CVCT WASHINGTON, DC US

Maison Française, French Embassy

11th Global Cardio Vascular Clinical Trialists Forum

Course Directors:

Faiez ZANNAD, Nancy - FRA, Bertram PITT, Ann Arbor - USA

FINAL PROGRAM

DECEMBER 2014

FRIDAY 5 - SUNDAY 7

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GENERAL PRESENTATION

11th Global Cardio Vascular Clinical Trialists Forum

CVCT WASHINGTON, DC US

Participatory design or cooperative design is "an approach to design attempting to actively involve all stakeholders in the design process in order to help ensure the product designed meets their needs and is usable". The term is used in a variety of fields e.g. software design, urban design, architecture, landscape architecture, product design, sustainability, graphic design, planning or even medicine as a way of creating environments that are more responsive and appropriate to their inhabitants' and users' cultural, emotional, spiritual and practical needs.

Over the last 10 years, the Global CardioVascular Clinical Trialists Forum has aimed to provide a platform for engaging stakeholders to evaluate current and future clinical trial designs in cardiovascular medicine therapeutics (both pharma and devices), actively involving PIs, trialists, industry R&D, regulators (FDA, EMA, PMDA), institutions (NHLBI, EU FP, H2020, Inserm), journal editors (NEJM, The Lancet, Circulation, JACC, EHJ), learned societies (ACC, ESC, HFSA, ASN, EACPT, ISCP), analysts, CROs, payers, practitioners, patients and citizens.

All stakeholders are invested in these important discussions. Regulators are keen to learn from academy and industry are just desperate to find out the right answer in order to address the unmet need when it comes to the clinical need but also to satisfy the regulators.

This year, for the first time, CVCT is held in Washington, DC, home of our important partners in clinical trials, i.e. **FDA, NHLBI, ACC, HFSA, ASN** and other partners.

In order to keep up with the traditional CVCT French Touch, the venue of the meeting is the "La Maison Française" at the **French Embassy** in Georgetown, Washington, DC, thanks to support from His Excellence, The French Ambassador to the USA and the scientific attaché of Inserm.

A lot has happened in the field of clinical trials over the last 10 years.

Where initial CVCT programs tackled drug therapy trials and classical design features, in recent years new developments have resulted in a diversification in content addressed at the meeting.

We have noted a slowing down of innovation in drugs and an increase in innovations taking place in biologics, implantable devices, biomarkers and remote monitoring.

In addition to fresh thoughts brought to CVCT by device and biologics trials, more classical areas on drugs remain high on the program, in particular heart failure, diabetes, anti-coagulants, atherosclerosis and biomarkers.

We are delighted to welcome you to Washington, DC, for our first CVCT Forum held in the US. We encourage you to engage actively in this open debate and we look forward to a lively exchange of ideas.

Pr Faiez Zannad *Dr Bertram Pitt*

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- **American College of Cardiology (ACC):** Henry Solomon (Washington, DC, USA), Deepak Bhatt (Boston, USA)
- **American Society of Nephrology (ASN):** Murray Epstein (Miami, USA)
- **CardioRenal Clinical Trialists (CRCT):** Patrick Rossignol (Nancy, FRA)
- **Duke University:** Christopher O'Connor (Durham, USA)
- **Editors:** John Jarcho (NEJM, Boston, USA), Stuart Spencer (The Lancet, London, UK)
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Summary

SCIENTIFIC PROGRAM

PROGRAM AT-A-GLANCE

DAY 1 – **FRIDAY 5 DECEMBER 2014**

	8.30 am - 10.30 am	COFFEE BREAK	11.00 am - 1.00 pm	LUNCH BREAK	1.30 pm - 4.30 pm	COFFEE BREAK	5.00 pm - 6.00 pm	6.30 pm
BALLROOM	STREAMLINING TRIALS		STREAMLINING TRIALS cont.		NEW DRUGS AND FUTURE TRIALS IN HEART FAILURE OPTIMIZING TRIAL DESIGN TO PUTATIVE MECHANISM OF ACTION		NEW DRUGS AND FUTURE TRIALS IN HEART FAILURE OPTIMIZING TRIAL DESIGN TO PUTATIVE MECHANISM OF ACTION cont.	
THEATRE	THROMBOSIS		THROMBOSIS cont.		HYPERKALEMIA		KEYNOTE CVCT DEBATE	KEYNOTE LECTURE

DAY 2 – **SATURDAY 6 DECEMBER 2014**

	8.00 am - 10.00 am	COFFEE BREAK	10.30 am - 11.30 am	11.30 am - 1.00 pm	LUNCH BREAK	1.30 pm - 3.00 pm	COFFEE BREAK	3.30 pm - 6.30 pm
BALLROOM	EXPEDITED TRIALS		EXPEDITED TRIALS cont.	BIOLOGICS		BIOLOGICS cont.		ATHEROS-CLEROSIS
THEATRE	DIABETES		DIABETES cont.	RENAL DENERVATION/ MODULATION		RENAL DENERVATION/ MODULATION cont.		PARADIGM

DAY 3 – **SUNDAY 7 DECEMBER 2014**

	8.30 am - 10.30 am	COFFEE BREAK	11.00 am - 12.00 noon
BALLROOM	PULMONARY HYPERTENSION		PULMONARY HYPERTENSION cont.
THEATRE	POLYPILL		POLYPILL cont.

CVCT WASHINGTON, DC US

FRIDAY 5 DECEMBER 2014

BALLROOM

8.30 am - 1.00 pm
STREAMLINING CLINICAL TRIALS
CVCT – NHLBI – EU joint session

Moderators: Michael Lauer (NHLBI, USA), Aldo Maggioni (Florence, ITA)

- Drug regulatory agencies should ensure that the benefits of drugs outweigh their risks, but licensed medicines sometimes do not perform as expected in everyday clinical practice. Gaps may relate to lower than anticipated efficacy or a higher than anticipated incidence or severity of adverse effects. The problem of benefit–risk is to a considerable degree a problem of variability in drug response. Biological and behavioral variability as well as geographical and health care system variability contribute to the efficacy–effectiveness gap.
- Wider use of electronic medical records generates big data that are being increasingly used in streamlined prospective clinical trials as well as in registry and observational studies. Results are offered as hypothesis generating or as assessments of effectiveness, occasionally challenging the results of clinical trials, and hopefully complementing these results.
- Still, implementation is an issue. Industry sponsors seem reluctant to take advantage of innovative designs, even when regulators are endorsing innovative approaches, maybe because of valuing predictability more than cost saving. It is timely to discuss a way forward.

Future of clinical research and the ripple effect of big data
Robert Califf (Durham, USA)

Embedding trials in existing longitudinal cohorts: pitfalls and challenges
Denise Bonds (NHLBI, USA)

Is it possible to randomize at point of care, have no study visits?
Lou Fiore (Jamaica Plain, USA)

Group randomized trials and other streamlined protocols
Speaker: Yves Rosenberg (NHLBI, USA)
Discussant: Jerry Menikoff (FDA, USA)

Methodological issues in analyzing big data
Speaker: David Madigan (Columbia, USA)
Discussant: Nevine Zariffa (AstraZeneca, USA)

Interaction between regulatory and DSMBs during the conduct of a trial
Jeffrey Borer (New York, USA)

What are academic/government institutions doing to help with registries, streamlining clinical trials, using big data?

- **NIH's perspective on streamlining trials -** Catherine Meyers (NIH/NCCAM, USA)
- **EU -** Virginija Dambrauskaite (EC, BEL)
- **ESC -** Aldo Maggioni (Florence, ITA)
- **ACC -** Deepak Bhatt (Boston, USA)

How useful are registries, streamlined clinical trials and big data to regulatory bodies?

- **FDA -** Robert Temple (FDA, USA)
- **EMA -** Gonzalo Calvo (Barcelona, ESP)

Major journals' editorial perspective:

- **The Lancet -** Stuart Spencer (London, UK)
- **NEJM -** John Jarcho (Boston, USA)
- **JAMA -** Robert Golub (Chicago, USA)
- **Circulation -** Marc Pfeffer (Boston, USA)

Moderated discussion with audience participation

Panelists: Deepak Bhatt (Boston, USA), Denise Bonds (NHLBI, NIH, Bethesda, USA), Jeffrey Borer (New York, USA), Robert Califf (Durham, USA), Gonzalo Calvo (Barcelona, ESP), Virginija Dambrauskaite (EC, BEL), Lou Fiore (Jamaica Plain, USA), Robert Golub (Chicago, USA), John Jarcho (Boston, USA), Michael Lauer (NHLBI, USA), Lars H Lund (Stockholm, SWE), David Madigan (Columbia, USA), Aldo Maggioni (Florence, ITA), Jerry Menikoff (FDA, USA), Catherine Meyers (NIH/NCCAM, USA), Marc Pfeffer (Boston, USA), Yves Rosenberg (NHLBI, USA), Tabassome Simon (Paris, FRA), Stuart Spencer (London, UK), Robert Temple (FDA, USA), Andrew Zalewski (GSK, USA), Nevine Zarifa (AstraZeneca, USA)

THEATRE

8.30 am - 1.00 pm
THE THROMBOSIS TRIALISTS WORKSHOP

Moderators: Roxana Mehran (New York, USA), Lars Wallentin (Uppsala, SWE)

- New antiplatelets and new anticoagulants are at the helm of a golden age. NOAC trials have accumulated a sizeable level of evidence with 73,000 patients in the 4 AF trials alone, and around 20,000 in the VTE trials and are life-saving therapies after ACS.
- Among big issues is how to get physicians and patients to do the right thing--keep taking the drugs and at doses that optimize clinical outcomes.
- Whether optimizing therapy should generally involve monitoring, even if you can beat standard therapy without it, is another issue that may merit specific trial designs.
- Although prasugrel is an effective and relatively safe agent in the invasive management of ACS, will comparative effectiveness and/or registry data better inform on whether we should refrain from giving it upfront before the cathlab, or from giving it late in patients on clopidogrel? Or is ticagrelor the better choice for all options in ACS?
- Duration of therapy, combination strategies and where new therapy might fit within the current antiplatelet armamentarium is a new matter of debate.
- Approvability issues were raised recently with occasionally divergent decisions among major agencies.

  Is the bleeding not too heavy? Regulatory agencies across the Atlantic differ in their interpretation of the available data. Are more trials needed?
- Antidotes are the big challenge, how to study a rare event, but even more challenging is how to get regulatory approval of a rare event.
- But do we need an antidote, since all trials show a reduction in fatal bleeding when compared to warfarin, where we do have adequate antidote and bridging therapies?

Prasugrel or Ticagrelor in ACS? A case study on how trial, comparative effectiveness and registry data may be used in conjunction, short of a head-to-head comparison.
Lars Wallentin (Uppsala, SWE)

Cangrelor: how to use it? Why was it not approved?
Speaker: Michael Gibson (Boston, USA)
Discussant: Freek Verheugt (Amsterdam, NED)

Bivaluridin trials in PPCI: has the dust settled?
Speaker: Roxana Mehran (New York, USA)
Discussant: Efthymios Deliargyris (MedCo, USA)

A glimpse into the future: what space is left for new anti Xas and for the actively controllable IXa blocker aptamer?
Freek Verheugt (Amsterdam, NED)

Evaluating rare events: how to get regulatory approval for target-specific oral anticoagulants antidotes
Speaker: Robert Califf (Durham, USA)
Discussant: James Costin (Perosphere, USA)

Approvability issues: FDA–EMA divergence explained?
Speaker: Thomas Marciniak (FDA, USA)
Discussant: Angeles Alonso (EMA, UK)

Moderated discussion with audience participation

Panelists: Angeles Alonso (EMA, UK), Robert Califf (Durham, USA), James Costin (Perosphere, USA), Efthymios Deliargyris (MedCo, USA), Pete diBattiste (Janssen, USA), Marc Ditmarsch (AstraZeneca, UK), Amani El-Gazayerly (EMA, NED), Michael Gibson (Boston, USA), Thomas Marciniak (FDA, USA), Roxana Mehran (New York, USA), Martin Rose (FDA, USA), David Rutledge (Abbott, USA), Martin Unverdorben (Daiichi-Sankyo, USA), Freek Verheugt (Amsterdam, NED), Lars Wallentin (Uppsala, SWE)

1.00 pm – 1.30 pm - LUNCH BREAK

BALLROOM

1.30 pm - 6.00 pm

NEW DRUGS AND FUTURE TRIALS IN HEART FAILURE: OPTIMIZING TRIAL DESIGN TO PUTATIVE MECHANISM OF ACTION

CVCT – HFSA joint session

Moderators: JoAnn Lindenfeld (Denver, USA), Christopher O'Connor (Durham, USA)

Recent trials are adopting different strategies attempting to better define patient populations enrolled in the trials.

- Is it possible to target homogenous trial populations within the heterogeneous HF population?
- What approaches are most promising (e.g. biomarkers, hemodynamics, echo parameters, omics, other?)
- How to better target a primary pathophysiology?
- How to deal with the confounding role of concomitant comorbidity?
- What are the implications for industry?

On another hand, many new drug entities are being tested and novel trials are being designed or are being enrolling in HFREF and HFPEF. Targeting these to individual patient populations most likely to benefit from each respective new class of agents is a challenging issue and will be the focus of this session.

Also, failure to improve outcome in patients with worsening heart failure and the increasing burden of heart failure hospitalization are the main drivers for a shift from chronic to worsening heart failure trials.

Ongoing trials: therapies on the horizon?

- **Ivabradine -** Jeffrey Borer (New York, USA)
- **Serelaxin -** John Teerlink (San Francisco, USA)
- **Finerenone -** Faiez Zannad (Nancy, FRA)
- **Natriuretic peptides -** Alexandre Mebazaa (Paris, FRA)
- **Vericiguat -** Lothar Roessig (Bayer, GER)
- **Omecamtiv mecarbil -** Fady Malik (Cytokinetics, USA)
- **Targeting the mitochondria -** James Carr (Stealth Peptides, USA)
- **NOACS** - Faiez Zannad (Nancy, FRA)
- **Biased ligand (Trevena) -** Javed Butler (Atlanta, USA)
- **Myocardial matrices: cell therapies to reverse/delay progression? -** Marc Penn (Akron, USA)
- **Auto Servo Ventilation in sleep disordered breathing -** Faiez Zannad (Nancy, FRA)

Shifting from chronic to worsening heart failure
Javed Butler (Atlanta, USA)

Remote monitoring trials
Speaker: William Abraham (Columbus, USA)
Discussant: Steven Ruble (BSCI, USA)
Discussant: Ileana Piña (New York, USA)

Biomarker guided trials
Speaker: James Januzzi (Boston, USA)
Discussant: Kirkwood Adams (Chapel Hill, USA)

Moderated discussion with audience participation:
Time to change approach? Mechanism-based therapy and personalized HF therapy

Panelists: William Abraham (Columbus, USA), Kirkwood Adams (Chapel Hill, USA), Jeffrey Borer (New York, USA), Javed Butler (Atlanta, USA), James Carr (Stealth Peptides, USA), Robert Cody (Janssen, USA), Pete diBattiste (Janssen, USA), Amany El-Gazayerly (EMA,NED), Mona Fiuzat (Durham, USA), Karen Hicks (FDA, USA), Johannes Holzmeister (Cardiorentis, CHE), James Januzzi (Boston, USA), Marty Lefkowitz (Novartis, USA), JoAnn Lindenfeld (Denver, USA), Lars H Lund (Stockholm, SWE), Aldo Maggioni (Florence, ITA), Fady Malik (Cytokinetics, USA), Alexandre Mebazaa (Paris, FRA), Christopher O'Connor (Durham, USA), Milton Packer (Dallas, USA), Marc Penn (Akron, USA), Ileana Piña (New York, USA), Marc Pfeffer (Boston, USA), Francis Plat (Juventas Therapeutics, USA), Ricardo Rochas (Novartis, USA), Lothar Roessig (Bayer, GER), Steve Ruble (BSCI, USA), Luis Ruilope (Madrid, ESP), Dan Schaber (Medtronic, USA), Martin Unverdorben (Daiichi-Sankyo, USA), Holger Woehrle (ResMed, GER), Faiez Zannad (Nancy, FRA)

THEATRE

1.30 pm - 4.30 pm

MANAGING HYPERKALEMIA FOR OPTIMAL RAAS INHIBITOR THERAPY AND OTHER INDICATION FOR POTASSIUM BINDERS: TRIAL DESIGN AND APPROVABILITY ISSUES

CVCT - INI CardioRenal Clinical Trialists joint session

Moderators: Murray Epstein (Miami, USA), Patrick Rossignol (Nancy, FRA)

- The use of renin-angiotensin-aldosterone inhibitors or blockers may lead to hyperkalemia, particularly in patients with heart failure and concomitant chronic kidney disease. Interventions to control serum potassium reliably during renin-angiotensin-aldosterone inhibition, which have not been available to date, would be of particular value with the use of mineralocorticoid receptor antagonists that have been shown to lower mortality in patients with heart failure and reduced left ventricular ejection fraction.
- Adoption of optimal therapy including mineralocorticoid receptor antagonists (MRAs) is slow and hindered by concerns over the risk of hyperkalemia, especially in the elderly and in patients with concomitant CKD and diabetes
- Whether potassium-binding polymers may lower the incidence of hyperkalemia and allow a higher proportion of heart failure patients to receive life-saving multiple renin-angiotensin-aldosterone inhibitors is an attractive solution being currently tested in several clinical trials.
- Two novel potassium binders (patiromer and ZS-9) under development may open the field for new indications beyond the classical hyperkalemia in CKD and hemodialysis patients.

Therapeutic options to manage hyperkalemia: update on recent and ongoing trials

Speaker: Bertram Pitt (Ann Arbor, USA)
Discussant: Mikhail Kosiborod (Kansas City, USA)

New therapeutic options development programs: live examples

• **Industry viewpoint**
Speaker: Lance Berman (Relypsa, USA)
Discussant: Henrik Rasmussen (ZS Pharma, USA)

What should the indication be for a drug that lowers serum potassium?
Treatment vs. prevention vs. a broad treatment/prevention of hyperkalemia

- **Target populations' issues: what are the unmet needs?**
  Nephrology indications: George Bakris (Chicago, USA)
  Cardiology indications: Patrick Rossignol (Nancy, FRA)
- **Acute critical care indications**
  Alexandre Mebazaa (Paris, FRA)
- **How to adapt trial design to the clinical indication: methodological issues**
  Janet Wittes (Washington, DC, USA)
- **What indications are approvable?**
  Speaker: Luis Ruilope (Madrid, ESP)
  Discussant: Aliza Thompson (FDA, USA)

Moderated discussion with audience participation:
Would safe and effective therapy for hyperkalemia impact prescribing RAAS inhibitors?
Could this be an approvable claim for novel potassium binders?

Panelists: Angeles Alonso (EMA, UK), Georges Bakris (Chicago, USA), Lance Berman (Relypsa, USA), Murray Epstein (Miami, USA), Mikhail Kosiborod (Kansas City, USA), Alexandre Mebazaa (Paris, FRA), Bertram Pitt (Ann Arbor, USA), Patrick Rossignol (Nancy, FRA), Luis Ruilope (Madrid, ESP), Henrik Sandvad Rasmussen (ZS Pharma, USA), Norman Stockbridge (FDA, USA), Aliza Thompson (FDA, USA), Janet Wittes (Washington, DC, USA)

4.30 pm – 5.00 pm - COFFEE BREAK

THEATRE

5.00 pm - 6.00 pm
KEYNOTE DEBATE: DO CURRENT TRIALS MEET SOCIETY'S NEEDS?
A REVIEW OF RECENT EVIDENCE

Moderators: Stuart Pocock (London, UK), Roxana Mehran (New York, USA)

6.00 pm – 6.30 pm - KEY NOTE LECTURE
Gary Gibbons, Director (NHLBI, USA)

SATURDAY 6 DECEMBER 2014

BALLROOM

8.00 am - 11.30 am

WORKING WITH REGULATORY PARTNERS ON EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS: HOW DOES THIS APPLY TO CARDIOVASCULAR CLINICAL RESEARCH?

