpoints in clinical trials

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Co-Authors: J. Lenk, H.-D. Düngen, A. Stahn, Edelmann F, Pieske B.
Organization: Charité - Universitätsmedizin Berlin

Background: New therapeutic compounds target obesity, cachexia, sarcopenia, and other body composition (BC) imbalances in Heart Failure (HF) patients. To date, clinical trials assess BC based on body weight, body mass index and waist-to-hip-ratio. Yet, thorough non-invasive and feasible approaches for surrogate endpoint assessment are becoming increasingly important. The present study compares BC assessments by basic anthropometry, dual energy x-ray absorptiometry (DXA), bioelectrical impedance spectroscopy (BIS), and air displacement plethysmography (ADP) for the estimation of Fat (FM) and Fat Free Mass (FFM) in a HF population.

METHODS AND RESULTS: In this prospective, single-centre, observational, non-interventional pilot study we enrolled 52 patients with HF [33 HF with reduced ejection fraction (HFrEF), 19 HF with preserved ejection fraction (HFpEF); mean age was 67.7±9.9 y, 41 male] and 20 healthy controls. Left ventricular ejection fraction was 31.6±7.2 %, left atrial diameter was 45.8±7.5 mm in HFrEF and 58.2±5.3 % and 43.8±2.7 mm in HFpEF patients. DXA was used as a reference standard for the measurement of FM/FFM. In the HF population, linear regression for DXA-FM and waist-to-hip-ratio [r=-0.05 (CI -0.32 to 0.23)], BMI [r=0.47 (CI 0.23 to 0.669)], and Body Density [r=-0.87 (CI -0.93 to -0.87)] was obtained. In HF, Lin's concordance correlation coefficient of DXA-FM[%] with ADP-FM[%] was 0.76 (95% CI 0.64 to 0.85) and DXA-FFM[kg] with DXA-ADP[kg] was 0.93 (95% CI 0.88 to 0.96. DXA-FM[%] for BIS-FM[%] was 0.69 (95% CI 0.54 to 0.80) and 0.73 (95% CI 0.60 to 0.82) for DXA-FFM[kg] and BIS-FFM[kg].

CONCLUSION: In this study we compare four common methods of BC assessment in a typical, well-characterized HF population. Compared to established anthropometric indices (BMI/WHR), body density is a promising surrogate for FM. ADP was found capable for estimating FM[%] and convincing for FFM[kg] in HF patients. BIS showed mixed, but especially for the estimation of FM[%] in HFrEF and for FFM[kg] in HFpEF patients, acceptable results. Based on our findings, we encourage the use of ADP for BC assessments, while BIS may be considered to complement currently established anthropometric indices. Future clinical trials focusing on BC surrogate endpoints may benefit from the presently studied methods

Efficacy and safety of Edoxaban in 4681 patients with atrial fibrillation enrolled in North America

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Organization: Columbia University Medical Center

PURPOSE: Both dose regimens of edoxaban (higher-dose edoxaban [HDE] 60/30mg and lower-dose edoxaban 30/15mg) were non-inferior to warfarin and significantly reduced bleeding in the ENGAGE AF-TIMI 48 trial. Geographic variability in the outcome of trials with antithrombotic therapies has been previously reported and explained by possible regional differences in patient characteristics and practice patterns. We report here outcomes in ENGAGE AF-TIMI 48 in North America (NA).

METHODS: Patients enrolled in the US and Canada were considered NA patients (N=4681); and all others classified as non-NA (N=16424). The primary efficacy endpoint was stroke or systemic embolic events (SEE) and principal safety outcome was ISTH major bleeding. We report outcomes for HDE vs. warfarin in NA.

RESULTS: NA patients were significantly older (mean age NA 73 vs non-NA 70 yrs), had higher CHA2DS2-VASc (74 vs 70% with score >4) and HAS-BLED (56 vs 44%, score >3), and more likely to have CrCl < 50 ml/min (22 vs 19%) (each P<0.001). They were more likely to have had prior revascularization (25 vs 9%), be on aspirin at baseline (38 vs 27%), and be VKA experienced (76 vs 54%) (each P<0.001). The median TTR with warfarin was 73% in NA (vs 67% in non-NA, P=0.11). In NA, the HR for HDE vs warfarin for stroke/SEE was 0.55 (95%CI 0.33-0.92) on treatment. Directionally similar effects with HDE were seen for hemorrhagic stroke (HR 0.38 [0.15-0.97]) and ischemic stroke (HR 0.65 [0.35, 1.22]). Major bleeding in NA was similar between HDE and warfarin (HR 0.91 [0.72-1.15]) as was the net clinical outcome (HR 0.82 [0.68-0.98]). See Figure for definitions and additional outcomes. Results in non-NA were qualitatively similar (all P-int >0.05). Results in US (N=3904) and Canada (n=777) will be detailed.