Moderators: Robert Califf (Durham, USA), Pieter de Graeff (Amsterdam, NED)

The FDA has released a draft guidance entitled 'Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics' (June 2013). This guidance outlines the four FDA programs intended to expedite the development and review of new drugs that address an unmet medical need in the treatment of a serious or life-threatening condition. In addition to clarifying the established programs, it adds the new 'Breakthrough Therapy' designation that may help to facilitate early approval of treatments for serious or life threatening diseases.

- **Fast Track:** designation granted to a drug that is intended to treat a serious condition and nonclinical/clinical data demonstrate the potential to address an unmet medical need.
- **Priority Review:** designation granted to an application for a drug that treats a serious condition and if approved, would provide a significant improvement in safety or effectiveness.
- **Accelerated Approval:** is a pathway for a drug that treats a serious condition and provides meaningful advantages over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.
- **Breakthrough Therapy:** this designation was instituted under the 2012 FDA Safety and Innovation Act (FDASIA) and is a designation for a drug that treats a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. A drug that qualifies for breakthrough therapy designation would also qualify for the fast-track designation features. It would receive intensive guidance from the FDA for an efficient drug development program and organizational commitment from senior management at the FDA.

The guidance has stimulated a lot of excitement within the drug development community. How much elements of the guidance may apply to CV diseases is an issue that may benefit from discussion among the various stakeholders usually attending CVCT meetings.

To which CV disease is the 'serious conditions' track applicable?
Robert Temple (FDA, USA)

What are 'breakthrough', 'fast track' and 'priority'?
Fortunato Senatore (FDA, USA)

Novartis experience with expedited programs
Patricia Kay-Mugford (Novartis, USA)

European Medical Agency position
Pieter de Graeff (Amsterdam, NED)

Unmet clinical needs in cardiovascular disease
- **Investigator viewpoint:** Robert Califf (Durham, USA)
- **Industry viewpoint:** Joerg Koglin (Merck, USA),
- **Analyst viewpoint:** Eric Dimise (GlobalData, USA)

Panelists: Angeles Alonso (EMA, UK), Robert Califf (Durham, USA), Luther Clark (Merck, USA), Pieter de Graeff (Amsterdam, NED), Eric Dimise (GlobalData, USA), Patricia Kay-Mugford (Novartis, USA), Joerg Koglin (Merck, USA), Ricardo Rochas (Novartis, USA), Fortunato Senatore (FDA, USA), Robert Temple (FDA, USA)

THEATRE

8.00 am - 11.30 am
DIABETES CV SAFETY TRIALS

Moderators: Gonzalo Calvo (Barcelona, ESP), Deepak Bhatt (Boston, USA)

- Obesity epidemic and diabetes are increasing throughout the world, and will have major impact on CV disease worldwide
- The FDA guidance outlines a new approach to CV safety requirements, designed to gather sufficient data during a development program to show that new anti-diabetic or weight loss therapies are not associated with an unacceptable increase in CV risk. A large number of trials have since been initiated, adhering to the new guidance.
- The SAVOR and EXAMINE trials represent the first studies in the post-FDA new guidance that have reported results. TECOS is to deliver results short after CVCT, likely early in 2015. While Saxaglitin and Alogliptin proved to be non-inferior to placebo on the primary outcome of MACE, the results of the two trials diverged regarding effects on heart failure events. SAVOR, EXAMINE and TECOS trial data will be great case-studies for discussing the appropriateness and challenges of FDA Guidance trials to establish the effect of diabetes on CV outcomes, and discuss the likely important consequences on clinical practice.
- A recent FDA Advisory Committee meeting completely repudiated the findings that led to doing CV safety studies for DM drugs. Oddly, FDA responded by leaving its guidance in place. With calls for CV safety, studies are springing up in many other places – not just the weight loss drugs. An overarching guidance on when there is enough evidence to merit asking for studies is much needed.
- How to design/conduct prevention studies? Should CV safety trials detract from seeking efficacy (CV prevention) as an endpoint?
- How big are the challenges of large sample size, long follow-up? How to overcome? Where will resources come from (i.e., may not be attractive for industry due to need for long trial)? Will the regulatory environment adapt to facilitate/promote research in this area?

Why assess CV efficacy/safety in diabetes? Surrogacy challenged
Faiez Zannad (Nancy, FRA)

Methodological issues: non-inferiority, using interim data in regulatory decisions, composite endpoints, comparisons across trials
Speaker: Stuart Pocock (London, UK)
Discussant: Nancy Geller (NHLBI, USA)

CV safety endpoints: the heart failure issue

- **Trial data**
  - EXAMINE: Faiez Zannad (Nancy, FRA)
  - SAVOR: Deepak Bhatt (Boston, USA)
  - AleCardio Jean Claude Tardiff (Montreal, CAN)
- **Mechanistic insights in DPP4 heart physiology and neurohormonal interactions**
  Speaker: Nancy Brown (Nashville, USA)
  Discussant: John Burnett (Rochester, USA)

Regulatory issues: Gonzalo Calvo (Barcelona, ESP), Ray Lipicky (North Potomac, USA)

Moderated discussion with audience participation:
Shouldn't we be aiming at CV prevention, rather than simple CV safety?

Panelists: Deepak Bhatt (Boston, USA), Nancy Brown (Nashville, USA), John Burnett (Rochester, USA), Gonzalo Calvo (Barcelona, ESP), Luther Clark (Merck, USA), Mads Engelmann (Novo Nordisk, DEN), Nancy Geller (NHLBI, USA), Boaz Hirshberg (AstraZeneca, DEN), Stuart Kupfer (Takeda, USA), Ray Lipicky (North Potomac, USA), Shamik Parikh (AstraZeneca, USA), Stuart Pocock (London, UK), Arantxa Sancho (EMA, ESP), Norman Stockbridge (FDA, USA), Jean Claude Tardiff (Montreal, CAN), Faiez Zannad (Nancy, FRA)

10.00 am - 10.30 am - COFFEE BREAK

BALLROOM

11.30 am - 3.00 pm
THE SPECIFIC FRAMEWORK OF CELL AND GENE THERAPY TRIALS

Moderators: Ileana Piña (New York, USA), Steve Winitsky (FDA, USA)

- There are an increasing number of patients with significant morbidity despite optimal medical management. Researchers are studying whether cellular and gene therapies may be capable of repairing a diseased heart through mechanisms such as modulation of paracrine pathways or regeneration of cardiac tissues. Preclinical data that provide an enhanced understanding of cardiac repair mechanisms are critical for the field to progress, as preclinical knowledge can be used to inform the design of efficient clinical programs for development of biologic products.
- Cellular therapies for the treatment of cardiac disease generally meet the definition of "biological product" in section 351(i) of the Public Health Service Act (42 U.S.C. 262(i)), and are regulated by the Center for Biologics Evaluation and Research (CBER).
- The aims of this session are to:
  - Familiarize clinical trialists with specific issues related to development of cell and gene therapies, with a focus on considerations for Phase 1 and Phase 2 clinical trials (which collectively may be referred to as "early phase clinical trials"), including:
    - A brief overview of the main categories of cell and gene therapies that are being developed to treat cardiac disease, with a focus on stem cell derived products (autologous and allogeneic cell therapies, iPSC and ESC derived product, gene therapies)
    - Discuss what needs to be done before a product can be used in a Phase I trial (safety of manufactured product, lot release specs, initial stability and shipping tests, manufacturing issues, i.e. donor testing, reagent quality, cell banking, lot release testing requirements, i.e. sterility, purity, identity, potency)
    - Identify challenges – the end product often is a complex mixture and there may be very limited time material to test the final product
  - Discuss preclinical considerations (animal species/model selection, preclinical study design, data submission to support an IND for a Phase 1 study)
  - Overview of FDA Guidance Document, 'Cellular Therapy for Cardiac Disease'
  - Discuss study design elements

An introduction to CBER and its function

- **Chemistry, Manufacturing, and Controls (CMC) considerations for early-phase cardiovascular cell and gene therapy studies**
  Brenton McCright, (FDA, USA)
- **Preclinical considerations for early-phase cardiovascular cell and gene therapy studies**
  Wei Liang (FDA, USA)
- **Clinical considerations for early-phase cardiovascular cell and gene therapy studies**
  Steve Winitsky (FDA, USA)

Trial design issues

- **Heart failure trials: clinically meaningful endpoints**
  Carl Pepine (Miami, USA)
- **Discrepancies in design, methods, or results**
  Graham Cole (London, UK)
- **Industry viewpoint**
  Janice Pogoda (Celladon, USA)
  Francis Plat (Juventas Therapeutics, USA)

Moderated discussion with audience participation:
Guidance for future trials of cellular therapy for cardiac disease

Panelists: Graham Cole (London, UK), Wei Liang (OCTGT Preclinical Reviewer FDA, USA), Brenton McCright, (OCTGT CMC Reviewer, FDA, USA), Marc Penn (Akron, USA), Carl Pepine (Miami, USA), Ileana Piña (New York, USA), Francis Plat (Juventas Therapeutics, USA), Janice Pogoda (Celladon, USA), Steve Winitsky (FDA, USA)

THEATRE

11.30 am - 3.00 pm
RENAL DENERVATION/MODULATION TRIALS

Moderators: Cecilia Linde (Stockholm, SWE), Henry Black (New York, USA)

- Rigorous evaluation of safety and efficacy is required for neural modulation device therapy that involves invasive procedures, which are costly in comparison to generic drug therapy (i.e., for hypertension), and have an unknown benefit versus risk profile.
- Designing pivotal trials to test these devices is challenging because of complexities related to blinding, patient selection, choice of control group, and selecting appropriate endpoints.

  SIMPLICITY-HTN3 testing catheter-based renal denervation for the treatment of resistant hypertension failed to achieve its primary efficacy end point, which was a sustained reduction in systolic blood pressure at six months.
- Based on positive results from registry data, a sizable group of investigators are challenging the design of SIMPLICITY-HTN3. Many more sham-controlled trials will soon deliver. Reassessing the evidence is extremely timely.
- For other, neural modulation therapies in cardiovascular medicine, clinical experience is limited from which to base assumptions about effect size, sustainability of treatment effect, and long-term safety. Several pivotal trials are ongoing that, once complete, will begin to provide the data necessary to evaluate these treatment approaches and inform future clinical trial design with these or similar devices.

Hypertension

- **Gaps in hypertension trials and management post JNC 8**
  Henry Black (New York, USA)
- **Renal denervation: how to reconcile trial results with registry data**
  - **Evidence from trials and registries**
    Darrel Francis (London, UK)
  - **Methodological commentary**
    Speaker: Stuart Pocock (London, UK)
    Discussant: Nancy Geller (NHLBI, USA)
- **Barostimulation: how to leverage enough evidence to become standard of care?**
  Speaker: John Bisognano (Rochester, USA)
  Discussant: Patrick Rossignol (Nancy, FRA)

Heart failure

- **Lessons learnt post NECTAR-HF**
  Faiez Zannad (Nancy, FRA)

Industry perspective: Steve Ruble (BSCI, USA), Nadim Yared (CVRx, USA)

Regulatory perspective: Angeles Alonso (EMA, UK), Bram Zuckerman (FDA, USA)

Moderated discussion with audience participation:
What level of evidence? Effectiveness and cost-effectiveness issues

Panelists: Angeles Alonso (EMA, UK), William Abraham (Columbus, USA), Georges Bakris (Chicago, USA), John Bisognano (Rochester, USA), Darrel Francis (London, UK), Nancy Geller (NHLBI, USA), Cecilia Linde (Stockholm, SWE), Stuart Pocock (London, UK), Patrick Rossignol (Nancy, FRA), Steve Ruble (BSCI, USA), Luis Ruilope (Madrid, ESP), Philippe Wanstok (CVRx, USA), Nadim Yared (CVRx, USA), Faiez Zannad (Nancy, FRA), Bram Zuckerman (FDA, USA)

3.00 pm - 3.30 pm - COFFEE BREAK

BALLROOM

3.30 pm - 6.30 pm
THE ATHEROSCLEROSIS TRIALISTS WORKSHOP

Moderators: Wolfgang Koenig (Ulm, GER), Robert Rosenson (New York, USA).

On the way to personalized medicine: what are promising future strategies to deal with the high standard of care in today`s clinical trials to identify those patients that might have an additional benefit?

Widespread early intervention in acute coronary syndromes (ACS) and complete revascularization of stenotic lesions complemented by aggressive polypharmacy has considerably reduced early mortality and improved prognosis in patients after ACS. Still, there are a fairly high percentage of patients who develop secondary fatal or non-fatal events. The challenge for today`s clinical practice is to adequately identify and treat those subjects rather than providing additional therapy to all patients after an event. Thus, despite all our current efforts there is room for improvement.

- A very active clinical research program is delivering an important number of new potential therapeutic targets that may be ready for trial testing. These may be lipid or lipid-associated targets or complementary anti-inflammatory strategies.
- There is a strong need for better markers to identify high-risk subjects after an ACS. Can OMICS technology help in terms of new specific biomarkers for improved risk stratification? Could there be a role for genetic testing to identify the population at risk for additional therapy?
- One major question relates to the value of biomarker-guided and/or risk guided therapy and how to design appropriate trials to test these therapeutic strategies. Should therapy be targeted to patients with specific biomarkers profiles? e.g. dysfunctional HDL, high inflammatory burden (elevated CRP), high Lp-PLA2 activity etc.?
- In summary, a fairly large number of lipid-associated new targets or targets reflecting other pathways of the complex atherosclerotic process are being evaluated in mechanistic imaging studies but also in large randomized controlled clinical trials looking for major cardiovascular endpoints. In all of these trials the standard of care is much better than seen in the real world situation. Thus, the question arises, whether these additional compounds will lead to a clinically significant reduction in cardiovascular events on top of optimal standard care.
- Finally, results of IMPROVE-IT, soon to be known, can affect the acceptability of upcoming new drugs for treating hyperlipidemia.

MRI imaging in clinical trials
Speaker: Robin Choudhury (Oxford, UK)
Discussant: Ahmad Tawakol (Boston, USA)

IMPROVE-IT: insight and consequences on the lower is better strategy and ongoing PCSK9 trials
Robert Califf (Durham, USA)

Identifying new risk markers and potential targets: the value of the proteome, metabolome, microRNAs or the transcriptome?
Manuel Mayr (London, UK)

STABILITY and SOLID: could targeted intervention with an Lp-PLA2 inhibitor work?
Wolfgang Koenig (Ulm, GER)

Do negative Mendelian randomization studies rule out a relevant therapeutic effect of an intervention?
Robert Rosenson (New York, USA)

Clinical trials with antisense therapy targeting triglycerides and Lp(a): geared for the big picture
Sam Tsimikas (ISIS Pharmaceuticals, USA)

Industry perspective: Sam Tsimikas (ISIS Pharmaceuticals, USA)

Regulatory perspective: Arantxa Sancho (EMA, ESP)

Moderated discussion with audience participation:
How to design new trials for approval of new anti-atherosclerosis agents

Panelists: Angeles Alonso (EMA, UK), Denise Bonds (NHLBI, USA), Robert Califf (Durham, USA), Gonzalo Calvo (Barcelona ESP), Luther Clark (Merck, USA), Robin Choudhury (Oxford, UK), Efthymios Deliargyris (MedCo, USA), David Gordon (NHLBI, USA), Dave Kallend (MedCo, USA), Armin Koch (EMA, GER), Wolfgang Koenig (Ulm, GER), Joerg Koglin (Merck, USA), Michael Lauer (NHLBI, USA), John Lawrence (BMS, USA), Manuel Mayr (London, UK), Carl Pepine (Miami, USA), Yves Rosenberg (NHLBI, USA), Robert Rosenson (New York, USA), David Rutledge (Abbott, USA), Arantxa Sancho (EMA, ESP), Walter Singleton (ISIS Pharmaceuticals, USA), Jean Claude Tardiff (Montreal, CAN), Ahmad Tawakol (Boston, USA), Sam Tsimikas (ISIS Pharmaceuticals, USA)

THEATRE

2.30 pm - 6.30 pm
ASSESSING THE 'PARADIGM' TRIAL IN HEART FAILURE THERAPY?

Moderators: Bertram Pitt (Ann Arbor, USA), Faiez Zannad (Nancy, FRA)

- The PARADIGM trial is unique among HF trials.
- It has been stopped prematurely for an excess of benefit. Although, in HF, such early termination is not uncommon (CIBIS II, BEAUTIFUL, RALES, EMPHASIS-HF all went through this process), there are issues with this, since stopping a trial prematurely tends to overstate benefits and understate safety observations.
- This phase 3 trial was planned without a prior phase 2 study. However, it came after OVERTURE, a trial that tested another neprelysine inhibitor. The trial offers a great opportunity to discuss when and how skipping phase 2 might be occasionally advisable.
- The trial wasn't placebo-controlled. It evaluated LCZ696, a novel potential treatment for chronic heart failure combining in a single molecule an ARB and a NEP inhibitor, instead of – not on top of – an old-standby ACE inhibitor. Whether this trial may open up the minds to head-to-head comparison trials, rather than on-top-of trials, is an interesting case for discussion.
- PARADIGM is the largest-ever drug trial in chronic HF. Was it overpowered? Still, the trial shows that in very well treated patients with systolic heart failure (mostly mild to moderate), there is room for improvement. How much further improvement is possible?
- The trial enrolled mainly mild to moderate Caucasian patients. How many results may apply to asymptomatic or more severe patients? Are we prepared to initiate patients on LCZ696, rather than on ACE inhibitors? How about patients on ACE inhibitors? Should we switch them to LCZ696? Is safety secured enough, especially in African Americans who did not tolerate omapatrilat, a not so different compound?

PARADIGM: the main findings and application for patient type?
Milton Packer (Dallas, USA)

PARADIGM trial design: when and how could phase 2 be skipped?
Speaker: Christopher O'Connor (Durham, USA)
Discussant: Marty Lefkowitz (Novartis, USA)

Challenges, interpretation and generalizability issues relative to stopping the trial early
Speaker: Stuart Pocock (London, UK)
Discussant: Marc Pfeffer (Boston, USA)

Moving to HFPEF: PARAGON, the ultimate design?
Speaker: Scott Solomon (Boston, USA)
Discussant: Javed Butler (Atlanta, USA)

Moderated discussion with audience participation:
What's next – when to substitute from ACE inhibitor therapy to LCZ696?

Panelists: Javed Butler (Atlanta, USA), Nancy Geller (NHLBI, USA), Marty Lefkowitz (Novartis, USA), Felipe Martinez (Cordoba, ARG), Milton Packer (Dallas, USA), Marc Pfeffer (Boston, USA), Bertram Pitt (Ann Arbor, USA), Stuart Pocock (London, UK), Luis Ruilope (Madrid, ESP), Scott Solomon (Boston, USA), Janet Wittes (Washington,USA), Faiez Zannad (Nancy, FRA)

SUNDAY 7 DECEMBER 2014

BALLROOM

8.30 am -12.00 noon
TOWARD A NEW STANDARD OF CLINICAL TRIALS
IN PRIMARY PULMONARY ARTERIAL HYPERTENSION?

Moderators: Nazzareno Galié (Bologna, ITA), Gérald Simonneau (Bicêtre, FRA)

- Pulmonary arterial hypertension (PAH) includes a series of clinical conditions characterized by progressive increase of pulmonary vascular resistance leading to right heart failure and premature death. Randomized controlled studies so far resulted in the regulatory approval of 8 drugs of three pharmacological classes: endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and prostanoids. These therapies improve symptoms, exercise capacity, haemodynamics, and outcome but the clinical relevance of these effects have been recently challenged and, despite important progresses on medical therapy, many patients with PAH remain with relevant symptoms and poor outcome.
- Meta-analyses of trials with approved drugs, utilized either as monotherapy or in combination, have shown improvements on all-cause mortality or clinical worsening, respectively. Therefore, the effect on survival of these compounds has not been appropriately assessed in individual trials because limited improvements observed on the exercise capacity and the short duration and the small sample size of the individual studies.
- A new standard of clinical trials in PAH is being set with larger outcome trials, such as the completed SERAPHIN trial with macitentan, using the composite endpoint of symptomatic worsening and death and the ongoing lagest trial in the area, GRIPHON with the prostacyclin (PGI2) Receptor agonist Selexipag, using a morbidity-mortality endpoint is just terminated and is positive, setting new standards of morbidity-mortality trials in PAH.
- Discussion on the optimal design of future PAH trials is ongoing, including the selection of patient populations (representativity, geographical variations, severity, etc), endpoint related issues (relevance of soft endpoints, need for M&M trials), sample size and duration of follow up with the challenges related to a rare disease and approvability.
- A number of treatments for PAH will lose patent protection in the coming years including treprostinil, iloprost, sildenafil, tadalafil.
  Riociguat was approved recently and is one of the many first-in-class entrants, such as Actelion's oral prostacyclin receptor antagonist selexipag, as well as ambrisentan and macitentan. Oral treprostinil has also been recently finally approved by the FDA after 2 initial rejections.

Critical appraisal of randomized clinical trials and meta-analyses in PAH
Nazzareno Galié (Bologna, ITA)

Imaging in pulmonary hypertension
Ahmad Tawakol (Boston, USA)

Individual experiences and lessons learnt from recent trials: will outcome trials prevail? Macitentan (SERAPHIN) Selexipag (GRIPHON)
Speaker: Gérald Simonneau (Bicêtre, FRA)
Discussant: Sebastien Roux (Actelion, CHE)

Ambrisentan, from ARTEMIS, ARIES to AMBITION
Speaker: Olivier Sitbon (Paris, FRA)

The 6-minute walk test trials: Riociguat (PATENT, CHEST), Treprostinil (FREEDOM), Imatinib (IMPRES), Tadalafil (PHIRST)
Speaker: Stuart Rich (Chicago, USA)

Industry perspective:
Neil Davie (Bayer, GER), Sebastien Roux (Actelion, CHE)

Regulatory perspective:
Amani El-Gazayerly (EMA, NED), Kaori Shinagawa (PMDA, JAP), Martin Rose (FDA, USA)

Moderated discussion with audience participation:
How should evolve the new standard of clinical trials in pulmonary arterial hypertension?

Panelists: Angeles Alonso (EMA, UK), Neil Davie (Bayer, GER), Amani El-Gazayerly (EMA, NED), Nazzareno Galié (Bologna, ITA), Hunter Gillies (Gilead, USA), Stuart Rich (Chicago, USA), Martin Rose (FDA, USA), Sebastien Roux (Actelion, CHE), Kaori Shinagawa (PMDA, JAP), Gérald Simonneau (Bicêtre, FRA), Olivier Sitbon (Paris, FRA), Mary Ross Southworth (FDA, USA), Ahmad Tawakol (Boston, USA), Robert Temple (FDA, USA)

THEATRE

8.30 am - 12.00 noon
WORKSHOP TO ADDRESS POLYPILL CLINICAL TRIALS AND REGULATORY APPROVAL
Wellcome Trust – CVCT – ISCP joint session

Moderators: Gheorghe-Andrei Dan (Bucharest, ROM), Anthony Rodgers (Sydney, AUS)

- A fixed-dose combination of blood pressure, cholesterol lowering and antiplatelet treatments into a single pill, or polypill, has been proposed as one strategy to reduce the global burden of CVD given its potential for better adherence, lower costs and improved treatment affordability.
- Polypill formulations have now been approved in almost a dozen countries in Europe, South America, Central America, Europe and India (e.g. Trinomia®, Polycap) and applications are underway or planned for other products.
- Potential patient populations can be divided into three target groups:
  - Patients recommended to receive all the components (e.g. established coronary disease) who are currently being treated with the same medications as separate pills i.e. straight substitution.
  - Patients recommended to receive all the components who are not currently being treated with all medications i.e. step-up substitution.
  - Patients without current indications to all components who are nevertheless at raised cardiovascular risk and could benefit from all components e.g. high-risk primary prevention with non-optimal BP and lipid levels but without hypertension or dyslipidaemia.

Regulatory approvals have focused on the first of these three groups, while polypill clinical trialists have focused on the last two groups.

- More than half of all new cardiovascular products in Europe are combinations (defined as products containing two or more agents from the classes of blood pressure lowering, cholesterol lowering, antiplatelet and glucose lowering).
- Some have noted that fixed dose combination therapy contradicts a key principle of clinical pharmacology of individualization of therapy and the paradigm of precision and personalized medicine.

  Dosing is a significant issue, and one area of debate is whether different polypills with different doses of medication should be developed, and if so how many. Concern has been expressed that lack of dose versions will lead to deterioration in risk factor control.
- Many have expressed concern that use of a polypill would lead to patients neglecting diet, exercise and other lifestyle measures.
- Results from several large, long-term polypill clinical trials have become available in the last year that will help address these issues. Several trials are due to complete in the next few years.
- Given the results to date, and the type of evidence that will soon be emerging, what are the challenges and opportunities for regulatory approvals?
- What are the regulatory issues for under-treated patient population?
- When can approval be made on surrogate outcomes and when are event trials needed?
- How can there be a rational approach to the number of dose versions?
- What post-approval pharmacovigilance studies are required?

Clinician perspective:

- **The problem of CV drug adherence worldwide**
  José M. Castellano (Madrid, ESP)

- **Fixed dose combinations in cardiovascular disease. Opportunities and challenges**
  Anthony Rodgers (Sydney, AUS)
- **Focusing on polypills in CV secondary prevention: the FOCUS trial and beyond**
  Felipe Martinez (Cordoba, ARG)

Industry perspective: Fabiana d'Aniello (Ferrer Grupo, ESP)

Regulatory perspective:

- EMA Pieter de Graeff (EMA, NED), Armin Koch (EMA, GER)
- FDA Norman Stockbridge (FDA, USA)

Payers' perspective: Deneen Vojta (United Health, USA)

Moderated discussion with audience participation:
Regulatory approval routes for cardiovascular combination pills

Panelists: José M. Castellano (Madrid, ESP), Gheorghe-Andrei Dan (Bucharest, ROM), Fabiana d'Aniello (Ferrer Grupo, ESP), Pieter De Graef (EMA, NED), David Guez (Servier, FRA), Armin Koch (EMA, GER), Felipe Martinez (Cordoba, ARG), Anthony Rodgers (Sydney, AUS), Natalia París Sotes (Ferrer Grupo, ESP), Norman Stockbridge (FDA, USA), Koon Teo (Hamilton, CAN), Deneen Vojta (United Health, USA)

10.30 am - 11.30 am - COFFEE BREAK

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 2014:

Tariq Ahmad, USA
Rasha Al-Bawardy, USA
Allan Böhm, SVK
Marc Brouwer, NED
Fanny Cazade, FRA
Joshua Chai, UK
Marion Chatot, FRA
Anca-Rodica Dan, ROM
Jacob Doll, USA
Ciham El Asri, FRA
Ryusuke Fujino, JAP
Parul Gandhi, USA
Etienne Gayat, FRA
Ofek Hai, USA
Erik Howell, USA
Rahma Kallel, TUN
Anita Kelkar, USA
Jacob Kelly, USA
Ricardo Ladeiras-Lopes, PRT
Luke Laffin, USA
Matthieu Legrand, FRA
Daniele Massera, USA
Hiroki Matsumoto, JAP
Karen Modesto, USA
Selma Mohammed, USA
Benjamin Pollock, USA
Kazem Rahimi, AUS
Abhinav Sharma, CAN
Sakima Smith, USA
Deephak Swaminath, USA
Jessica Rose Wilson, USA
Lampouguin Yenkoidiok-Douti, USA

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

▸ CVCT PUBLICATIONS REFERENCE LIST - *Visit www.globalcvctforum.com to read the articles in full.*

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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. 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 Diseases and Advanced Heart Failure/ Transplant Cardiology at the University of Colorado. Dr. Abraham spends the majority of his clinical time managing heart failure patients in the inpatient and outpatient settings. He has been recognized as one of the "Best Doctors in America" for 12 consecutive years and has been ranked among the top 10% of physicians nationally in patient satisfaction. He 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 authored more than 700 original papers, abstracts, book chapters, and review articles. In 2014, he was named to the *Thomas Reuters Highly Cited Researchers list* and as one of *The World's Most Influential Scientific Minds*.

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 is principal investigator for the US multicenter database, UNITE-HF, which focuses on registries in patients with heart failure. His current research interests are heavily focused on personalized cardiovascular medicine through biomarkers and Omics. He serves on the Executive Committee of the NHLBI sponsored trial GUIDE-IT; studying the use of NT-proBNP to guide therapy for heart failure.

Angeles Alonso (EMA, UK)

Honorary Consultant in Cardiology. Imperial College Healthcare. NHS. United Kingdom
Senior Medical Assessor in the Medicines and Healthcare products Regulatory Agency (MHRA)
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Dr. Alonso graduated from the School of Medicine at the Universidad Autónoma de Madrid (1979). Ph.D at the Medical School (1991). Staff member of the Department of Cardiology at the Academic Hospital Puerta de Hierro (Madrid), since 1987. Head of the Coronary Care Unit (1987-2000). Senior Consultant as a Clinical Cardiologist (involved in clinical trials on Heart Failure, Ischaemic Heart Disease and Cardiovascular Prevention) 2000-2012. Member of the Committee for Ethics and Clinical Investigation (2000-2009). Coordinator, Chairperson and speaker of several post-degree Ph D Courses at the Academic Hospital Puerta de Hierro de Madrid since 1986. Member of the Heart Failure, Ischemic Di seases, 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).

George Bakris (Chicago, USA)

George Bakris MD, Hon. D, FASH, FASN, FAHA is a Professor of Medicine and Director of the ASH Comprehensive Hypertension Center in the Department of Medicine at the University of Chicago Medicine. Dr. Bakris has published over 700 peer-reviewed articles and book chapters in the areas of diabetic kidney disease, hypertension and progression of nephropathy. He is the Editor or Co-Editor of 18 books, in the areas of Kidney Disease Progression and Diabetes. Additionally, he is an Associate Editor of

the International Textbook of Cardiology. He also serves as a Special Government Employee to the Cardio-renal Advisory Board of the FDA and to CMS. He was a co-principal investigator on the NIH Clinical Research training grant for clinical research (K30) (1999-2004). He chaired the first National Kidney Foundation Consensus report on blood pressure and impact on renal disease progression (2000). He has also served on many national guideline committees including: the Joint National Committee Writing Groups VI & 7, the JNC 7 executive committee (2003), the ADA Clinical Practice Guideline Committee (2002-2004), the National Kidney Foundation (K-DOQI) Blood Pressure Guideline committee (2002-2004 & 2013) and Diabetes Guideline committee (2003-2005 & 2014). Dr. Bakris is the past-president of the American College of Clinical Pharmacology (2000-2002) and the American Society of Hypertension (ASH). He is the current Editor of *Am J Nephrology*, the Hypertension Section Editor of *Up-to-Date* and an Assoc. Ed of *Diabetes Care*.

ABSTRACT

What Should the Indication be for a Drug that Lowers Serum Potassium?
Target populations' issues: what are the unmet needs? Nephrology indications

George Bakris (Chicago, USA)

Hyperkalemia ([K^+]> 5.5 mEq/l) is associated with a significant increase in cardiovascular events (1). It is commonly seen among patients with advanced Stage chronic kidney disease (CKD) Stages 3b (eGFR <45 ml/min/1.73m^2) or higher (2). While those with diabetes in this CKD range are more susceptible to hyperkalemia, this is risk holds regardless of concomitant cardiovascular disease such as heart failure, post myocardial infarction. Post hoc analyses of renal endpoint trials such as RENAAL and EMPHASIS-HF demonstrate that those who failure to achieve maximal dosing of the randomized drug, i.e. losartan, failed to achieve maximal slowing of diabetic nephropathy progression (3-5). Lastly, predictors of hyperkalemia derived from clinical trials and outpatient analyses demonstrate that those with an eGFR <45 ml/min/1.73m^2 and a baseline serum potassium of >4.5 mEq/L, already on a diuretic where four to eight times more likely to develop hyperkalemia than either variable alone or compared to people with higher eGFR values (6). Thus, an indication for a drug that lowers potassium could read something like this. Agent X may be used to lower serum potassium in patients who have documented persistent elevations in serum potassium i.e. > 5.5 mEq/l. *Agent X could be used chronically, based on tolerability and safety data, to attenuate the risk of recurrent hyperkalemia secondary to required therapy for an underlying pathologic condition*.

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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 M.S. in Pharmaceutical Medicine from Hibernia College.

ABSTRACT

New therapeutic options development programs
Clinical development programs for new therapeutic options to treat hyperkalemia:
A live example

Lance Berman (Relypsa, USA)

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 CKD. Hyperkalemia frequently occurs in settings where the underlying disorder is not curable, will not resolve over time and is generally progressive. Given the sustained or recurring nature of hyperkalemia in these conditions, treatment of hyperkalemia must be continued for long periods of time and often needs 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. Specifically, sodium polystyrene sulfonate (Kayexalate®) is the only oral cation-exchange resin indicated in the US for the treatment of hyperkalemia (calcium polystyrene sulfonate is marketed outside the US for the same indication). Kayexalate is not well tolerated and its use can be associated with life threatening side effects including intestinal necrosis. Further, sodium is used as the counter exchange ion in Kayexalate 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 be highly effective and better tolerated than currently available potassium binders.

The active moiety of patiromer for oral suspension is a metal-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 RLY5016 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 chronic kidney disease, 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 demonstrate the safety and tolerability, particularly with repeated and long term use.

An important issue in designing the clinical development program was the choice of a suitable control group. Given the importance of assessing safety and efficacy in subjects with serum potassium levels > 5.5 mEq/L, it was considered unethical to treat subjects with placebo. Given the lack of tolerance and treatment limiting side effects of sodium or calcium polystyrene sulfonate, an active control was also considered inappropriate.

This talk deals with this clinical trial design issue and presents an industry view-point on the key supporting data necessary to evaluate the risk/benefit profile of a new medication to treat hyperkalemia. The talk will provide perspective on the possible indications for a hyperkalemia treatment and the necessary clinical data to support the proposed indication.

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Deepak Bhatt (Boston, USA)

Deepak L. Bhatt MD, MPH, FACC, FAHA, FSCAI, FESC, is Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart & Vascular Center and Professor of Medicine at Harvard Medical School. He is also a Senior Physician at Brigham and Women's Hospital and a Senior Investigator in the TIMI Study Group. Dr. Bhatt has been listed in Best Doctors in America from 2005 to 2014. He was selected by Brigham and Women's Hospital as the 2014 Eugene Braunwald Scholar.

Dr. Bhatt's research interests include acute coronary syndromes, preventive cardiology, and advanced techniques in cardiac, cerebral, and peripheral intervention. He has authored or co-authored over 700 publications and is listed as a Thomson Reuters Highly Cited Researcher.

He is the editor of Atherothrombosis in Clinical Practice published by Oxford University Press and of Peripheral and Cerebrovascular Intervention published by Springer. He was the international PI for the CHARISMA and CRESCENDO trials and co-PI of the three CHAMPION trials. He served as chair of COGENT and helped lead STAMPEDE. He serves as co-chair of the REACH registry and chairs REDUCE-IT. He is co-PI of SAVOR-TIMI 53, SYMPLICITY HTN-3, and THEMIS. He is the current Chair of the AHA-GWTG Steering Committee. He is Senior Associate Editor for News and Clinical Trials for ACC.org. Dr. Bhatt has been a visiting lecturer at a number of prestigious institutions throughout the world. He has been interviewed extensively by news agencies on numerous topics. He is the Editor of the peer-reviewed *Journal of Invasive Cardiology*, Chief Medical Editor of *Cardiology Today's Intervention* for healthcare professionals, and Editor-in-Chief of the *Harvard Heart Letter* for patients.

John Bisognano (Rochester, USA)

John D. Bisognano, MD, PhD is a Professor of Medicine and Director of Outpatient Services in the Division of Cardiology at the University of Rochester Medical Center. He received bachelor's degrees in applied biology and in political science from Massachusetts Institute of technology and then received his MD and PhD in Physical Chemistry from the State University of New York. He completed a residency in Internal Medicine and fellowship in Hypertension and Preventive Cardiology at the University of Michigan Hospitals before going to the University of Colorado for fellowships in Cardiovascular Diseases and Advanced Heart Failure and transplantation. His research areas of interest 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.

He has received numerous teaching awards at the University of Rochester including the Medical Center Board Award for Excellence in Clinical Care, as has served as past President of the New York State Chapter of the American College of Cardiology and Monroe County American Heart Association. He is presently president-elect of the American Society of Hypertension and Director of the ASH Comprehensive Hypertension Center at the University of Rochester. He has over 80 peer-reviewed articles and has published two books in the area of heart failure and outpatient cardiology.

ABSTRACT

Barostimulation: how to leverage enough evidence to become standard of care?

John Bisognano (Rochester, USA)

For nearly a half-century, the sympathetic nervous system has been a primary target for treatment of blood pressure. Various implantable baroreflex stimulator devices were tested in the 1960's, but none even began to meet the need for a therapy that was easy to tolerate and effective. Advances in electronics and in surgical techniques has moved this therapy back into consideration in the early millennium and recent clinical trials of these devices has been extremely encouraging. We have recently been an era of diminished drug development for hypertension while there has also been a greater recognition --- both physiologically and economically -- of the great toll that severe, resistant hypertension has in the population. These patients have adverse events that cannot, given the present approved technology and drug armamentarium, be adequately controlled. Moreover, patients do not have an unlimited ability to tolerate an expanding regimen of drug therapy as these treatments are often limited by side effects, ability to adhere to the regimen, concern over long-term drug side effect, and other patient preferences. With this dire need for newer therapies for this largely orphan population, close attention has to be paid to encouraging investigators and businesses to develop and to test newer devices. While safety and efficacy of these devices must remain a paramount goal, it should always be kept in mind that this is a population of patients who are desperately in need of additional therapies to prevent their heart attacks, strokes, and renal failure and that all clinical data obtained in trials must be evaluated for target population as well as areas of potential improvement and application. The same approach that has applied to large-scale drug therapies for hypertension may not necessarily be the ideal approach for this targeted therapy for specific sub-populations in great need of a new therapy.

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Henry Black (New York, USA)

Henry R. Black, MD, MACP, FASH is an Adjunct Professor of Internal Medicine at the New York University School of Medicine in New York City having joined the faculty in March, 2007, He is a member of the Section of Cardiology and the Center for the Prevention of Cardiovascular Disease. He retired as the Charles J. and Margaret Roberts Professor of Preventive Medicine and Professor of Internal Medicine at Rush University Medical Center in Chicago, Illinois at the end of 2006. He had served as chairperson of the Department of Preventive Medicine at Rush from May, 1992 until June, 2005 and as Associate Vice President and Associate Dean for Research from 2000 to 2005. Dr. Black joined Rush after spending nearly 20 years on the faculty at the Yale University School of Medicine where he rose to the rank of Professor of Internal Medicine and Director of the Preventive Cardiology Service.

Dr. Black has had a leadership role in several landmark clinical trials including the Systolic Hypertension in the Elderly Program (SHEP), Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE), the Antihypertensive and Lipid Lower Trial to Prevent Heart Attack (ALLHAT), and the Women's Health Initiative (WHI). He served as President of the American Society of Hypertension from May, 2008 - May, 2010 and in May, 2010 he was inducted into the inaugural class of Fellows of the American Society of Hypertension. Dr. Black served as a member of the Food and Drug Administration CardioRenal Advisory Committee from 2007-2011. He has published more than 400 papers, chapters and reviews and is an author or co-author of more than 220 abstracts. He is a co-editor of *HYPERTENSION*, *A Companion to Braunwald's Heart Disease*, now in its second edition and the Hypertension Primer which has had 4 editions. He does a weekly webcast on Medscape Cardiology entitled, "Black on Cardiology".

ABSTRACT

Gaps in hypertension trials and management post JNC 8

Henry Black (New York, USA)

This presentation will review the development of guidelines for hypertension in the USA from 1976-2014 (JNC I to JNC 8). The primary focus of the JNC (Joint National Committee of the Detection, Evaluation and Treatment of High Blood Pressure) has been on the initial therapy for adults with high blood pressure but also discusses epidemiology, secondary causes (hypertension with an identifiable cause), evaluation (laboratory and imaging tests) and management strategies.