CONCLUSIONS: Despite higher risks of stroke and bleeding, patients treated with HDE had favorable efficacy and safety results with better net outcome compared to well-managed warfarin with a median TTR of 73% in NA.

Patiromer lowered serum potassium for up to 1 year in hyperkalemic patients with diabetes and advanced kidney disease on RAAS inhibitors

Authors: George Bakris[1], Bertram Pitt [2], Matthew Weir[3], Martha Mayo[4], Dahlia Garza[4], Yuri Stasiv[4], Rezi Zawadzki[4], Daniel Wilson[4], Lance Berman[4], David A. Bushinsky[5]

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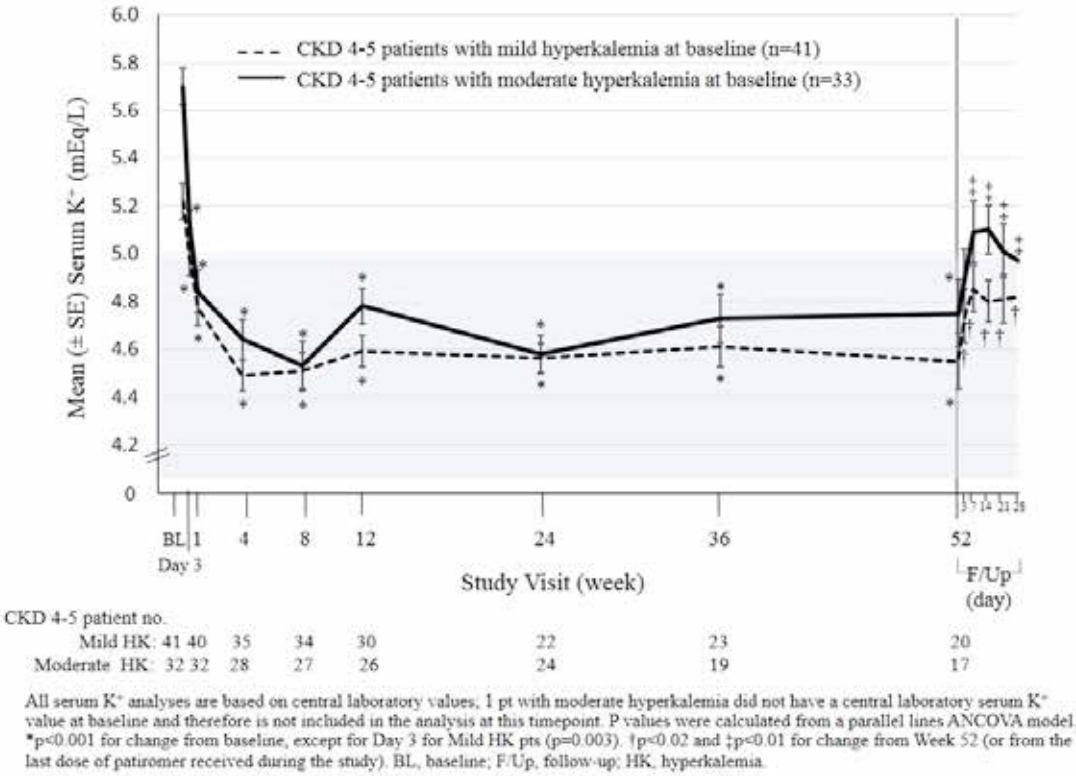
BACKGROUND: Diabetes is a well-recognized risk factor for chronic kidney disease (CKD) and the co-occurrence of CKD in diabetes confers an even higher risk of poor outcomes. Guidelines recommend renin-angiotensin-aldosterone (RAAS) inhibitors to slow the progression of diabetic kidney disease (DKD), however patients with DKD are at high risk for hyperkalemia, which may limit or prevent RAAS inhibitor use. Currently available potassium (K+)-binding agents for hyperkalemia treatment are generally poorly tolerated, which may limit long-term use. AMETHYST-DN evaluated the novel agent patiromer, the active moiety of which is a nonabsorbed potassium (K+)-binder, in a 1-yr trial of patients with diabetes and CKD on RAAS inhibitors. In this post hoc subanalysis, we report the results of long-term patiromer therapy in patients with advanced CKD (stages 4-5).