The most recent guideline (so-called) JNC 8, focused on only three questions:

1. In adults with HTN, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
2. In adults with HTN, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
3. In adults with HTN, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

These questions were chosen by the appointed panel, but failed to discuss many of the other issues that clinicians face when treating hypertensive patients:

1. Should we further adjust our classification system? OMITTED
2. Where & how should we measure blood pressure? OMITTED
3. Are our goals correct? COVERED
4. How quickly should BP be lowered? OMITTED
5. How should new clinical trials be integrated into guidelines? PARTLY COVERED
6. Should we recommend treating prehypertensives with drugs? OMITTED
7. Should beta blockers become a 4th line drug for hypertension? COVERED
8. Will diuretics still be recommended for initial therapy and should we no longer recommend that all 2 drug combinations include a diuretic? PARTLY COVERED
9. Is it really about only blood pressure or might it really be "beyond blood pressure?" OMITTED

10. Should cost considerations be part of the document? OMITTED
11. What about sodium? OMITTED

In addition, the recommendations of other Guideline Committees in 2014-2014 (NICE, ESC/ESH, ASH/ACC) will be reviewed.

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Denise Bonds (NHLBI, NIH, USA)

Denise E. Bonds, MD, MPH receive her medical degree from Creighton University, completed her internal medicine residency at Alameda County Medical Center and a research fellowship and Masters in Public Health at Boston University. Dr. Bonds was a faculty member at Wake Forest University and the University of Virginia before joining National Heart Lung and Blood Institute (NHLBI) in 2009. During her time as a faculty member, she worked on cardiovascular clinical trials including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Women's Health Initiative. Since joining NHLBI, Dr. Bonds has continued to focus on clinical trials. She is a member of the project team for the Systolic Blood Pressure Intervention Trial (SPRINT), Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE), the Health Care Systems Research Collaboratory, and the Best Endovascular vs. Best Surgical Therapy in Patients With Critical Limb Ischemia (BEST-CLI). Her research interests include developing new methods to stream line and reduce the cost of conducting clinical trials. She is the program officer for RFA HL-12-019 Pilot Studies to Develop and Test Novel, Low-Cost Methods for the Conduct of Clinical Trials and RFA HL-14-019 Low-Cost Pragmatic Patient-Centered Randomized Controlled Intervention Trials.

ABSTRACT

Embedding trials in existing longitudinal cohorts: pitfalls and challenges

Denise Bonds (NHLBI, USA)

The establishment and conduct of a randomized controlled trial is expensive and time consuming. Use of ongoing longitudinal cohort studies and disease registries could result in faster start-up times and lower costs. This talk will discuss the potential risks and benefits of this practice and provide examples of successful integration of clinical trials into observational study infrastructure.

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Jeffrey Borer (New York, USA)

Jeffrey S. Borer is Professor of Medicine, Cell Biology, Radiology and Surgery at SUNY Downstate Medical Center. For 4 years, was Chairman, Department of Medicine, at Downstate, a position he relinquished, but continues to serve as Chief, Division of Cardiovascular Medicine, and Director of two research institutes. His BA is from Harvard, MD from Cornell, trained at the Massachusetts General Hospital, spent 7 years at the 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. Back at NIH, he developed stress radionuclide cineangiography, the first non-invasive assessor of cardiac function with exercise. He returned to Cornell for 30 years as Harriman Professor of Cardiovascular Medicine and Chief, Division of Cardiovascular Pathophysiology. He performs clinical service, teaching and research, the latter primarily in valve diseases and in therapeutic efficacy of heart rate modification. He has been a USFDA Advisor for 37 years, chaired the CardioRenal Drugs Advisory Committee for 3 terms and the Circulatory Devices Advisory Panel for 1 term, was a life sciences Advisor to NASA for 24 years, served as officer/board member of national professional societies (currently President, Heart Valve Society of America), published almost 500 scientific papers and 6 books, participated in numerous clinical trials, is editor-in-chief of the journal, *Cardiology*, and received several recognitions for his work (most recently, the Lifetime Achievement Award of the joint heart valve societies (2014), and a Legend of Cardiology Award at the 10th Annual Complex Catheter-based Cardiovascular Therapeutics conference (2014).

Nancy Brown (Nashville, USA)

Nancy J. Brown, MD is Hugh Jackson Morgan Professor of Medicine and Pharmacology, Chair of the Department of Medicine and Physician-in-Chief at Vanderbilt University School of Medicine. A graduate of Yale College and Harvard Medical School, Dr. Brown conducts translational research in cardiovascular pharmacology. In particular, her group studies interactive effects of the renin-angiotensin-aldosterone and kallikrein-kinin systems on glucose homeostasis and risk of thrombotic events. In 2000, Dr. Brown co-founded the Vanderbilt Master of Science in Clinical Investigation program to train investigators in patient-oriented research. From 2006-2010, Dr. Brown served as Associate Dean for Clinical and Translational Scientist Development, and established infrastructure to promote the development of physician-scientists. She served on the NIH National Advisory Research Resources Council from 2007-2011. Dr. Brown is an active member of the American Heart Association Council for Hypertension. Her honors include the American Society of Hypertension Young Scholar Award, American Federation for Clinical Research Outstanding Investigator Award, the Grant Liddle Award, the E.K. Frey- E. Werle Foundation Promotion Prize, the AHA Harriet Dustan award, membership in American Society for Clinical Investigation and in Association of American Physicians. She is a fellow of the American Association for the Advancement of Science and member of the Institute of Medicine.

ABSTRACT

Mechanistic insights in DPP4 heart physiology and neurohormonal interactions

Nancy Brown (Nashville, USA)

In addition to decreasing the degradation of incretins such as glucagon-like peptide 1 (GLP-1), dipeptidyl peptidase IV (DPP4) inhibition alters the degradation of vasoactive peptides. DPP4 is a serine exopeptidase that cleaves the amino-terminus dipeptide from peptides with a proline or alanine as the penultimate amino acid. Vasoactive substrates of DPP4 include GLP-1, brain natriuretic peptide (BNP), substance P, NPY, and peptide YY. Among these, substance P stands out as a substrate common to ACE and DPP4. Substance P is inactivated by ACE and neprilysin at its carboxy terminus, and by DPP4 at the amino terminus.

In this talk we will explore evidence for an interactive effect of angiotensin-converting enzyme (ACE) inhibition and DPP4 inhibition on blood pressure and sympathetic activity. We will present data regarding the effect of DPP4 inhibition on vascular responses to substance P, GLP-1, and brain natriuretic peptide (BNP). Lastly, we will consider these data in the context of recent clinical trials exploring the cardiovascular safety of DPP4 inhibitors.

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Javed Butler (Atlanta, USA)

Dr. Butler is the chief of cardiology and co-director of the heart institute at the Stony Brook University. He is board certified in internal medicine, cardiovascular medicine, and advanced heart failure and transplant medicine. He also serves as the deputy chief science officer to the American Heart Association. Prior to joining Stony Brook, he was professor of medicine at the Emory University. Dr. Butler has published over 220 peer-reviewed publications. Dr. Butler is the recipient of the Simon Dack Award by the American College of Cardiology and the Time, Feeling, and Focus award by the American Heart Association. He has been cited in America's Best Doctors numerous times. He serves on the ACC/AHA heart failure guidelines committee, on several NIH study sections, chairs the NIH heart failure network's ancillary studies committee; and he is a member of the executive council of the Heart Failure Society of America. He serves on the editorial board of several peer reviewed cardiovascular journals.

After completing his medical school from the Aga Khan University in Pakistan, he completed his residency at Yale, cardiology fellowship and advanced heart failure and transplant fellowship at Vanderbilt, and cardiac imaging fellowship from the Massachusetts General Hospital. Prior to joining Emory, he served as the director of the cardiac and heart-lung transplant programs at Vanderbilt. He has completed Masters degree in Public Health from Harvard University and is currently pursing Masters in Business Administration from Emory University.

Robert Califf (Durham, USA)

Robert M. Califf, MD, MACC, is the Donald F. Fortin, MD, Professor of Cardiology at the Duke University School of Medicine and Vice Chancellor for Clinical and Translational Research. Dr. Califf is also the director of the Duke Translational Medicine Institute (DTMI). The DTMI, which is supported by a Clinical and Translational Science Award from the National Institutes of Health, is Duke University's home for clinical and translational research activities.

Prior to assuming his role at DTMI, he served as the founding director of the Duke Clinical Research Institute (DCRI), the world's largest academic clinical research organization. An international leader in cardiovascular medicine, health outcomes, quality of care, and medical economics, he is the author or coauthor of more than 1,000 peer-reviewed articles, reviews, and editorials and is among the most frequently cited authors in medicine. Dr. Califf is the editor-in-chief of the American Heart Journal and has served on the FDA's Cardiorenal Advisory Panel, the Pharmaceutical Roundtable of the Institute of Medicine (IOM), and was the founding director of the coordinating center for the Centers for Education & Research on Therapeutics™ (CERTs), a public-private partnership focused on research and education to advance and optimize the use of medical products.

Dr. Califf is currently a member of the IOM Forum in Drug Discovery, Development, and Translation and the IOM Policy Committee. He also co-chairs the Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by Duke and the FDA, and serves as chair for the Clinical Research Forum (CRF), an organization of academic health system leaders; both CTTI and the CRF are devoted to facilitating systemic improvements to the clinical research enterprise. Most recently, Dr. Califf is the principal investigator for the coordinating center of the NIH Health Care Systems Research Collaboratory, an NIH Common Fund program that develops, tests, and disseminates innovative methodologies for pragmatic clinical research. He is also a co-director of the coordinating center for the Patient-Centered Clinical Research Network (PCORnet), an innovative nationwide initiative funded by the Patient-Centered Outcomes Research Institute (PCORI) that supports large-scale patient-centered trials and comparative effectiveness research.

Gonzalo Calvo (Barcelona, ESP)

Gonzalo Calvo is a consultant in Clinical Pharmacology at the Hospital Clinic of Barcelona and Associate Professor of Pharmacology at the University of Barcelona (UB). After receiving his medical degree, he specialized in Clinical Pharmacology at CSU Vall d'Hebron (1993) and became a doctor of medicine in 1997.

Pr. Calvo's main area of expertise is drug regulation, with particular interest in cardiovascular and onco-haematology. He has been principal investigator of around 50 clinical trials and has co-authored 85 peer-reviewed papers and 2 books.

From 2002 to 2011, he represented the Spanish Agency on Medicines and Healthcare Products (AEMPS) at the EMA Committee for Human Medicinal Products (CHMP) as rapporteur of more than 60 new drug applications.

Pr. Calvo has been the chair of the CHMP Cardiovascular Working Party since 2002.

He was elected President of the European Association of Clinical Pharmacology and Therapeutics (EACPT) in 2011.

James Carr (Stealth Peptides, USA)

Jim Carr is Vice President of Cardiovascular and Renal Clinical Development at Stealth Biotherapeutics. Jim received his Doctor of Pharmacy degree at the University of Minnesota in 1990 and did a fellowship focusing on cardiovascular pharmacology and clinical toxicology at the same institution. For many years, prior to joining the pharmaceutical industry, Jim was on the clinical faculty of the University at Buffalo where he led a clinical pharmacology consulting service and also taught clinical pharmacokinetics. After joining the Medical Affairs group at GSK in 1996, Jim soon became involved in supporting the launch of carvedilol and was instrumental in guiding the clinical development of the compound in pursuit of additional indications. Jim subsequently pursued other roles within industry, which included leading the clinical development of bucindolol for heart failure for Arca biopharma. After leaving Arca biopharma in 2010, Jim resumed his career at GSK working in the Global Cardiovascular and Metabolism group. Recently, Jim left GSK to assume his current role at Stealth Biotherapeutics with a goal of developing a novel peptide for the treatment of heart failure.

ABSTRACT

Ongoing trials: therapies on the horizon?
Targeting the mitochondria

James Carr (Stealth Peptides, USA)

Bendavia™, with its multi-organ beneficial actions on function and metabolism, is an excellent candidate to target the complex interplay of factors that ultimately result in the syndrome of clinical HF. Indeed, Bendavia™™ has been shown using animal models to beneficially impact all of the major potential therapeutic targets for HF. The use of Bendavia™™ to treat the multiple organ systems and organelles that contribute to the HF state represents an important opportunity to address an unmet clinical need in healthcare.

To date, over 250 patients or human volunteers have received Bendavia™ and the drug has been shown to be safe and well-tolerated.

Based on recent observations, a clinical profile appears to be emerging that is consistent with the pharmacologic profile that was predicted in pre-clinical animal models. After confirming the expected clinical effects, the goal is to initiate a trial in a high unmet medical need population. For example, discussions are underway to study Bendavia™ in chronic heart failure patients with co-existing chronic kidney disease that have experienced a recent hospitalization.

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José M. Castellano (Madrid, ESP)

Dr. Jose M. Castellano gained his medical degree in 2005 in the University Clinic of Navarra in Pamplona, Spain, after completing a BSc from Brown University in Providence, Rhode Island. He subsequently completed his fellowship in Cardiology at the University Clinic of Navarra, in Pamplona, in 2010. While doing his fellowship he obtained his PhD degree studying the role of cardiotrophin-1 on cardiac structure and function in patients with metabolic syndrome. Dr. Castellano completed a PostDoc degree on advanced clinical research under the direction of Dr. Fuster at Mount Sinai, Medical Center in New York, NY, USA. Currently, Dr. Castellano holds a position as an Adjunct Professor of Medicine at the Mount Sinai Medical Scholl in New York, NY, USA. He is the Coordinator of Clinical Trials at Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Madrid, Spain. He is involved in numerous trials worldwide that study different interventions in preventive cardiovascular medicine.

ABSTRACT

The problem of CV drug adherence worldwide

José M. Castellano (Madrid, ESP)

The deteriorating health of the population and the increasing prevalence of chronic diseases is a global problem whose causes are multifactorial and complex. The Western lifestyle does not promote healthy living, and the consequences are most devastating when social inequalities, together with the economic and population explosion of recent decades, are considered. The expansion of poor nutritional habits, obesity, sedentarism and hypertension are increasingly contributing to the development of a cardiovascular disease epidemic. Recent data on the rates of compliance with lifestyle modification and adherence to prescribed medication are alarming. Over 50% of patients, on average, decide to abandon the treatment prescribed, and the objectives to improve their habits (quit smoking, lose weight or engage in physical activity) are met by an equal or lower percentage. Beyond the impact it has on individual health, it carries a huge economic cost, as it is associated with a failure in achieving therapeutic goals, higher rate of hospitalization, and death. Improving communication between doctors and patients, the active involvement of other health professionals, and the development of combination drug formulations (polypill) are potential strategies for improving adherence and reducing costs.

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Robin Choudhury (Oxford, UK)

Robin Choudhury qualified in medicine at the University of Oxford with postgraduate training in London (Royal Brompton & Hammersmith) and Oxford. At Mount Sinai School of Medicine, New York, he worked on lipoproteins and vascular disease and on developing MRI to characterize atherosclerosis. He is currently a Wellcome Trust Senior Research Fellow in Clinical Science and Professor of Cardiovascular Medicine at the University

of Oxford; Consultant Cardiologist at the John Radcliffe Hospital and Clinical Director of the Oxford Acute Vascular Imaging Centre. His research interests focus on: (1) the development and application of imaging techniques for the characterization of atherosclerosis, thrombosis and vascular inflammation and in particular on the development of molecular imaging approaches (2) functional genomics approaches to investigate inflammation in acute MI and atherosclerosis. He serves on the Editorial Boards of the Journal of the American Journal of Cardiology (Section Editor, Clinical Cardiology); Arteriosclerosis, Thrombosis and Vascular Biology and European Heart Journal - Cardiovascular Pharmacology. At the British Cardiovascular Society, he serves on the Academic Committee and the Programme Committee and chairs the Clinical [Research] Studies Group Committee, which promotes interactions between UK clinicians, scientists; industry and charity/government funders.

ABSTRACT

MRI imaging in clinical trials

Robin Choudhury (Oxford, UK)

Vessel wall imaging for the quantification and characterization of atherosclerosis has advanced considerably over the past 20 years. Magnetic resonance imaging characterizes soft tissues, including atherosclerosis in large arteries accurately, reproducibly, noninvasively and without the need for ionizing radiation. For these reasons, magnetic resonance imaging has emerged as a powerful tool to track plaque response in clinical trials. Furthermore, in addition to anatomical imaging of the vessel wall and atherosclerotic plaque, magnetic resonance imaging offers potentially important insights into arterial compliance, pulse wave velocity and endothelial function, which may also reflect aspects of vascular disease and dysfunction. More recently, preclinical studies have shown impressive possibilities for molecular and cellular imaging with MRI, although except in a small number of cases, these have not yet found clinical application either in diagnosis or in monitoring response to treatment.

This presentation will attempt a critical review of the current status of MRI context of cardiovascular trials, now that MRI occupied a mature position as an imaging technique in this context. It will consider both the strengths and limitations of MRI in relation to both established and emerging therapeutic agents.

Even in so-called 'high-risk' secondary prevention populations, event rates on contemporary treatment are low. Current approaches to phase III trials using ever-larger numbers of unselected patients are unsustainable. In populations with low event rates, subject to drugs with modest incremental effects, the numbers needed to treat for such indications become impractical. The current approach of treating all-comers with very modest attempts at selection or stratification is not sustainable. Consideration will be given to the potential and limitations of current and emerging MRI techniques to stratify patients in ways that are potentially informative to the selection and monitoring of specific treatments. In particular, new methods for automated lipid quantification in carotid atherosclerosis using T2 mapping will be discussed.

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Robert Cody (Janssen, USA)

Dr. Cody is currently Cardiovascular Franchise Development Lead in the Cardiovascular/Metabolism Therapeutic Area, of Janssen Pharmaceuticals, Johnson and Johnson. He previously was Global Director for Scientific Affairs-Cardiovascular at Merck & Co. Prior to Merck, Dr. Cody was Vice-President for Medical Affairs and Chief Medical Officer of CVRx, Inc., a medical device company in Minneapolis, MN, (while on leave from the University of Michigan). At the University of Michigan Health System, Dr. Cody was a Professor of Internal Medicine and Associate Chief of the Division of Cardiovascular Disease. He was also Director of the Heart Failure & Transplant Management Program, and co-chair of the Institutional Review Board.
Dr. Cody has previously held faculty/clinical positions at the Ohio State University Medical Center and Weill Cornell Medical School, New York-Presbyterian Hospitals. Dr. Cody has led the design and execution of international clinical trials in heart failure, and served as Chair of numerous Data and Safety Monitoring Boards

for cardiovascular trials. Dr. Cody received his M.B.A. degree from the University of Michigan, and his MD degree from Penn State University. Dr. Cody completed a Residency in Internal Medicine at the Cleveland Clinic Foundation, and his Cardiovascular Fellowship at Massachusetts General Hospital and Harvard Medical School.

Graham Cole (London, UK)

Graham Cole graduated in medicine from Cambridge University in 2004. Following training in general medicine, he has been training as a specialist in cardiology since 2008 and is currently a Clinical Research Fellow in Cardiac Imaging at Imperial College London.

His interests lie in heart failure and the rational use of cardiac imaging for both clinical and research purposes.

His published work has also spotlighted the potential consequences of insecure research (PMID: 23904357, PMID: 25172044), identified previously unheralded serious research misconduct in a pioneering group (PMID: 23830344) and drawn attention to an association between discrepancies in trial reports and observed effect size (PMID: 24778175).

His response to these problems has been on two levels. Firstly to encourage scrutiny of trial design (PMID: 25169179, PMID: 24480181) and research behaviour (PMID: 25242341), and secondly to develop bias-resistant reproducible technology for research purposes (PMID: 21093935, PMID: 24699322, PMID: 24770912).

ABSTRACT

Discrepancies in design, methods, or results

Graham Cole (London, UK)

Discrepancies, defined as two statements that cannot both be true, occur widely in clinical trial reports. Earlier this year we demonstrated an association between the number of discrepancies present in trial reports of bone marrow cell therapy and the effect size presented (Nowbar *et al*. Brit. Med. J., 2014).

But what does the presence of discrepancies mean? Errors, after all, occur in every field of human endeavor including clinical science.

A senior colleague within the field has argued publicly (Moyé, Circ. Res., 2014) that our work should be "set aside" and that trial reports unable to consistently describe whether 15 or 16 patients were studied simply contain "very small mistakes". It has also been argued that, in nascent fields such as cell therapy, initial overstatement of effect size followed by subsequent less impressive efficacy should be accepted as the *Proteus* effect.

The results of our study oppose that view. Our community would be unwise to ignore discrepancies in trial reports. In many cases, the mechanism by which the discrepancy arose simply cannot be deduced. It is possible that some are perfectly innocent typographical errors, but also possible that some are markers of unreliability, or even, in some cases, outright fiction.

How should we deal with trial reports in which patients who died or were lost to follow-up are still shown to be taking drugs, reporting symptoms, and undergoing invasive tests? As a community, how should we behave when a pre-specified primary endpoint is not reported and the alternative presented is discrepant between figures and abstract? If the same study is presented in one report as randomized and in another report as accepter-rejecter, which is correct? Can we believe a trial report where a patient has an NYHA class of *minus* 5?

I believe our community has much to gain if all stakeholders - investigators, editors, publishers, funders and regulators - were able to agree how to handle discrepancies.

There is no reason to suggest that the pressures experienced by workers in bone marrow cell therapy is different from other emerging "hot" fields. At all stages of the scientific process, therapeutic discovery may benefit from us being polite but discerning "consumers" of the science we read.

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James Costin (Perosphere, USA)

James C. Costin is Vice President of Clinical and Medical Affairs a Perosphere, Inc. in Danbury, CT, USA. He obtained his MD degree from Emory University School of Medicine and competed his cardiology training at Yale University School of Medicine where he was on the full time faculty before joining the pharmaceutical industry. Prior to Perosphere, he was Corporate Vice President of Scientific Affairs at Carter-Wallace and was also at ICI Americas prior to that. He has worked on the research and development of numerous drugs including Tenormin (atenolol), Felbatol (felbamate), and Astelin (azelastine). Currently he oversees the clinical development of ciraparantag (PER977, recently completing Phase II trials), which is a reversal agent for factor Xa and IIa oral anticoagulants, unfractionated and low molecular weight heparins, and fondaparinux.

ABSTRACT

Evaluating rare events: how to get regulatory approval for target-specific oral anticoagulants antidotes

James Costin, Bryan Laulicht, Sasha Bakhru, Solomon Steiner

Perosphere, USA

Given that no reversal agent for the target specific or new oral anticoagulants (NOAC) has yet been approved by any regulatory authority in the world, the presentation may be premature. However, the approaches being used by the companies seeking regulatory approval in the United States are similar. The approaches benefited from a Cardiac Safety Research Consortium (CSRC) meeting at the FDA in April 2014 that focused on approval pathways for NOAC reversal agents. Evaluating rare events such as the need for reversal of a NOAC is difficult in practice as most often, it will be due to bleeding in anticoagulated patients. Since both gastrointestinal (GI) and intracranial bleeding are severe events that usually occur in patients with significant co-morbidities and have different etiologies, the endpoint becomes a challenge since reversal of anticoagulation does not necessarily mean cessation of bleeding. One successful approach was used in studies of Prothrombin Complex Concentrate (Human). The efficacy of the replacement product was evaluated in warfarin anticoagulated patients with GI bleeds but the endpoint in the study was a return to laboratory hemostasis, not cessation of the bleeding. As discussed at the CSRC meeting, a different approach is being used in the development of both andexanet alfa and PER977. Since there is little to suggest that reversal of anticoagulation is any different in patients taking the NOAC for an indication versus normal subjects, both development programs have focused on using normal human volunteers in the phase 1-3 trials with the possibility of confirmatory trials or registries in bleeding subjects after approval. Other study designs such as stepped-wedged approaches and non-randomized trials could be tried but all have their shortcomings. The various enrichment strategies employed in many cardiovascular and oncology trials and as reviewed by the FDA in a Guidance for Industry document would not appear to have any value in trials with reversal agents for anticoagulants. One reasoncomplicating standard trial design may be because the therapeutic target for reversal agents is not an endogenous receptor or abnormality, but rather an exogenous target (i.e., the anticoagulant itself). The current unmet medical need for a NOAC reversal agent has necessitated a novel scientific and regulatory approach to efficacy trials and approvals for these rare events.

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After receiving her medical degree at Vilnius University, Lithuania in 1997 and completing her cardiology training at Vilnius University Hospital, she served as a clinical research fellow in the Cardiac Ultrasound research group at the Catholic University of Leuven, Belgium, where in 2002 she obtained a Masters degree in Medical Imaging. In 2008 she obtained a PhD in Biomedical Sciences at Vilnius University, Lithuania. From 2004 till 2006 she already worked as a national seconded expert for the European Commission in cardiovascular disease research area.

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Dr. Davie started his industry career at Encysive Pharmaceuticals Europe and took on the role of Director of Scientific Affairs. He was actively involved in the clinical development and launch of Thelin (an endothelin receptor antagonist) for PAH in 2006. In 2009, Dr. Davie joined Pfizer (following the acquisition of Encysive) as Early Candidate Medical Director in Pfizer's Specialty Care Business Unit. His main role was the identification and early clinical development of novel therapeutic targets to answer unmet medical needs in pulmonary vascular disease through research partnerships, clinical development, and business development. In addition, Dr. Davie worked on the development program for Revatio.

In January 2012, Dr. Davie joined Bayer as Global Clinical Lead for Riociguat. Dr. Davie is responsible for global clinical programs with riociguat, together with clinical aspects of the worldwide regulatory submissions. He was the Scientific Lead and Moderator for the FDA Advisory Committee for Riociguat in August 2013. In June 2014, Dr. Davie was appointed Vice President and Head, Pulmonary Group, Global Clinical Development. Dr. Davie is also Visiting Professor of Cellular Medicine at the University of Newcastle in the UK.

Efthymios Deliargyris (MedCo, USA)

Efthymios "Makis" Deliargyris was a high-volume academic cardiologist having performed thousands of interventional procedures in both the United States and Europe prior to his arrival at The Medicines Company in 2010 where he now serves as the global medical lead for the acute cardiovascular care business. Dr. Deliargyris has been the recipient of multiple research awards, including the prestigious Society of Cardiac Angiography & Interventions (SCAI) Fellowship Award in 1999 for his groundbreaking work linking inflammatory mediators to ACS and is internationally recognized for his original research in the area of acute coronary syndromes and antithrombotic therapy. Current activities include global scientific oversight of all activities relating to late stage cardiovascular products such as bivalirudin, clevidipine, and cangrelor and participation in early phase development of pipeline assets such as MDCO-216, the Apo A-I Milano HDL mimetic, and a PCSK9 synthesis inhibitor.

ABSTRACT

Bivaluridin trials in PPCI: has the dust settled?

Efthymios Deliargyris (MedCo, USA)

Bivalirudin has been extensively studied in multiple ACS randomized trials against heparin with or without GPI, and 4 of those trials specifically included STEMI patients undergoing PPCI. The 3 multicenter trials (HORIZONS-AMI, EUROMAX and BRIGHT) reported significant reductions in their primary endpoint in favor of bivalirudin, while the single center HEAT-PPCI trial reported opposing findings with a significant benefit in favor of heparin. In a meta-analysis of all 4 trials that included 9,806 patients in total, bivalirudin compared to a heparin based strategy (with or without GPI) was associated with significantly less major bleeding, transfusions and thrombocytopenia at the expense of an increased risk of AST. Overall ischemic outcomes (MACE) were comparable, but net clinical benefit (NACE) favored bivalirudin.

The absolute risk increase for AST was approximately 1% and the risk was confined to the first 4 hours after the end of the primary PCI procedure which could be explained by the combination of the rapid elimination of bivalirudin following discontinuation of the infusion and the delayed bioavailability of the oral P2Y12 inhibitors in the STEMI setting. In fact, preliminary data support this by suggesting that neither prasugrel nor ticagrelor can mitigate this early risk for AST, but a strategy of prolonging the bivalirudin infusion at full dose during that risk window may. Finally, even though rates of ST may be higher with bivalirudin, mortality after ST with bivalirudin is significantly lower than with heparin ± GPI.

Effective thrombin and P2Y12 inhibition are the cornerstones of the pharmacologic management of acute arterial thrombosis. Bivalirudin, when dosed adequately, is associated with the best outcomes for STEMI patients undergoing primary PCI. We eagerly anticipate the presentation of the randomized MATRIX and VALIDATE trials in 2015 that will report in over 13,000 ACS patients including about 7000 STEMI patients.

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ABSTRACT

Unmet clinical needs in cardiovascular disease Breakthrough therapies in the CV space – NOAC antidotes as case study

Eric Dimise (GlobalData, USA)

History has demonstrated that granting of the FDA's Breakthrough Therapy designation does not necessarily translate into regulatory approval. At present, two NOAC antidotes, Portola Pharmaceutical's andexanet alfa and Boehringer Ingelheim's idarucizumab, have been granted the breakthrough designation, and we at GlobalData expect that these two therapies are poised to meet the FDA's regulatory demands. As a result, GlobalData expects that andexanet alfa and idarucizumab will spur the NOACs to more robust sales growth over the course of the next 10 years. This discussion will focus on the impact that GlobalData expects these two antidotes to have on the NOAC market, and will include GlobalData's market analysis and forecast over a 10-year period. Using the market forecast as a guide, the impact of market size, competitive landscape, and commercial reach and positioning will be examined. Concluding remarks will focus on why the breakthrough designation has, thus far, been more amenable to drug development strategies outside the cardiovascular space, and how the NOAC antidotes differ from previous CV therapies that have struggled in this regulatory pathway.

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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.

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Dr. Epstein has authored over 400 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, 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.

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Lou Fiore (Jamaica Plain, USA)

Louis Fiore MD, MPH completed his residency and fellowships in Hematology and Oncology at the VA Medical Center in Boston and has remained there throughout his career as a clinical research scientist. He co-founded the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) in 1996 and was "re-schooled" in Clinical Effectiveness at the Harvard School of Public Health. In 2006 he was awarded a VA Co-operative Studies Program Clinical Trial Coordinating Center at MAVERIC. His focus at the coordinating center was in applying informatics to improve the quality of observational, interventional and biobanking studies. In 2008 MAVERIC was awarded three national 'Transformative Initiatives': The Point of Care Research Program, the Million Veteran Program (MVP) and the Genomic Information System for Integrated Science (GenISIS). These projects intersect at the junction of clinical care, research and healthcare system learning activities. Most recently he is creating a VA regional Precision Oncology Program, a partnership between research and clinical care stakeholders.

Nazzareno Galiè (Bologna, ITA)

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ABSTRACT

Critical appraisal of randomized clinical trials and meta-analyses in PAH

Nazzareno Galié (Bologna, ITA)

The progress made in the medical treatment of pulmonary arterial hypertension (PAH) in the past 15 years is unique, particularly for a rare and severe condition: almost 40 randomised controlled trials (RCTs) have been completed and more are either ongoing or planned. Nine drugs (ambrisentan, bosentan, epoprostenol, iloprost, macitentan, riociguat, sildenafil, tadalafil, treprostinil) acting on three pathways (endothelin, nitric oxide and prostacyclin pathways) administered by four different routes (oral, inhaled, subcutaneous, and intravenous) have been currently approved by the Food and Drug Administration and/or by the European Medicines Agency.(1)

The traditional primary endpoint of the RCTs performed in PAH has been the 6 min walk distance (6MWD) that assesses the exercise capacity, and secondary endpoints have included haemodynamics and clinical worsening (CW), a composite endpoint including death, hospitalization, and disease progression.(2) The use of 6MWD as a primary endpoint has allowed reasonable study sample sizes (from 100 to 500 patients) and randomized study duration (from 2 to 6 months), which are favorable feasibility characteristics in a rare and severe disease.(3) On the other hand, these same characteristics have prevented the observation of effects on CW beyond 3-6 months and on the mortality rate except for studies enrolling the most severe patient population.(3, 4)

Meta-analyses including RCTs testing drugs either on monotherapy or on combination therapy have shown a reduction of 40% in all-cause mortality risk as compared to the placebo group.(3, 5) When only RCTs testing drugs in combination therapy were included in the meta-analyses, the risk reduction for mortality was not statistically significant but the risk reduction for the composite CW was about 50% and statistically significant.(6, 7) However, the limitation of all these meta-analyses is that the average duration of the included RCTs was about 3 to 4 months. The traditional RCTs design did not allow meaningful data on the long-term outcome and confirmed that combination therapy did not induce meaningful increase in 6MWD as compared to monotherapy.

In the fourth World Meeting on Pulmonary Hypertension, the PH community proposed to implement a new generation of RCTs based on CW as primary end point to allow both more information on the effects of the drugs on the long term outcome, in particular if combination therapy was planned.(2) This has leaded to the accomplishment of four RCTs (AMBITION(8), COMPASS-2, GRIPHON, SERAPHIN(9)) which study duration was not fixed but based on the fulfillment of a pre-specified number of events such as mortality, hospitalizations, disease progression and unsatisfactory clinical response.

This important evolution in the RCTs design has allowed to improve the level of evidence for efficacy of the new drugs or the new strategies investigated in PAH, shifting from a test measuring exercise capacity to a true clinical efficacy measure. In addition, the increased length of the randomized phase (from 24 to 36 months) has provided more information on long-term treatment effect, in particular for combination therapy.

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Dr. Gibson pioneered our understanding of the "open artery hypothesis" as well as our understanding of the importance of restoring flow downstream in the capillary bed in the "open microvasculature hypothesis" in heart attack patients. Dr. Gibson invented several of the measures of coronary blood flow that are widely used today, such as the TIMI frame count and the TIMI myocardial perfusion grade.

Dr. Gibson is on the editorial board of numerous leading cardiovascular journals. For four years in a row he has been voted by his peers as one of Boston's Top Doctors in *Boston Magazine, US News & World Report* lists him as one of America's top doctors, and in 2014 he was named one of the world's most influential scientific minds of the past decade by Thomson Reuters. His work has been presented in over 1000 manuscripts, abstracts, trial summaries, textbooks and textbook chapters.

Robert Golub (Chicago, 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.

James Januzzi (Boston, USA)

Dr. James Januzzi is currently the Roman W. DeSanctis Endowed Distinguished Clinical Scholar in Medicine at the Massachusetts General Hospital and Hutter Family Professor of Medicine at Harvard Medical School. He is also a faculty member at the Harvard Clinical Research Institute. Dr. Januzzi has contributed greatly to the understanding of cardiac biomarker testing, where his work with the natriuretic peptides and troponin has set international standards for use in diagnosis, prognosis, and management of patients suffering from acutely decompensated heart failure, chronic heart failure as well as those with acute coronary syndrome. He has published more than 400 manuscripts, book chapters, and review articles, has edited two text books on cardiac biomarker testing. He is on the editorial board of numerous scientific journals, including current service as an Associate Editor at the Journal of the American College of Cardiology: *Heart Failure*. He was the chairman of the NT-proBNP Consensus Panel, is the lead author of the Heart Failure Section for the Universal Definition of MI Biomarker Task Force, was a section editor and member of the working group for the 2013 ACC/AHA Clinical Practice Guidelines for Heart Failure, and is a member of the Heart Failure Society of America.

ABSTRACT

Biomarker guided trials

James Januzzi (Boston, USA)

Several biomarkers have been identified that independently predict the likelihood for adverse cardiovascular outcome. In this regard, biomarkers are now widely used as an inclusion criterion for clinical trials, providing enrichment of event rates. As well, in recent clinical trials such as RELAX-AHF, reduction in several key biomarkers was linked to improved outcome, implying biomarker "response to therapy" is a pivotal finding in benefit from drugs for heart failure. Finally, biomarkers are also being used as surrogate endpoints, such as was done in the PARAMOUNT study of LCX696 in patients with heart failure and preserved ejection fraction.

Thus, biomarkers provide numerous uses for the clinical trialist. That said, while reduction in a biomarker may be a surrogate outcome in clinical trials such as PARAMOUNT, one question that remains surprisingly unanswered and still debated is whether biomarkers can be viewed as a target of therapy for patients with heart failure.

In other words, can the risk informed from biomarker measurement trigger decisions regarding the need to therapy adjustment? Is the biomarker a "target" for therapy? Can the risk predicted by this biomarker be reduced by such therapy adjustments? Can a candidate biomarker tell us about discrete pathophysiologies in heart failure, such as risk for ventricular remodeling or risk for arrhythmia? Will we ultimately be using a panel of markers to "guide" therapy, rather than a single test?

NT-proBNP-guided heart failure care is currently being examined in a pivotal prospective clinical trial (GUIDE IT), but numerous questions will remain after this trial: Are there patients that don't profit from biomarker-guided care (Elders, HFpEF)? Will other biomarkers be superior to the natriuretic peptides or add to them?

In this regard, newer biomarkers have been identified that are additively prognostic to natriuretic peptides, and some have potential mechanistic associations that support a possible therapeutic response with drugs specifically targeting the pathophysiology leading to their release. However, much remains poorly understood regarding newer biomarkers; in this regard, the same standards that were applied for the natriuretic peptides must be met. Focused efforts with the best leading candidates in the novel biomarker field are crucially important to optimize the likelihood for progress in this complex area. If novel markers are no different than an updated BNP or NT-proBNP, little value is likely from them. On the other hand, great value might exist if therapeutic opportunities are found that are different from those triggered by natriuretic peptides.

John Jarcho (Boston, USA)

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

Patricia Kay-Mugford (Novartis, USA)

Dr. Patricia Kay-Mugford is a Doctor of Veterinary Medicine with a Masters in Pharmacology, and over 15 years in Regulatory Affairs in the pharmaceutical industry, across multiple therapeutic areas including cardiovascular, metabolic diseases, immunology and anti-infectives. In her current role as Global Therapeutic Area Lead, Drug Regulatory Affairs, Novartis Pharmaceuticals, responsibilities include leading and managing a team of regulatory liaisons responsible for regulatory strategic oversight of cardio-metabolic programs through development, registration and approval, and post-marketing. She is responsible for ensuring the regulatory integrity of development programs for new molecular entities and biologics by ensuring implementation of strategic and operational advice from phase I through phase IV to meet global registration standards.

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Armin Koch (EMA, GER)

Professor Armin Koch studied mathematics and chemistry at Heidelberg University and was a research assistant at the German Centre for the Research on Cancer (DKFZ) between 1984 and 1991. Thereafter he was an employee at the Institute of Medical Biometry at Heidelberg University until in 1999 when he joined the Federal Institute for Drugs and Medical Devices (BfArM) in Germany. From 2001 to 2008 he was head of the Biostatistics and Experimental Design unit. Since 2008 he has been Director of the Institute for Biostatistics at Hannover Medical School. Pr. Koch is a member of the Scientific Advice Working Party (SAWP) and the Biostatistics Working Party (BSWP) at the European Medicines Agency (EMA).

Wolfgang Koenig (Ulm, GER)

Wolfgang Koenig, MD, PhD, FRCP, FESC, FACC, FAHA is a Professor of Medicine and Cardiology at the University of Ulm Medical School, Ulm, Germany. He graduated from the University of Munich and received his MD from the University of Heidelberg and the PhD from University of Ulm. He is Board certified in internal medicine, cardiology, and in intensive care medicine with special interest in invasive and interventional cardiology. He also trained in cardiovascular disease epidemiology and is a former Director of the WHO-MONICA Augsburg Myocardial Infarction Register. Previous Hospital Appointments include: Director of the Emergency Room 1995-2000; Deputy Director, Departments of Internal Medicine 1995-2000; Director of the Intensive Care Unit 2003-2004, and Director of Cardiovascular Laboratories 2004-2005. At present he serves as a Consultant in Cardiology, and is the Director of the Preventive Cardiology Program and the Clinical Trial Unit (CTU) at the Department of Internal Medicine II - Cardiology of the University of Ulm Medical Center.

Dr. Koenig`s research interests involve the molecular basis of atherothrombogenesis including genetics, the clinical pharmacology of cardiovascular active compounds, and the clinical epidemiology of cardiovascular disorders, focusing on the identification and evaluation of new biomarkers for cardiometabolic diseases.

Dr. Koenig has published extensively in many leading peer-reviewed journal. He has an H-Index of 60. He is a member of the Editorial Board of Clinical Chemistry and was Associate Editor of *Atherosclerosis* (2008 - 2014). In 1999, he served as a Visiting Professor at the Department of Pharmacology, University of Pennsylvania, School of Medicine, Philadelphia, USA. Presently he serves on the Steering Committee of various large international randomized clinical trials testing innovative targets in cardiovascular medicine.