METHODS: Advanced CKD patients had diagnosed diabetes (mean, 14 yr) and median urine albumin-to-creatinine ratio (ACR) of 632 mg/g at baseline. Patiromer induced significant ($p<0.01$) reductions in mean serum K+ in these patients at the first post-baseline assessment, 48 hr after the first dose, from baseline means of 5.2 mEq/L (mild hyperkalemia) and 5.7 mEq/L (moderate hyperkalemia). Similar effects were observed across starting dose groups. In advanced CKD patients mean serum K+ was controlled (≤5.0 mEq/L) at 48 hr (mild hyperkalemia) and at Week 1 (moderate hyperkalemia) and maintained for 52 weeks. Cessation of patiromer treatment led to a rise in mean serum K+. Of the randomized advanced CKD patients, 56% completed the trial (the most common reasons for early withdrawal were consent withdrawal [13.3%] and adverse event [9.3%]). Constipation was the most common gastrointestinal adverse event (9.5%, none severe; led to discontinuation in 1 [1.4%] patient). Six patients (8.1%) had serum K+ <3.5 mEq/L (none <3.0 mEq/L) and 3 (4.1%) had serum Mg <1.2 mg/dL (none <1.0 mg/dL).



All serum K+ analyses are based on central laboratory values; 1 pt with moderate hyperkalemia did not have a central laboratory serum K+ value at baseline and therefore is not included in the analysis at this timepoint. P values were calculated from a parallel lines ANCOVA model. *$p<0.001$ for change from baseline, except for Day 3 for Mild HK pts ($p=0.003$). †$p<0.02$ and ‡$p<0.01$ for change from Week 52 (or from the last dose of patiromer received during the study). BL, baseline; F/Up, follow-up; HK, hyperkalemia.

CONCLUSION: Chronic treatment with patiromer in hyperkalemic patients with advanced DKD receiving RAAS inhibitors was well tolerated and maintained serum potassium ≤5.0 mEq/L for up to 1 yr. Serum K+ monitoring may be required after patiromer discontinuation.

Wide range in variation in serum potassium in hyperkalemic patients with ckd, response to a fixed 60 mEq potassium diet

Authors: David Bushinsky[1] Martha Mayo[2] Dahlia Garza,[2] Yuri Stasiv,[2] Daniel Wilson,[2] Charles Du Mond,[2] Lance Berman,[2] Murray Epstein[3]

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BACKGROUND: Serum K (s-K+) levels are affected by diurnal variation, fasting/feeding cycles, and medications. In this study we characterized the differences in inter-individual variation in s-K+ on a random diet prior to entry and the effect of a controlled K+ diet on s-K+ levels in hyperkalemic (HK) pts with CKD (stage 2-4) on stable doses of RAASi, during the run-in phase of a treatment trial.

METHODS: A total of 27 pts with s-K+ ≥5.5 to ≤6.2 mEq/L were monitored in a clinical research unit. At baseline pts were fed a 60 mEq K+, 100 mEq Na+ diet. S-K+ was measured at baseline and at prespecified intervals for the next 72 h. We calculated individual difference (maximum-minimum) in s-K+ at each time point for the remaining observation period to determine variation in s-K+.

RESULTS: Mean s-K+ at baseline was 5.86±0.22 mEq/L and rose to 5.94±0.17 mEq/L at 72 h following the start of the fixed K+ diet. Over 72 h, 6/27 pts had "low" (0.0–0.2 mEq/L), 9/27 "moderate" (0.3–0.4 mEq/L), and 12/27 "high" (0.5–1.1 mEq/L) variation in s-K+. Variation in s-K+ decreased at each time point over the 72-h period of observation on the controlled diet (Table).