Joerg Koglin (Merck, USA)

Joerg Koglin, MD, PhD, is Executive Director and Section Head, Cardiovascular Clinical Research, at Merck Research Laboratories, Rahway, New Jersey, USA

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

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

Mikhail Kosiborod (Kansas City, USA)

Mikhail Kosiborod, MD, FACC, FAHA, is a cardiologist at Saint Luke's Mid America Heart Institute in Kansas City, Missouri and a Professor of Medicine at the University of Missouri-Kansas City School of Medicine. Dr. Kosiborod graduated Summa Cum Laude from the City University of New York, and received his medical degree from Mount Sinai School of medicine in New York, NY, after being elected into the Alpha Omega Alpha medical honor society. He trained in internal medicine at Yale-New Haven Hospital and completed his fellowship in cardiovascular disease, as well as the Robert Wood Johnson Clinical Scholars program at Yale University School of Medicine, receiving several awards for clinical and academic excellence. 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 numerous 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. 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.

ABSTRACT

Therapeutic options to manage hyperkalemia: update on recent and ongoing trials

Efficacy and safety of sodium zirconium cyclosilicate (ZS-9) in patients with hyperkalemia: results from the HyperkAlemia RandoMized interventiON multI-dose ZS-9 maintEnance (HARMONIZE) clinical trial

Mikhail Kosiborod (Kansas City, USA)

Background: Hyperkalemia is common in patients with cardiovascular disease, associated with poor prognosis, and difficult to manage due to lack of effective therapies. ZS-9 is a non-absorbed zirconium-based cation exchanger that selectively binds potassium (K+) in the intestine. ZS-9 has been shown to acutely lower serum K+ in patients with hyperkalemia. However, its long-term efficacy in maintaining normokalemia has not been evaluated in clinical trials.

Methods: HARMONIZE is an international, multicenter, randomized, double-blind trial designed to evaluate the long-term efficacy and safety of ZS-9 in ambulatory patients with hyperkalemia (serum K+ ≥ 5.1 mEq/L). Exclusions were dialysis requirement, life-threatening arrhythmias, and active treatment with resins (i.e. sodium polystyrene sulfonate). All patients received 10 g of ZS-9 TID for 48 hrs in the acute open label phase. Patients achieving normokalemia (K+ 3.5-5.0) were then randomized to one of 3 ZS-9 doses (5, 10, or 15 g once daily) or placebo (PBO) for 28 days in the maintenance phase. K+ was measured on Days 1, 2, 5, 8, 12, 15, 19, 22, 26 and 29. Primary endpoint was mean K+ in each ZS-9 dose vs. PBO during Days 8-29 of the maintenance. Secondary endpoints were the proportion of patients achieving and maintaining normokalemia in the acute and maintenance phases respectively, and safety. Pre-specified subgroups were patients on RAAS inhibitors, heart failure (HF), CKD and diabetes.

Results: The HARMONIZE study plans to enroll ~275 patients in the acute open label phase, with 232 patients being subsequently randomized in the long-term maintenance phase. To date, 448 patients have been screened, and 240 enrolled in the acute open label phase. Full efficacy and safety results of the HARMONIZE study will be presented at the meeting.

Conclusion: HARMONIZE is the first clinical trial

examining the long-term efficacy and safety of ZS-9 for the treatment of hyperkalemia. Given the serious consequences of hyperkalemia, and lack of effective long-term therapies, the results of HARMONIZE may have significant clinical impact.

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Stuart Kupfer (Takeda, USA)

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

Michael Lauer (NHLBI, USA)

Michael Lauer, MD, is Director of the Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute, where he leads the Institute's program for research on the causes, prevention, and treatment of cardiovascular diseases. He received education and training at Rensselaer Polytechnic Institute, Albany Medical College, Harvard Medical School, Harvard School of Public Health, and the NHLBI's Framingham Heart Study. He spent 14 years at Cleveland Clinic as Professor of Medicine, Epidemiology, and Biostatistics. During his tenure at the Clinic, he led a federally-funded internationally renowned clinical epidemiology program that applied big data from large-scale electronic health platforms to questions regarding the diagnosis and management of cardiovascular disease. Since coming to the NHLBI in 2007 he has promoted efforts to leverage big data infrastructure to enable high-efficiency epidemiology, comparative effectiveness research, and clinical trials. He has received numerous awards including the NIH Equal Employment Opportunity Award of the Year and the Arthur S. Flemming Award for Exceptional Federal Service in recognition of his efforts to grow a culture of learning and accountability.

Marty Lefkowitz (Novartis, USA)

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

Wei Liang (FDA, USA)

Dr. Liang is a Preclinical Reviewer in the Office of Cellular, Tissue, and Gene Therapies (OCTGT) in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA). She joined OCTGT in 2006. Her primary focus is the review of preclinical studies that are intended to support the conduct of clinical studies of cellular and gene therapy-based products as therapeutics for cardiovascular indications.

ABSTRACT

An introduction to CBER and its function Preclinical considerations for early-phase cardiovascular cell and gene therapy studies

Wei Liang (FDA, USA)

The presentation will discuss preclinical testing programs for gene therapies and cellular therapies intended to treat cardiovascular disease, including animal species/model selection, preclinical study design, and accompanying data needed to support an Investigational New Drug (IND) application for a first-in-human clinical trial.

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 the first to show a benefit of CRT in mild heart failure. She is presently the PI of the ongoing MiracelEF study focusing on CRT in mild to moderate heart failure and LVEF 36-50%. Dr. Linde is the author of more than 200 papers, reviews and meeting abstracts in a wide variety of fields including CRT, haemodynamic monitoring and the molecular biology of arrhythmias, and she serves on the editorial board of several journals. She has been a board member of the European Heart Rhythm Association (EHRA), an official branch of the European Society of Cardiology. She has been involved in the EHRA Task Force for guidelines in pacing and CRT published 2007 updated 2010 and is a member of the scientific committee of the European cardiac resynchronization therapy survey. She is chair of the scientific program committee for EHRA Europace Cardiostim in Milan 2015 and a member of the Board EHRA.

Joann Lindenfeld (Denver, USA)

Dr. JoAnn Lindenfeld is currently director of the Advanced Heart Failure and Transplant Program at the University of Colorado and Co-Director of the Center for Women's Health Research at the University of Colorado.

Dr. Lindenfeld is the current President of the Heart Failure Society of America and the Immediate past chairman of the Heart Failure Society Clinical Guidelines Committee. She served on the FDA Cardiorenal Advisory panel for nine years and currently serves as an ad hoc member of the FDA Devices panel. Her research interests include mechanisms of hypertension and renal function in heart transplant recipients and genetic polymorphisms that predict responses to calcineurin inhibitors. Heart failure interests include the cardiorenal syndrome and mechanisms of mineralocorticoid receptor antagonists in heart failure. She has been a member of steering committees, DSMBs, and clinical endpoint committees of many large randomized

clinical trials in heart failure. She is funded by the NIH and AHA. She has published over 200 original manuscripts, reviews, and book chapters. Dr. Lindenfeld has been awarded the «Gold Headed Cane Award» at the University of Colorado indicating the best physician role model in the medical center. The award has been presented only nine times in the 120 year history of the school.

Dr. Lindenfeld is currently a member of the Steering Committees for multicenter, randomized trials including COAPT, FIX-IT, and CAT-HF.

Dr. Lindenfeld co-founded and co-directs the Center for Women's Health Research--a center designed to promote research and education in women's health. The Center is currently a recipient of the 2.5 million dollar NIH «Building interdisciplinary careers in women's health» grant that has just been renewed for another 4 years. The Center has 23 active grantees and last year the former grantees of the Center generated 21 million dollars in NIH, ADA, and AHA grant funding.

Ray Lipicky (North Potomac, USA)

Raymond John Lipicky, MD is the Director of LIPICKY, LLC (a consulting company) having left (March 2002, after 21 years of service) the U.S Food and Drug Administration (FDA) where he held the position of Director, Division of Cardio-Renal Drug Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research. Previously, he was on the faculty of University of Cincinnati, College of Medicine (for 14 years) where he held the positions of Professor of Pharmacology and Professor of Medicine and Director, Division of Clinical Pharmacology at the time he joined FDA. He is a graduate of the University of Cincinnati College of Medicine, trained in Internal Medicine and Cardiology. He also had an appointment as Visiting Scientist at the Marine Biological Laboratory (Woods Hole, MA) where, for about 30 years, he had a summer laboratory pursuing an interest in drug effects on electrically-excitable membranes, research which continued during his entire tenure at FDA.

ABSTRACT

CV safety endpoints: the heart failure issue Regulatory issues

Ray Lipicky (North Potomac, USA)

The apparent controversy about the need to rule out adverse cardiovascular effects as an "adverse effect" of oral (or even parenteral) treatments for diabetes (that became part of the US regulatory policy in 2008, I think), although perhaps worth talking about, is only the tip of the iceberg. The real and protracted discussion should revolve about how to handle approvals that have as the basis of approval only effects upon well-proven surrogates (that HbA1c is not) or only upon symptoms. That is the real problem and requires a re-think of the entire development process.

I think available data indicate that the entire process of therapeutic development needs a wholesale revision and focal conflicts like oral hypoglycemic agents are addressing the wrong issues.

David Madigan (Columbia, USA)

David Madigan is Executive Vice President and Dean of the Faculty of Arts & Sciences at Columbia University in New York City. He received a bachelor's degree in Mathematical Sciences and a PhD in Statistics, both from Trinity College Dublin. He has previously worked for AT&T Inc., Soliloquy Inc., the University of Washington, Rutgers University, and SkillSoft, Inc. He has over 150 publications in such areas as Bayesian statistics, text mining, Monte Carlo methods, pharmacovigilance and probabilistic graphical models. He is an elected Fellow of the American Statistical Association, the Institute of Mathematical Statistics, and the American Association for the Advancement of Science. He recently completed a term as Editor-in-Chief of *Statistical Science* and is the current editor of *Statistical Analysis and Data Mining*.

ABSTRACT

Big data versus bias. And the winner is? Methodological issues in analyzing big data

David Madigan (Columbia, USA)

Observational healthcare data, such as administrative claims and electronic health records, play an increasingly prominent role in healthcare. Studies routinely estimate temporal associations between medical product exposure and subsequent health outcomes of interest and the results influence prescribing patterns and healthcare policy more generally. Some authors have questioned the reliability and accuracy of such studies, but few previous efforts have attempted to measure their performance. We have conducted a series of experiments to empirically measure the performance of various observational study designs with regard to predictive accuracy for discriminating between true drug effects and negative controls. I describe this work, explore opportunities to expand the use of observational data to further our understanding of medical products, and highlight areas for future research and development.
http://www.omop.org http://www.ohdsi.org

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Aldo Maggioni (Florence, ITA)

Aldo Maggioni received his medical degree from the University of the Milan School of Medicine, where he also completed a fellowship in internal medicine. He performed a residency in cardiology at the University of Padua before becoming a clinical cardiologist in the Division of Cardiology at General Hospital "G. Fornaroli" in Magenta, Milan, then at General Hospital Fatebenefratelli ed Oftalmico, also in Milan.

Dr. Maggioni is Member of the Steering Committee of the GISSI studies and Director of the Research Center of the Italian Association of Hospital Cardiologists in Florence. Since 2010 Dr. Maggioni is the Scientific Coordinator of the EUROObservational Research program of the European Society of Cardiology.

Dr. Maggioni served as a member of the Steering Committee, Event Evaluation Committee, Data and Safety Monitoring Board of more than 50 clinical studies in areas including myocardial infarction, secondary prevention, diabetes, stroke, and acute and heart failure.

Fady Malik (Cytokinetics, USA)

Fady I. Malik, MD, PhD, 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 B.S. 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.

Thomas Marciniak (FDA, USA)

Dr. Marciniak has been a Medical Team Leader and Clinical Reviewer for 13 years in the Cardiovascular and Renal Products Division of the FDA. At the FDA he has performed more hands-on analyses of complete data from cardiovascular outcomes trials in NDA submissions than any other reviewer. Overall he has forty years of experience in clinical research, epidemiology, and Federal regulation of medical products (at the FDA, NIH, and the Centers for Medicare and Medicaid Services) and a bibliography of more than 50 professional publications. His educational background is a board-certified internist trained at Northwestern University and the Mayo Clinic.

ABSTRACT

Approvability issues: FDA–EMA divergence explained?

Thomas Marciniak (FDA, USA)

The EMA and the FDA not infrequently diverge on approvals and labels for cardiovascular drugs. The reasons for the divergences may not seem obvious. I propose three simple principles explaining EMA-FDA divergence: (1) The red lobster metaphor. (2) Show me the money? (3) If you've seen one . . . I illustrate these principles with examples from past EMA-FDA divergences.

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Felipe Martinez (Cordoba, ARG)

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

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

ABSTRACT

Focusing on polypills in CV secondary prevention: the FOCUS trial and beyond

Felipe Martinez (Cordoba, ARG)

Mortality due to cardiovascular diseases (CVD) is still rising in low and middle-income countries, and is expected to become the leading cause of death by 2030. Lack of compliance with prescribed lifestyle modification and lack of medication adherence, are defined as fundamental factors impacting the strategies for CVD secondary prevention. It has been estimated that adherence to CV medications is about 57% after a median of 2 years. To address the determinants of poor adherence, a strategy based on the use of a fixed-dose combination (FDC) or polypill, including key medications to reduce CV risk as a once daily dose pill, has been recently introduced. Several trials like the SPACE Collaboration, tempus, Tips and others, have tested the effect of such an approach on adherence in high risk patients including those with established CV disease with promising results. The FOCUS (Fixed Dose Combination Drug for Secondary Cardiovascular Prevention) project was designed, using an appropriate conceptual framework, to better understand the adherence to medication in the post MI setting, the factors that influence the lack of adherence and the effect of a FDC on adherence in this high risk population. The study was performed in Europe and South America, and included 2118 patients in Phase 1 and 870 in Phase 2. This group was randomized to either the polypill or the three drugs (aspirin, ramipril and sinvastatin) separately for phase 2.

Primary end-point was adherence to the treatment measured at the final visit by the self-reported Morisky-Green questionnaire) and pill count (patients had to meet both criteria for adherence at the in-person visit in order to be considered adherent). Compared with the three drugs given separately, the use of a polypill strategy met the primary endpoint for adherence- increased self-reported and direct measured medication- for secondary prevention following an AMI. This result is consistent with previous trials and strongly support the benefit of polypills in secondary cardiovascular prevention.

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Manuel Mayr (London, UK)

Manuel Mayr qualified in Medicine from the University of Innsbruck (Austria) in 1999, where he graduated "sub ausspiciis praesidentis", the highest distinction awarded for academic education. He soon decided that his interests lay in research and therefore took up full-time research training in 2001, when he moved to St George's Hospital Medical School to undertake a PhD with Professor Qingbo Xu. His PhD was awarded by the University of London in 2005, on the topic of "Cardiovascular Proteomics: Linking Proteomic and Metabolomic Changes". He obtained a BHF Intermediate Research Fellowship in 2005 and in 2006 moved to King's College London as Lecturer in the Cardiovascular Division. In 2008, he was successful in obtaining a BHF Senior Research Fellowship and this was recently renewed for a second term. In parallel, he achieved promotion to Senior Lecturer in 2008, to Reader in 2010, and to Professor in 2011. His academic achievements have been recognised by the inaugural Michael Davies Early Career Award of the British Cardiovascular Society (2007), the inaugural Bernard and Joan Marshall Research Excellence Prize of the British Society for Cardiovascular Research (2010), and the Outstanding Achievement Award by the European Society of Cardiology Council for Basic Cardiovascular Science (2013).

ABSTRACT

Identifying new risk markers and potential targets: the value of the proteome, metabolome, microRNAs or the transcriptome?

Postgenomics technologies for cardiovascular biomarker discovery

Manuel Mayr (London, UK)

Cardiovascular disease (CVD) results from a complex interplay of genes and environmental factors. A clear picture of how these different factors impact on individuals is yet to emerge. My group uses proteomics in combination with other postgenomics technologies, such as lipidomics and microRNA profiling, to integrate biological information in disease-specific networks for CVD. Unlike genomics, post-genomics approaches are not "off-the-shelf technologies". We try to push the boundaries of the field in developing and pioneering specialist methodology to identify novel biomarker candidates. While studying molecular interactions has been a research focus for many years and has provided important insight into biology, the attention has now shifted towards a more integrative network biology approach. Similarly, routine clinical measurements tend to evaluate individual biomarkers. By linking cutting-edge postgenomics technologies to population studies, our aim is to explore biomarker panels derived from a multi-omics approach (proteomics, lipidomics and microRNA-omics) in a primary preventive setting. This integration of emerging technologies has the potential to improve our understanding of the aetiology, prediction and stratification of CVD.

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Brenton McCright (FDA, USA)

Brent McCright, PhD, is a research Biologist in the Center for Biologics Evaluation and Research, Food and Drug Administration (Division of Cellular and Gene Therapies). Dr. McCright joined the Division of Cellular and Gene Therapies, in the Office of Cellular, Tissue, and Gene Therapies, at the Center for Biologics Evaluation and Research of the FDA in 2002. Dr. McCright reviews INDs and works on policy development for cellular therapies. In addition, Dr. McCright's lab investigates the function of key signaling molecules during organogenesis and tissue repair. The goal of Dr. McCright's current research is to identify molecules that may be useful in predicting the effectiveness of cellular therapies.

ABSTRACT

An introduction to CBER and its function

Chemistry, Manufacturing, and Controls (CMC) considerations for early-phase cardiovascular cell and gene therapy studies

Brenton McCright (FDA, USA)

A wide variety of cellular and gene therapies are being developed and used in clinical trials to repair, regenerate, and restore cardiovascular function. Prior to use of a new therapy in a clinical trial, product manufacturing information needs to be submitted to the FDA in an Investigational New Drug (IND) application. For early phase trials, FDA's primary objectives in reviewing an IND are to assure the safety and rights of subjects, while in later phases it is important to assure that the quality of the characterization of the product is adequate to permit a scientific evaluation of effectiveness and safety. Cellular therapies can be derived from pluripotent stem cell sources, from adult tissues, and may be combined with substrates to form a cell-scaffold combination product. When cellular material is obtained from allogeneic (non-self) sources, the donor must be tested and screened for relevant communicable diseases per 21 CFR 1271. At the beginning of a Phase 1 or 2 trial, product characterization should include manufacturing process documentation, initial lot release specifications, and product stability/shipping data. Growth factors, antibodies, and animal products that are used in the manufacture of cellular products play a large role in determining the testing needed to ensure the safety of the product and only high quality reagents should be used in the manufacture of cellular products. As product development proceeds, manufacturing protocols should be finalized, a validated potency assay should be in place, and scale-up issues need to be addressed.

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.

ABSTRACT

Ongoing trials: therapies on the horizon?

Natriuretic peptides

Effects of Ularitide on the short-term clinical course and long-term mortality of patients with acute heart failure: the TRUE-AHF trial

Alexandre Mebazaa (Paris, FRA)

Natriuretic peptides comprise a family of structurally related molecules that possess several beneficial effects including potent diuretic and vasodilating effects. The kidney synthesizes its own natriuretic peptide, urodilatin, that is secreted luminally to act downstream at distal segments of the nephron to regulate sodium and water reabsorption. Ularitide is a chemically synthesized analogue of urodilatin, which (when given intravenously) leads to systemic and renal vasodilation, diuresis and natriuresis, and inhibition of the renin-angiotensin system in patients with heart failure. The TRUE-AHF is a randomized, double-blind, parallel-group, placebo-controlled trial which is evaluating the effects of a 48-hour infusion of ularitide on the short-term clinical course and long-term mortality of patients with acute heart failure. The trial has two primary endpoints: (1) the clinical course of patients during their index hospitalization and (2) cardiovascular mortality during long-term follow-up. The clinical course is evaluated using the clinical composite endpoint, which combines information regarding changes in symptoms and the persistence or the occurrence of in-hospital worsening heart failure events and death.

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.