Table. Variation in s-K^+ (max-min) over 72 h during run-in on a 60 mEq K^+ diet, n=27

Time	baseline	+10 h	+24 h	+36 h	+ 48 h	+62 h	+71 h
Mean±SD Δ in s-K^+, mEq/L	0.44± 0.24	0.42± 0.24	0.39± 0.24	0.34± 0.24	0.29± 0.21	0.15± 0.12	0.12± 0.09
P-value*	-	0.0830	0.0027	0.0001	0.0001	<0.0001	<0.0001

*Comparing values from baseline to values at +10, +24, +36, +48, +62 and +71 h via paired t-test with Bonferroni correction (α=.05; P ≤0.0083 is significant).

CONCLUSIONS: A wide range of inter-individual variation in s-K+ occurred in HK pts with CKD on RAASi who were on an uncontrolled diet prior to entry. Variation decreased significantly after 24 h on a 60 mEq K diet. These findings have implications for management of pts with HK and CKD, and for interpreting clinical trials assessing directional change in s-K+ with an intervention

Chronic diuretic therapy does not impair the effectiveness of patiromer in hyperkalemic patients with CKD

Authors: Matthew Weir[1], Martha Mayo[2], Dahlia Garza[2], Yuri Stasiv[2], Susan Arthur[2], Lance Berman[2], David Bushinsky[3], Daniel Wilson[2], Murray Epstein[4]

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BACKGROUND: Loop diuretics control volume in advanced CKD and may reduce elevated serum K+, but can induce intravascular volume depletion or gout and may not be ideal for long-term hyperkalemia (HK) management. Thus, the efficacy of investigational serum K+ binders in HK pts on chronic diuretics is of interest. We compared

patiromer's effects in RAASi-treated CKD pts with HK on diuretics to those not on diuretics in the treatment phase of the 2-part OPAL-HK study.

METHODS: Pts (n=243) with baseline (BL) s-K+ 5.1 to 6.5 mEq/L on RAASi received patiromer (4.2 or 8.4 g BID to start) for 4 wks. For this post hoc analysis, Δs-K+ from BL to wk 4 was assessed in pts stratified by diuretic use and type. Pts (n=22) receiving aldosterone antagonists were excluded.

RESULTS: Mean (SD) age was 64 (10.5) yr; 58% were male. Mean s-K+ decreased from BL at wk 4 in all subgroups (Table). Reductions in s-K+ did not differ in pts receiving any diuretic vs those not on diuretics. Patiromer was well tolerated; mild–moderate GI constipation was the most common AE. Hypokalemia (s-K+<3.5 mEq/L) was infrequent.

Table: Efficacy, safety, and disease characteristics in pts on patiromer ± diuretics[a]

	Loop (n=51)	Thiazide/ T-like (n=51)	Combination Loop/thiazide (n=15)	Any diuretic (n=117)	No diuretic (n=104)
BL					
HF, %	49.0	25.5	66.7	41.0	32.7
S-Creatinine Mean±SD (mg/dl)	2.4±0.9	2.0±0.8	2.0±0.7	2.2±0.8	2.1±1.2
Mean±SE BL s-K^+, mEq/L	5.61±0.06	5.58±0.07	5.67±0.13	5.58±0.04	5.57±0.05
Wk 4					
Mean±SE Δ s-K^+ BL to wk 4 (95% CI), mEq/L [p-value]	−1.02±0.06 (−1.14, −0.89) [<0.001]	−0.97±0.06 (−1.09, −0.86) [<0.001]	−0.69±0.19 (−1.11, −0.28) [0.0037]	−0.95±0.05 (−1.04, −0.86) [<0.001]	−1.03±0.05 (−1.13, −0.93) [<0.001]
Hypokalemia, %	2.0	0	6.7	1.7	3.9

[a]6 pts without a s-K^+ value at a weekly visit after day 3 were excluded.

CONCLUSIONS: The s-K+-lowering efficacy of patiromer in HK pts was unaffected by concomitant diuretics.

Patiromer reduced serum K+ in hyperkalaemic patients with HF and advanced CKD on RAAS inhibitors: Results from OPAL-HK and AMETHYST-DN

Authors: Bertram Pitt[1], Mathew Weir[2], David A. Bushinsky[3], Martha Mayo[4], Dahlia Garza[4], Yuri Stasiv[4], Charles Du Mond[4], Lance Berman[4], George Bakris[5]

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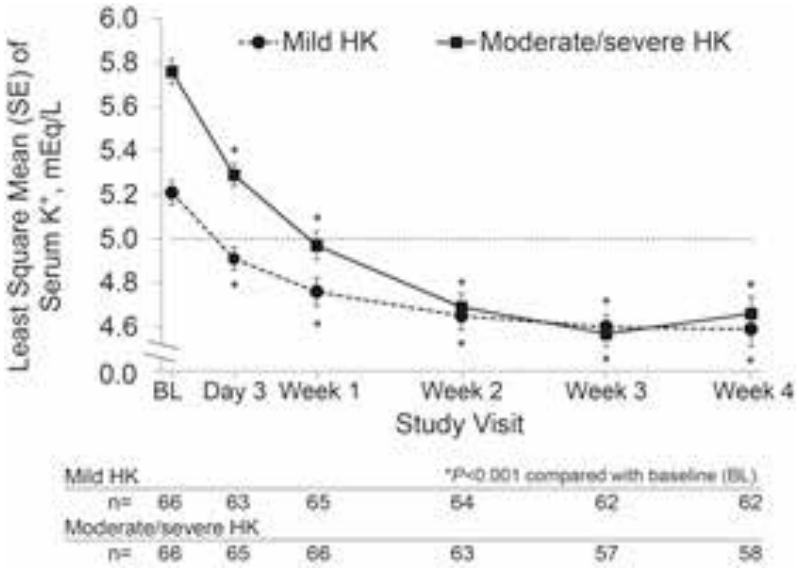
INTRODUCTION: RAAS inhibitors (RAASi) reduce mortality in patients (pts) with HF ± CKD, yet hyperkalaemia (HK) can limit RAASi use in these pts. We evaluated the effect of patiromer, a novel investigational K+ binder, on serum K+ (s-K+) in HK pts with HF and advanced CKD on RAASi.

METHODS: OPAL-HK (OP) was a 12-wk, 2-part, randomised, single-blind study; AMETHYST-DN (A-DN) was a 52-wk, randomised, open-label study. Eligible pts had eGFR 15-59, were on ≥1RASSi and, in A-DN, had T2DM; pts with NYHA class 4-5 HF were excluded. Entry s-K+ was 5.1-<6.5 mEq/L (OP) and >5.0-<6.0 mEq/L (A-DN). In a posthoc subgroup analysis, efficacy data were pooled over the 1st 4 wk in pts with HF and stage 3b-5 CKD and

analysed for s-K+ change from baseline (1° endpoint) by s-K+ strata: >5.0-5.5 (mild) and >5.5-<6.0 mEq/L (mod/severe) in A-DN; 5.1-<5.5 (mild) and 5.5-<6.5 mEq/L (mod/severe) in OP.

RESULTS: Of HF pts with advanced CKD, 66 had mild and 66 had mod/severe HK. Pts were primarily male (~60%) and ≥65 yr (62%); mean±SD eGFR was 29±10 in mild and 27±9 mL/min/1.73m2 in mod/severe pts. With patiromer mean s-K+ was reduced to <5.0 mEq/L by the first post-baseline visit (Day 3) in mild HK and by wk 1 in mod/severe HK pts and continued to improve (Fig).



By wk 4, mean (95% CI) s-K+ change from baseline was -0.62 mEq/L (0.74, 0.50) in mild HK and -1.13 mEq/L (-1.28, -0.97) in mod/severe HK pts; both P<0.001. One pt developed s-K+ <3.5 mEq/L through wk 4. AEs were predominately mild-to-moderate GI complaints; AEs led to patiromer discontinuation in 6 pts in each study over the entire study period.

CONCLUSIONS: Patiromer significantly reduced s-K+ in HK patients with HF and advanced CKD over 4 wk. If approved, patiromer may be an option for HK treatment in pts with HF and advanced CKD.

Prognostic value of chronotropic incompetence in heart failure patients with low peak VO2

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INTRODUCTION: Chronotropic incompetence worsens as heart failure (HF) progresses. Previously, we have shown that percent heart rate reserve (percent-HRR) as a marker of chronotropic incompetence was equivalent to peak VO2 in predicting poor outcomes in patients with heart failure. However, the prognostic value of percent-HRR in patients with advanced heart failure defined as peak VO2<14 ml/kg/minute and left ventricular ejection fraction (LVEF) below 30% is unknown.