Jerry Menikoff (FDA, USA)

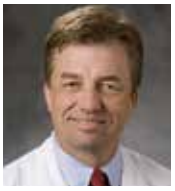
Jerry A. Menikoff, MD, JD, is the Director of the Office for Human Research Protections (OHRP), an office within the U.S. Department of Health and Human Services. That office is one of the lead units of the U.S. government responsible for protecting research subjects. Prior to joining OHRP, Dr. Menikoff served as the director of the NIH Office of Human Subjects Research, responsible for protecting subjects enrolled in NIH intramural research. Prior to that, he was Associate Professor of Law, Ethics and Medicine at the University of Kansas. Among the books he has authored or co-authored are Law and Bioethics: An Introduction (Georgetown University Press) and What the Doctor Didn't Say: The Hidden Truth about Medical Research (Oxford University Press).

Catherine Meyers (NIH/NCCAM, USA)

Catherine M. Meyers, MD, is the Director of the Office of Clinical and Regulatory Affairs at the National Institutes of Health (NIH), National Center for Complementary and Alternative Medicine (NCCAM). The Office plays a major role in planning, coordinating, and monitoring the NCCAM clinical research program. Dr. Meyers is also one of the lead Project Scientists for the NIH Common Fund Health Care Systems Research Collaboratory, an initiative to conduct pragmatic clinical trials in partnership with clinical investigators, patients and health care systems in the United States.

Dr. Meyers earned her undergraduate degree in Chemistry at the University of Chicago and received her MD from the University of Illinois at Chicago. She completed postgraduate residency training in internal medicine at the University of Chicago (Michael Reese Hospital) and a clinical/research nephrology fellowship at the University of Pennsylvania.

Prior to her 2009 arrival at NIH/NCCAM, Dr. Meyers was a Senior Scientific Advisor at the NIH National Institute of Diabetes and Digestive and Kidney Diseases for nearly a decade, where she directed a clinical trials program focused on end-stage kidney disease. Her previous appointments include a three-year tenure at the US Food and Drug Administration, as well as a faculty position at the University of Pennsylvania's School of Medicine, where she was a member of the Department of Internal Medicine, Renal-Electrolyte and Hypertension Division.



Christopher O'Connor (Durham, USA)

Dr. O'Connor is the Director of the Heart Center and Chief of the Division of Cardiology and Clinical Pharmacology at Duke University. He is a Professor of Medicine and Associate Professor in Psychiatry and Behavior Sciences. He is the Editor-in-Chief of JACC: Heart Failure. He is a Fellow of the ACC, the AHA, and the ESC. He has served on over 90 CEC and DSMC committees in 25 years and served as Chair or Co-Chair on many of these committees. He has an extensive record of successful mentorship of trainees and has published over 500 manuscripts. He has served as PI or Co-PI on over 20 national and international clinical trials with an extensive record of NIH/NHLBI and industry grants, and holds a number of leadership

positions in national societies and current clinical trials. His research interests include: acute heart failure; co-morbidities in heart failure; clinical trials; biomarkers; and novel pharmacological and non-pharmacological approaches for the treatment of heart failure.

Dr. O'Connor completed his undergraduate and medical school training at University of Maryland. He completed his Internal Medicine residency, Chief Medical Residency and Cardiology Fellowship at Duke University.

Milton Packer (Dallas, USA)

Dr. Packer is an internationally recognized clinical investigator, who has made seminal contributions to the field of heart failure, both in understanding its mechanisms and defining its management. His work has spanned more than 30 years and has been supported by numerous investigator-initiated grants from the NIH and from industry. He led the Division of Circulatory Physiology at Columbia University for 12 years and has been the principal investigator of more than 12 large international multicenter trials. He has served frequently as a member of government advisory committees, study sections, task forces or Data and Safety Monitoring Boards for the NIH. He served as a member of the Cardiac and Renal Drugs Advisory Committee to the US Food and Drug Administration from 1986-1992 and then as its Chair from 1997-2001. He was President of the Heart Failure Society of America from 2000-2002 and has served on numerous guidelines and standards committees for the American Heart Association and American College of Cardiology. He has received many teaching awards and has mentored dozens of young clinical investigators, many of whom have become leaders in research. He is currently the Stoffel Distnguished Chair in Cardiology and Professor and Chair of the Department of Clinical Sciences at the University of Texas Southwestern Medical Center in Dallas.

Marc Penn (Akron, USA)

Marc Penn, MD, PhD, FACC is a cardiologist and Director of Research and the Director of the Cardiovascular Medicine Fellowship at the Summa Cardiovascular Institute in Akron, Ohio and Professor of Medicine and Integrative Medical Sciences at Northeast Ohio Medical University where he leads the Skirball Laboratory for Cardiovascular Cellular Therapeutics. Dr. Penn was a staff cardiologist at the Cleveland Clinic from 2000-2011 where he served as the Director of the Coronary Intensive Care Unit, Director of the Bakken Heart-Brain Institute, and the Center for Cardiovascular Cell Therapy. Dr. Penn completed his undergraduate and postgraduate work at Case Western Reserve University completing a PhD in Biomedical Engineering (1989) and Doctor of Medicine (1994); Internal Medicine training at University Hospitals of Cleveland (1994-97) and a Cardiovascular Medicine Fellowship at Cleveland Clinic (1997-2000). He received the AHA 1999 Irvine H. Page Young Investigator award for Atherosclerosis Research. He is an active inventor and serial entrepreneur generating intellectual property in the fields of diagnostics, biologics and devices that has been licensed by numerous companies. He was Innovator of the Year at the Cleveland Clinic (2006). He is the inventor, founder, member of the BOD and CMO of Juventas Therapeutics, Inc. (Cleveland, OH) a private clinical stage regenerative medicine company; co-founder and CMO of Cleveland Heart Labs, Inc. (Cleveland, OH), a diagnostic company based on biomarkers of coronary artery disease and myocardial infarction. He is the PI of the Athersys MultiStem in AMI Phase I and II trials. He is recognized as one of the top 50 doctors in the history of the Cleveland Clinic (MedCity News, December 2011).

ABSTRACT

Ongoing trials: therapies on the horizon?
Myocardial matrices: cell therapies to reverse/delay progression?

Marc Penn (Akron, USA)

The potential for stem cell repair of injured tissue has garnered great hope for the prevention and treatment of cardiac dysfunction. In the early 2000's there was significant controversy regarding the validity of cardiac differentiation of stem cells following transplantation and engraftment in acutely injured myocardium. At that time, lost in the controversy regarding cardiac myocyte regeneration was the fact that stem cell transplantation in AMI and CHF led to improvements in cardiac function and remodeling.

Over the ensuing several years there was increasing understanding of the importance of the paracrine effects of stem cell based tissue repair. Work from Dzau and colleagues demonstrated that conditioned media from mesenchymal stem cells (MSC) could induce the same benefits as engraftment of the MSC and that the effects of conditioned media could be modulated by manipulation of the MSC secretome. Mayorga and colleagues further refined the signaling pathways responsible for cardiac protein expression in MSC, ultimately demonstrating that cardiac protein expression in MSC in response to TGF was not associated with cardiac regeneration but actually enhancement of the MSC secretome.

We participated in developing the multipotent adult progenitor cell (MAPC) to prevent cardiac dysfunction in AMI. Our preclinical studies we demonstrated significant preservation of cardiac function and neovascularization

post-AMI despite the limited survival of the MAPC 6 weeks after AMI. That non-surviving stem cells could induce clinical benefit was demonstrated in the first-in-man study in which MAPC were delivered to the adventitia of patients 2-5 days after primary stenting for first AMI. We observed a significant dose dependent increase in ejection fraction at 4 months after AMI that was sustained out to 1 year.

In 2000 we proposed the following hypothesis - that stem cell based repair of injured tissue is a natural process that does not lead to significant clinical benefit due to dysregulation of the reparative system, not the lack of stem cells. At that time we sought to define the molecular regulators of endogenous stem cell repair of injured tissue. We initially identified stromal cell derived factor-1 (SDF-1) as a key regulator of stem cell recruitment to the heart following AMI and demonstrated that the over-expression of SDF-1 leads to improvements in cardiac dimensions and function. Recently using mice that lack cardiac myocyte and cardiac stem cell CXCR4 expression, we demonstrated that the release of SDF-1 by MSC is critical for MSC induced inhibition of cardiac myocyte death and enhancement of cardiac stem cell recruitment. These data demonstrate that an important mechanism of effect of adult stem cell therapy is activation of endogenous stem cell repair and support our prior hypothesis that one benefit of adult stem cell therapy is the temporal realignment of SDF-1 secretion with CXCR4 receptor expression by end-organ cells (cardiac myocytes) and endogenous tissue specific stem cells (cardiac stem cells). The importance of temporal alignment of the SDF-1:CXCR4 axis has also been shown in the eye in response to retinal detachment.

In 2011we began testing the hypothesis that defining the molecular mechanisms of stem cell based tissue repair could lead to novel therapeutics in a Phase I clinical trial that sought to re-establish SDF-1 expression in the myocardium of patients with NYHA Class III chronic heart failure due to a history of myocardial infarction (NCT01082094). We have now completed enrollment of 3 Phase II trials in chronic heart failure (NCT01643590, NCT01961726) and critical limb ischemia (NCT01410331).

Stem cell based therapies have tremendous potential to prevent and treat the morbidity and mortality associated with chronic disease and end-organ dysfunction. Clinical trials testing the safety and effects of stem cells to prevent and treat cardiac dysfunction have overwhelmingly demonstrated the safety of the approach. Some trials have demonstrated meaningful and potentially clinically important findings whereas others have failed to demonstrate benefit. The overwhelming data suggests that these adult stem cells lead to activation of an endogenous stem cell based repair system; thus, the question is will future approaches utilize cells at all? In medicine when we want to induce the immune system we don't transfuse B and T-cells, we deliver adjuvants. The data to date suggests that there are adjuvants that prime endogenous stem cell repair. Whether the target is SDF-1 or other chemokines/growth factors remains to be determined. Importantly the field, funding agencies and peer review system needs to move from hand waving away the issues of mechanism of action and move to rigorous hypothesis based science that defines the biology of endogenous stem cell repair.

Just as important as developing therapies that can lead to improved clinical outcomes is the potential to expand our understanding of pathophysiology. A decade ago when we proposed stem cell based repair was a natural but clinically inefficient process, a corollary to our hypothesis was that mammals have evolved to scar instead of heal in an attempt to minimize tumor. While still an unproven hypothesis we would be remiss if we did not note that up-regulation of SDF-1, MCP-3, and NOTCH and down-regulation of disabled-2, all factors that in our hands enhance stem cell function, are all associated with the enhancement of tumor survival. These observations have led us to propose the concept that a patients predisposition to stem cell based healing they are either a "healer" or a "scarrer". If they heal they recover from end-organ injury but enhance dysplastic tissue/tumor growth; whereas if they scar in response to tissue injury they are prone to atherosclerosis and ischemic events but do not support tumor growth. Through defining the molecular mechanisms associated with stem cell based tissue repair these types of interesting and transformative hypotheses can be generated.

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Carl Pepine (Miami, USA)

Carl J Pepine, MD, MACC, is Professor of Medicine at the University of Florida (UF), College of Medicine, in Gainesville, Florida.

Dr. Pepine's fields of research interest are Ischemic Heart Disease/Hypertension/Heart Failure/Cell-based therapy/CVD in Women and he has had continuous peer reviewed funding (DoD, VA, VA Merit, NIH) for over 35 years. He has authored/co-authored more than 700 scientific publications and edited 5 textbooks all in the field of CV Medicine.

Currently he is Director of the CV Cell Therapy Program at UF and Principal Investigator (PI) of the NIH supported Cardiovascular Cell Therapy (CCTRN) Regional Center at UF (1996 to present). He is also PI of the UF Center for NIH-supported Women's Ischemic Syndrome Evaluation (WISE) (1996 to present). He is on the Leadership Committee of UF Clinical and Translational Science Institute (CTSI) where he is Director of the 12 Clinical Research Units.

Dr. Pepine is a Master of the American College of Cardiology (MACC) and a Fellow of the American Heart Association (FAHA), member of the American Society for Clinical Investigation (ASCI), Association of Professors of Cardiology, Board of Trustees of the American College of Cardiology (ACC) and a past president of the ACC. He has served /or is serving on a number of National Heart, Lung, and Blood Institute (NHLBI) clinical trial committees, including the FREEDOM, BARI2D, ACIP, PIMI, SOLVD, etc. in addition to numerous NIH Review Committees.

ABSTRACT

Trial design issues

Heart failure trials: clinically meaningful endpoints

Carl Pepine (Miami, USA)

Measuring effects of novel therapeutics in chronic heart failure (HF) trials is a formative challenge even for experienced investigators. It is important to emphasize that a clear, prospective description (written in protocol) of study outcomes/endpoints, planned with specifically declared assessments of type I error penalties, is a necessary perquisite. Likewise, objective, quantifiable, and meaningful outcome measures are essential to minimize the possibility of inconsistent results due to inherent limitations in the measures.

Clinically meaningful outcomes/endpoints used for HF trials, evaluating biologics and cell-based therapies, are numerous and each has strengths and weaknesses that create controversies regarding which is most appropriate relative to clinical importance, sensitivity, reliability, and consistency. They include the following categories:

1. *Overall clinical status evaluation*- usually as symptoms- (e.g. dyspnea/fatigue); functional capacity- exercise tolerance testing (CP testing, 6 minute walk test), NYHA functional class, global assessment of progress, and quality-of-life (QoL).
2. *Morbidity and Mortality*- usually as major clinical events/status change- (e.g. death and/or HF hospitalization). Death is the most definitive event, objective, quantifiable, not subject to bias, with unquestionable clinical importance that pre-empts all other efficacy/safety outcomes. For patients with clinical detrition but remain alive, HF hospitalization captures clinical deterioration for worsening symptoms that require intensive therapy, consume recourses, and impair QoL.
3. *Patient-reported outcomes (PROs)*. In HF, the majority of PROs related to health-related-QoL and depression measures. PROs are used to inform health decisions from patient decision-making to developing health policy aimed at improving population health.
4. *Composite endpoints.* In HF trials these include 'Packer's ordinal composite score', 'Cleland's patient journey', 'Braunwald's weighted unsatisfactory outcome'.

There is an unmet need for outcome measures assessing HF progression (nonfatal clinical deterioration). This remains problematic since HF patients may feel worse on certain days/certain periods, yet such worsening may not represent true change in the clinical course of their HF.

This unmet need also extends to better evaluation of symptoms, PROs, clinical composite endpoints, improved methods for weighting relative importance of individual components of composite endpoints, and safety endpoints.

In conclusion, except for death, no single endpoint evaluating HF status, including HF hospitalization, provides a uniformly sensitive and reproducible measure of the HF patient's response of treatment.

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Marc Pfeffer (Boston, USA)

Dr. Marc Pfeffer 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 and RED-HF. He is currently a leading investigator in TOPCAT and ELIXA, trials in patients with heart failure with preserved ejection fraction and diabetes, respectively.

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, as well as, the James B. Herrick Award, both from the American Heart Association. Dr. Pfeffer is an Honorary Fellow of the Royal College of Physicians and Surgeons of Glasgow.

Ileana L. Piña (New York, USA)

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

Dr. Piña served as principal investigator in multiple heart failure trials, including PRECISE, ELITE and ATLAS, co-investigator for VEST and Val-HeFT, and served

on the DSMB of WARCEF. She is a former member of the Heart Failure Society of America Executive Council and former Chair of NHLBI, via the HF-ACTION study and Clinical Trials Committee. A recent recipient of the prestigious AHA Chairman's Award (November 2013), Dr. Piña continues in her efforts to further AHA's strategic goals. She is currently on the Get With the Guidelines and Target HF committees and the Go Red for Women committee (AHA).

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

Bertram Pitt (Ann Arbor, USA)

Bertram Pitt is a professor of medicine emeritus at the University of Michigan School of Medicine. Dr. Pitt obtained his MD degree from the University of Basel in Switzerland in 1959. He subsequently did a fellowship in cardiology at the Johns Hopkins University School of Medicine and remained on the faculty there until 1977 when he left to direct the division of cardiology at the University of Michigan School of Medicine. He has been chairman or co-chairman of a number of clinical trials in cardiology including: SOLVD; ELITE I and II; Prevent; Rales and Ephesus. He is currently chairman of the steering committee of the NHLBI TOPCAT trial examining the effect of spironolactone in patients with HF and preserved LV systolic function; co-chairman of the Emphasis-HF trial examining the role of eplerenone in patients with NYHA Class II HF; chairman of Break-DHF; co-chairman of STOP-CKD; co-chairman of Exceed; cochairman 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 Universi.

Francis Plat
(Juventas Therapeutics, Inc., USA)

Dr. Francis Plat, MD, joined Juventas in 2014 as chief strategy officer. He brings over 24 years of international experience in clinical research, having worked within a number of global pharmaceutical companies. He began his industry career at Bristol Myers-Squibb where he occupied several positions of responsibility like medical director in France and international group leader in cardiovascular development. He spent four years at Novartis, where he was responsible for global clinical trials as vice president of cardiovascular clinical research. Dr. Plat then joined Daiichi Sankyo in 2005 as vice president of cardiovascular clinical development. Prior to joining Juventas he was vice president and therapeutic area head, Atherosclerosis and Cardiovascular, at Merck Research Laboratories.
Dr. Plat has been involved in the development and repositioning of numerous cardiovascular compounds from 'proof of concept' through to registration and approval.

Dr. Plat received his medical degree from the University of Paris and is a board-certified cardiologist. He spent 10 years practicing medicine in France, including post-cardiovascular surgery at the intensive care unit in the Hopital Marie Lannelongue and in cardiac rehabilitation at Broussais Hospital.

ABSTRACT

Trial design issues

The specific framework of biologics and cell therapy trials in heart failure

Francis Plat (Juventas Therapeutics, USA)

Despite aggressive revascularization therapy in ischemic heart disease a substantial proportion of patients experiences left-ventricular remodeling at the origin of left ventricular dysfunction. One novel way to modify this process in ischemic heart disease is cell therapy. Cellular transplantation has focused on use of various cell types, including differentiated cells such as skeletal myoblasts, cardiac myocytes, smooth-muscle cells, cardiac fibroblasts, and bone-marrow-derived cells. Recently some authors have attributed improvement in ventricular function to paracrine actions of Myocardial Stem Cells.

A large number of trials already provide a data set of evidence in favor of these interventions as attested in a recent meta-analysis. Nevertheless these data were generated in trials with different intervention, cells, cell number, mode of administration, endpoints and various categories of patients.

Proof of concept should be established on intermediate endpoints clearly related to clinical outcomes. Criteria for

regulatory approval of these interventions will be based on guidelines for the development of treatment of heart failure and cellular therapy for cardiac disease.

These points will be discussed.

Stuart Pocock (London, UK)

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

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

Janice Pogoda (Celladon, USA)

Dr. Pogoda has been the Executive Director of Biostatistics at Celladon Corporation (San Diego, CA) since October 2013. Prior to taking over the leadership of biostatistics at Celladon, Dr. Pogoda had worked for Celladon as a consultant since near the inception of its operations in 2004. She was heavily involved in the analysis of the Phase 1/2a trial of MYDICAR®, Celladon's lead gene therapy product candidate for the treatment of heart failure, and has been instrumental in implementing the use of the joint frailty model for the primary efficacy analysis of the Phase 2b trial of MYDICAR® currently in progress. Dr. Pogoda holds a BA in mathematics from the University of California at Santa Barbara and an MS and Ph.D. in biometry from the Keck School of Medicine at the University of Southern California. She has authored or co-authored over 60 articles in peer-reviewed journals.

ABSTRACT

Trial design issues

The joint frailty model in the analysis of recurrent events in the CUPID 2 trial

Janice Pogoda (Celladon, USA)

One of the challenges in heart failure clinical trials is selecting a primary efficacy outcome that will yield adequate power, preferably without having to enroll thousands of patients or follow them for decades. This is particularly important for smaller companies developing novel approaches to treatment, such as gene therapy. Analyzing recurring events – namely, heart failure-related hospitalizations – rather than a single event, such as first hospitalization or death, not only increases power but is more representative of a patient's entire experience over the course of the disease and the effect of treatment on the entire disease process. The joint frailty model is an attractive method of analysis for recurrent events because it not only considers multiple events per patient but also allows for informative censoring from terminal events. The CUPID 2 phase 2b trial, currently being conducted by Celladon, will be the first heart failure trial to present to the regulatory agencies an analysis of a primary endpoint using the joint frailty model to obtain marketing approval.