Methods: HF patients with NYHA class 2 or 3, in sinus rhythm, on stable medical therapy that underwent cardiopulmonary exercise (CPX) test between January 2011 and January 2015 at Montefiore Medical Center were studied. In a subgroup analysis, we evaluated the effect of chronotropic incompetence in patients with advanced HF defined as peak VO2<14 ml/kg/minute and LVEF below 30%. Percent-HRR was defined as (maximal HR achieved-resting HR)/ (maximum predicted HR-resting HR). A percent-HRR of below 45% was considered a marker for chronotropic incompetence. All patients were followed for heart failure hospitalization (HFH) or the combined end point of left ventricular assist device (LVAD) implantation, cardiac transplant or cardiac death.

Results: 83 patients met the inclusion/exclusion criteria. Baseline characteristics for the overall cohort: median age 57(51-67) years, 22 (26.51%) females, median BMI of 30.4(27.8-32.3) kg/m2, 42(50.60%) diabetes, 29 (34.94%) ischemic cardiomyopathy, 62(74.70%) NYHA class III. 100% were on beta-blockers, 75.90% on ACEI/ARBs. Baseline CPX

parameters: maximal peak VO2 of 11.2(9.7-12.5) ml/kg/minute, RER of 1.07(0.98-1.14), resting HR of 71(65-81) and maximal HR of 100(90-115) beats/minute.

There were 19 patients with percent-HRR ≥ 45% and 64 with < 45%. Over a median follow up of 16.4(4.5-28.1) months, 47 (56.63%) patients were hospitalized for heart failure and 22 (26.51%) reached the combined end point of LVAD implant, cardiac transplant or cardiac death. In survival analysis with cox proportional hazards model, percent-HRR below 45% was associated with an increased risk of HFH (cox-HR= 2.37, 95% CI: 1.10-5.12, p=0.028) and increased risk for the combined primary end point (cox-HR= 4.83, 95% CI: 0.99-23.5, p=0.051). Both relationships were true even after adjusting for age, gender, BMI, NYHA class, peak VO2 and LVEF.

Conclusions: Percent-HRR is an important predictor of adverse outcomes in heart failure and has important prognostic value even in advanced HF patients with already low peak VO2 and LVEF as well.

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  Chairpersons: Cheuk-Man Yu (Hong Kong), Toon-Wei Lim (Singapore), Chi-Keong Ching (Singapore)
- **Interventional Cardiology Trials**
  Chairpersons: Rosli Mohd Ali (Malaysia), Jack Tan (Singapore), Huay-Cheem Tan (Singapore)
- **Optimizing Clinical Trials in Asia Pacific**
  Chairpersons: Adrian Hernandez (US), Martin Cowie (UK), Khung Keong Yeo (Singapore)

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Middle East CardioVascular Clinical Trialists Forum

In Collaboration with
Gulf Heart Association

14-15 APRIL 2016

Dusit Thani Hotel, Abu Dhabi, United Arab Emirates

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Course directors

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Dr Wael Al-Mahmeed, MD
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GENERAL INFORMATION

CONGRESS VENUE

Embassy of France, 4101 Reservoir Rd NW, Washington D.C. 20007, USA

SCIENTIFIC SECRETARIAT

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REGISTRATION FEE

CVCT 2015 - Registration rates	ONSITE
CVCT Academia	$500,00
Only for doctors, physicians, clinicians or statisticians. This discount cannot be applied to industy	
CVCT Junior	$150,00
Trainee, assistant, junior.	
CVCT R&D partners	$1 100,00
Only R&D official partner companies of the event are permitted to register to the preferential rate mentioned above.	
CVCT Industry	$5 500,00
Staff of pharmaceutical and device companies who wish to participate in the CVCT and debate about the latest clinical trials are most welcome.	

REGISTRATION FEE

CVCT 2015 - Registration rates ONSITE
Participant registration fee includes

- Access to all scientific sessions
- Access to the Clinical Gathering Space
- Congress materials
- Lunches on 3, 4, 5 December 2015
- Daily coffee breaks
- Networking Reception on 4 December 2015 on invitation only. Please ask as the congress desk.

Opening hours of the welcome desk

- Thursday 3 December, 11.00pm-7.00pm
- Friday 4 December, 7.30am-6.00pm
- Saturday 6 December, 7.30am-6.00pm

CLINICAL GATHERING SPACE

The clinical gathering space, located in the Foyer, will showcase the latest results and findings of ongoing clinical trials.

OFFICIAL LANGUAGE

The official language of the meeting is English.

TRANSPORT

Event: 12TH GLOBAL CARDIOVASCULAR CLINICAL TRIALISTS FORUM
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