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Henrik Sandvad 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.

ABSTRACT

New therapeutic options development programs: live examples

Maintenance of normokalemia with ZS-9 once daily: results from a phase 3 multicenter, randomized, double-blind, multi-dose, placebo-controlled trials of patients with hyperkalemia

Henrik Rasmussen (ZS Pharma, USA)

Introduction: Renin-angiotensin-aldosterone inhibitor (RAASi) therapies improve outcomes for heart failure (HF) patients. However, optimal RAASi treatment is frequently limited by hyperkalemia (HK). Furthermore, HK is not only a limiting factor for the use of such life-saving RAASi therapies in patient populations that are expected to derive the greatest benefit, but is also an independent risk factor for mortality in patients with cardiovascular disease and/or chronic kidney disease (CKD). Current therapies, namely organic polymer resins (ie, sodium or calcium polystyrene sulfonates [SPS/CPS]), are suboptimal for both acute and chronic treatment in view of their questionable efficacy, association with poor gastrointestinal (GI) tolerability, and potential toxicity. Current options for the treatment of HK are limited, and there remains an unmet need for need for safe, effective, and consistent treatment in patients with HF in whom RAASi treatment is limited by hyperkalemia.

MOA: ZS-9 is a novel first-in-class nonabsorbed potassium trap specifically engineered to selectively entrap K+ in the GI tract. In contrast to SPS, which preferentially binds calcium [Ca2+] and magneseium [Mg2+] ions over K+, ZS-9 is >125-fold more selective for K+ and has 9.3-times more K+ binding capacity than SPS.

Phase 2: In clinical studies, ZS-9 has been well tolerated and has demonstrated activity in reducing serum K+ in patients with HK. A Phase 2 study of ZS-9 in CKD patients with HK demonstrated rapid and potent reduction of serum K+, with a low incidence of adverse events (AEs).

Phase 3 – Study 003: In the largest Phase 3 study in HK to date, we previously reported that ZS-9 significantly reduced serum K+ and maintained normokalemia in patients with all-cause HK, including the subgroup analysis of HF patients on RAASi therapy from this study.

Patient demographics were similar across treatment groups, with mean age of 65.6 years (range, 22-93 years). Fifty-nine percent were male, and 86% were white. Approximately 65% of all patients were on RAASi therapies, of whom 44% were on ACE inhibitors, 25% on angiotensin receptor blockers and <10% on mineralocorticoid receptor antagonists; fewer than 10% of patients were receiving combination RAASi therapy. At baseline, mean serum K+ was 5.3 mEq/L. At 48 hr, treatment with ZS-9 resulted in significant reductions of serum K+, with mean changes of -0.73, -0.54, and -0.46 mEq/L for the 10g (n=143), 5g (n=157), and 2.5g (n=141) dose groups, compared with -0.25 mEq/L for patients on placebo (n=158; P=10-31, 10-24, and <0.001, respectively). In the extended phase, ZS-9 maintained mean serum K+ at 4.5 and 4.7 mEq/L through Day 15 in patients who remained on 10g (n=63) and 5g (n=64) ZS-9 QD doses, respectively, compared with the placebo group (n=61 and 68 for patients switching from 10g and 5g ZS-9 doses, respectively), in whom mean serum K+ returned to hyperkalemic levels of 5.0 mEq/L by Day 15 (P<0.01 for both comparisons). Pre-specified subgroup analyses of patients stratified by baseline K+, eGFR levels, history of HF, CKD, and diabetes mellitus, or RAASi use demonstrated that normokalemia was achieved with ZS-9 10g and maintained across all subgroups, whereas patients who switched to placebo after the acute phase lost control of serum K+ and returned to HK. Of note, patients with the highest baseline K+ level exhibited the largest 48-hr decline in mean serum K+ (–1.10 mEq/L with baseline K+ >5.5 mEq/L vs.–0.57 mEq/L with baseline K+ ≤5.3 mEq/L), suggesting that achievement of normokalemia could potentially be normalized by ZS-9 based on the severity of HK.

For the subgroup analysis of patients with HF and on RAASi, among 753 patients, 300 (40%) had a history of HF at baseline, of whom 216 (72%) were on RAASi. Mean baseline serum K+ was 5.3 mEq/L in the HF-RAASi group. By 48 hr, mean K+ declined to 4.5 mEq/L in the ZS-9 10g dose group and 4.8 mEq/L in the 5g group, compared with 5.1 in the placebo group (P<0.05 for both comparisons). In the extended phase, 204 of 216 (94%) HF-RAASi patients

entered the extended phase; 20 remained on ZS-9 10g and 20 switched to placebo. Among HF-RAASi patients who remained on ZS-9 10g, mean serum K+ changed from 4.4 mEq/L (extended phase baseline) to 4.5 mEq/L on Day 15. In contrast, mean serum K+ in HF-RAASi patients who switched to placebo increased from 4.5 to 5.0 mEq/L on Day 15 (P=0.002; Figure).

Assessment of safety showed that rates of adverse events in the ZS-9 dose groups were similar to placebo, with no dose-response relationship was observed. During the acute phase, AEs were reported in 10.8% of patients on placebo, compared with 11.9% in the ZS-9 10g dose group; GI AEs were reported in 5.1% of patients on placebo, compared with 3.5% in the ZS-9 10g dose group. A similar trend was observed during the extended phase. The most common adverse event at all doses and during both phases was diarrhea (acute: 1.8% ZS-9 vs. 2.5% placebo; extended: 1.7% ZS-9 vs. 2.2% placebo). No cases of significant hypokalemia (K+<3.0 mEq/mL) or hypomagnesemia (Mg2+<1.2 mg/dL) were reported.

Conclusion: In the largest Phase 3 study in HK to date, ZS-9 demonstrated a strong safety and tolerability profile comparable to placebo and was effective in restoring and maintaining serum K+ <5.0 mEq/L in HF patients on RAASi therapy. Results from the subgroup analyses were similar to that of the overall study population, suggesting that optimal cardiorenal protection with RAASi may be enabled for HF patients who derive the greatest benefit from such life-saving therapies but are often limited by the development of HK.

Stuart Rich (Chicago, USA)

Dr. Stuart Rich is Professor of Medicine at the University of Chicago, and a faculty member of the Center for Pulmonary Hypertension within the Section of Cardiology. Dr. Rich is one of the world's most recognized experts on pulmonary hypertension. For more than three decades he has dedicated his research and clinical efforts to finding better solutions for pulmonary heart disease. He was principle investigator for the NIH Registry on Primary Pulmonary Hypertension, the first of its kind, and has been the leader of the largest clinical center in the USA for evaluating and treating patients with pulmonary hypertension since 1980. Dr. Rich has conducted pioneering research on the molecular mechanisms, epidemiology, clinical presentation, natural history and treatments of the disease. This knowledge has lead to the discovery of more effective treatments for pulmonary hypertension, including the use of anticoagulants, calcium channel blockers, and prostacyclins. His pioneering research has led to a greater understanding of all types of pulmonary hypertension. Dr. Rich has been listed among the top 1% of American doctors by Castle Connolly for more than 20 years. He has published hundreds of clinical articles and book chapters on pulmonary heart disease, and has been a leader in dozens of clinical research trials. In addition, he is currently on the Board of Directors of the Pulmonary Vascular Research Institute, and a member of the FDA Cardiovascular and Renal Drugs Advisory Committee.

Anthony Rodgers (Sydney, AUS)

Anthony Rodgers is Professor of Global Health at The George Institute for Global Health. He has more than 20 years of experience in clinical trials, public-private partnerships and innovation. Professor Rodgers helped initiate and run several landmark trials in prevention and treatment of cardiovascular disease. He also helped start the Asia Pacific Cohort Studies Collaboration, involving more than 50 studies and 600,000 participants that assessed the determinants of cardiovascular disease in the region. Professor Rodgers initiated a public-private partnership with Dr. Reddy's Ltd and a consortium of cardiovascular clinical trials groups to develop and test two four-in-one cardiovascular combination pills ('polypills'). An international clinical trial program involving 3,500 patients has received funding from organisations such as the Wellcome Trust, European Union and Australian National Health and Medical Research Council. Professor Rodgers also developed the first mHealth smoking cessation programme, with over 6,000 patients in clinical trials. This service has been rolled out by Departments of Health in NZ, UK and elsewhere. Pr. Rodgers was the Principal Author of the 2002 World Health Report, the main annual publication of the World Health Organization, entitled "Reducing risks, promoting healthy life". Professor Rodgers graduated in medicine in the United Kingdom and trained in epidemiology and public health in New Zealand.

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Lothar Roessig (Bayer, GER)

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

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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)

Yves 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 the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) an 8,000 participants, 400 sites trial. Dr. Rosenberg served as a member of the Society for Clinical Trials Board of Directors.

Robert Rosenson (New York, USA)

Robert S. Rosenson, MD, is Professor of Medicine at the Icahn School of Medicine at Mount where he serves as Director of Cardiometabolic Disorders. Dr. Rosenson earned his medical degree from Tulane University in New Orleans, Louisiana. He then served his residency in medicine at Brigham and Women's Hospital in Boston, Massachusetts. He later completed a fellowship in 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 has been involved in numerous grant-supported research investigations studying inflammation, thrombogenesis, and rheology. His laboratory was the first to demonstrate that statins reduce pro-inflammatory cytokine production. 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 served as Global Principal Investigator of the PLASMA I, PLASMA II and FRANCIS trials. He has authored 250 peer-review journal articles, and more than 600 book chapters, abstracts, and electronic publications for UpToDate Medicine.

ABSTRACT

Do negative Mendelian randomization studies rule out a relevant therapeutic effect of an intervention? Phospholipase A2 inhibitors as a valid therapeutic target for cardiovascular disease prevention

Robert Rosenson (New York, USA)

Mendelian randomization analyses provide critical information on causal pathways for inflammatory markers; however, selection of major polymorphisms associated with certain biomarkers cannot account for the multitude of variables that regulate gene expression or post-translational modification of gene product. The use of pharmacogenomics for selection of inhibitors that target a causal pathway may minimize risk of pharmaceutical development, but other considerations may impact the success of a therapeutic target including concomitant therapy that reduces substrate availability and enzyme activity; vascular effects that have a direct or indirect impact on the disease process, tissue penetration, and off-target toxicity of the selective inhibitor.

The association between secretory phospholipase A2-IIA (sPLA2-IIA) as a potential therapeutic target for cardiovascular disease (CVD) prevention was evaluated in a Mendelian randomization study using observational studies between the PLA2G2A rs11573156 variant with CVD events, and deductions from published data with the pan sPLA2 inhibitor varespladib methyl. The authors conclude reducing sPLA2-IIA mass is "unlikely to be a useful therapeutic target for reducing CVD events". Several assumptions related to the biology of sPLA2-IIA and pharmacological effects of varespladib methyl require further consideration: (1) absolute values for sPLA2-IIA levels and activity were not reported, which is important due to variable results with different analytical methods; (2) there are wide differences in baseline sPLA2-IIA levels in different cohorts, and marked differences in sPLA2 levels that results from the acute phase reaction in acute coronary syndrome (ACS) patients versus stable coronary heart disease (CHD) patients; (3) use of total sPLA2 activity as a surrogate for sPLA2-IIA activity does not account for the anti-atherogenic and pro-atherogenic contributions of other sPLA2 isoforms such as groups III, V and X sPLA2 ; (4) marginally significant correlation between PLA2G2A rs11573156 variant and sPLA2 activity despite the higher correlations between sPLA2-IIA mass and sPLA2 activity; (5) biomarker effects were reported FRANCIS where the protocol mandated that all patients have their statin therapy changed to atorvastatin 80 mg daily regardless of their prior statin regimen; and (6) varespladib methyl is a pan sPLA2 inhibitor with similar efficacy in lowering groups IIA, and X sPLA2 with somehow lower potency against group V.

The use of Mendelian randomization studies to deduce pharmacological effects dos not account for the properties of the specific inhibitor. Specifically, varespladib methyl is: (1) hydrophilic and may not penetrate into vascular tissues with sufficient potency to reduce intracellular effects versus the consistent effects on plasma biomarkers; (2) varespladib methyl inhibits sPLA2-X and a recent report by Lambeau reported that overexpresssion of sPLA2-X is atheroprotective, the non-specific effects of varespladib methyl as a pan inhibitor may have positive and negative effects; (3) VISTA-16 reported an increase in myocardial infarctions so the effect of varespladib methyl was harmful.

Lipoprotein associated phospholipase A2 (Lp-PLA2) provides an example where genetic studies were inconsistent and limited to certain regions of the world. In the two pivotal trials, STABILITY and SOLID, selective inhibition of Lp-PLA2 inhibition with darapladib had no effect on CVD outcomes. High-intensity statin therapy may have reduced the chances of efficacy through reduction in substrate (apoB-containing lipoproteins, oxidatively modified LDL particles), indirect effects on Lp-PLA2 mass and activity, and anti-inflammatory properties independent of Lp-PLA2.

In conclusion, careful review of primary data and cautious conclusions must be considered in pharmacogenomic analyses. Pro-inflammatory pathways are redundant, and multiple anti-inflammatory pathways modulate inflammatory responses.

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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) since 2014. 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 six years in 2013.

ABSTRACT

What should the indication be for a drug that lowers serum potassium?
Treatment vs. prevention vs. a broad treatment/prevention of hyperkalemia
Target populations' issues: what are the unmet needs?
Cardiology indications

Patrick Rossignol (Nancy, FRA)

Although the use of multiple RAAS-Inhibitors is associated with the development of worsening renal function and hyperkalemia in patients with heart failure with reduced ejection fraction, increased efforts should be expended to initiate and maintain target doses of these agents so as to provide their benefits on mortality and hospitalizations for heart failure. Should hyperkalemia occur, a temporary down-titration or discontinuation of RAAS inhibitors should be considered together with the use of potassium chelating agents. This may apply to other high cardiovascular risk patients, with and without chronic kidney disease, treated with RAAS inhibitors as well, especially in the secondary prevention setting.

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Sébastien Roux (Actelion, CHE)

Sébastien Roux, MD, studied cardiology both in France (Paris) and in Canada (Montreal Heart Institute). He did his MSc. in cell biology in the French research institute INSERM. He started his career in the pharmaceutical industry at F. Hoffmann La Roche (Switzerland) where he was leading drug discovery laboratories focused on antithrombotic research, vascular tone, atherosclerosis and angiogenesis. He moved to Actelion Pharmaceuticals Ltd in 2000 to lead the bosentan program which eventually allowed the worldwide registration of the first orally active endothelin receptor antagonist for the treatment of pulmonary arterial hypertension. He also was leading the endothelin program which encompassed various therapeutic areas such as scleroderma (digital ulcers), pulmonary fibrosis and subarachnoid hemorrhage. He is currently Head of Clinical Science Early Clinical Projects with a special mission to develop interface between Clinical Development and Drug Discovery groups at Actelion. He also has a special interest in the methodology of clinical trials and their adaptation to the specific situation of rare diseases. Actelion Pharmaceuticals Ltd is the top biopharmaceutical company in the field of pulmonary arterial hypertension.

Steve Ruble (BSCI, USA)

Stephen Ruble completed his PhD at the University of Arkansas, and a post-doctoral fellowship at the Medical College of Wisconsin. His research has focused on autonomic control of cardiovascular function in health and disease. After 9 years as a professor at Samford University in Birmingham, Alabama, he joined Boston Scientific Corporation, and is currently a Research Fellow where he serves as the chief scientist for the autonomic modulation therapy effort. He has more than 20+ peer-reviewed publications and 20+ patents.

Luis Ruilope (Madrid, ESP)

Luis M. Ruilope is Professor at the Public Health and Preventive Medicine department of the Autonoma University and head of the Cardiovascular and Renal Risk at Instituto de Investigación 12 de Octubre, both in Madrid, Spain. His main interested fields are Hypertension and Cardiovascular Risk. Dr. Ruilope is an international fellow of the Council for High Blood Pressure Research and the Council of the Kidney in Cardiovascular diseases of the American Heart Association. Scientific Committee Member of the ISH (International Society of Hypertension) and he was president of the Spanish Hypertension Society and the Hypertension Spanish League.

He is a member of the editorial board of several journals including Journal of Hypertension, Blood Pressure, Medicina Clínica, Hypertension, Journal of Human Hypertension, Journal of the American Society of Nephrology and Nephrology and Dialysis & Transplantation. He is also associate editor of the Current Hypertension Reports and Directive Committee member of the studies HOT, INSIGHT, SCOPE, CONVINCE, ROADMAP, ASCEND, and European coordinator of the IDNT study.

Arantxa Sancho (EMA, ESP)

Arantxa Sancho obtained her medical degree in Madrid, from the Autonomous University in 1997, and then completed a 4-year medical specialty in Clinical Pharmacology at Hospital La Paz, Madrid. She was granted a training opportunity and in 2002 joined the Spanish Agency on Medicines and Healthcare Products (AEMPS) where she worked as a clinical assessor mainly in the context of European procedures. In 2005 she moved to Hospital Puerta de Hierro, Majadahonda, where she has been working at the Clinical Pharmacology Department developing assistance and research activities at the hospital clinical research unit in collaboration with different medical departments. Her collaboration with the AEMPS-EMA continued during this time, focusing on the centralised scientific advice and marketing authorisation procedures for CNS, cardiovascular, endocrinology and ophthalmology medicinal products. She has been member of the EWP (2006-10), the CNS-WP (2007-10) and the RIWP since 2010. In 2011, she was nominated Alternate member of the CHMP- EMA. Since then, she has been rapporteur of more than 15 new drug applications, including haematologic,

oncologic and cardiologic medicinal products. Her areas of interest include drug regulation, drug place in therapeutics, with particular interest in CNS, rheumatology, viral diseases and onco-haematology. She has also been a member of the Research Ethics Committee since 2005.

Fortunato Senatore (FDA, USA)

Fortunato Fred Senatore, MD, PhD, FACC, is Medical Officer in the Division of Cardiovascular and Renal Products, Office of New Drugs, Center for Drug Evaluation Research at the Food and Drug Administration.

Dr. Senatore received his BA in Biochemistry and MS in Bio-engineering from Columbia University. He received his PhD in Chemical Engineering from Rutgers University. He was a professor of Chemical Engineering at Texas Tech University where his research focused on artificial organ technology, biocompatibility, biological devices, fluid mechanics, hemodynamics, and modeling/simulation of biological processes.

He attended Medical School at Texas Tech University Health Sciences Center School of Medicine simultaneous to his continued position as professor of chemical engineering. He trained in Internal Medicine at the Mayo Clinic and in Cardiology at the Massachusetts General Hospital.

Dr. Senatore was recruited to Merck as Associate Director in the Cardio-Renal Division. He spent the next 17 years in the Pharmaceutical Industry with appointments of increasing responsibility at Merck, Aventis, Sankyo, and Mitsubishi, the latter where he served as Head of Clinical Science in concert with serving as Head of Safety. Following multiple interactions with the FDA from the Sponsor side, he joined the FDA as a Medical Officer in the Center of Drug Evaluation Research, Office of New Drugs, Division of Cardiovascular and Renal Products, on September 10, 2012.

ABSTRACT

What are a 'breakthrough', 'fast track' and 'priority'?

Fortunato Senatore (FDA, USA)

Expedited programs are designed to accomplish 3 objectives: 1) fulfill an FDA commitment to bridge the gap between scientific discoveries and translation into treatment, 2) actively scrutinize, strengthen and streamline regulatory processes, and 3) develop a number of flexible and innovative approaches to expedite drug development. There are 4 expedited programs: three designations (i.e. Fast Track, Breakthrough, and Priority Review) and the Accelerated Approval Pathway. All four expedited programs represent efforts to address an unmet medical need in the treatment of a serious condition. An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. A serious condition is defined as being associated with morbidity that has substantial impact on day-to-day functioning, survival, or if left untreated, will progress from a less severe condition to a more serious one.

The qualifying criteria for a Fast Track (FT) Designation are the treatment of a serious condition, and clinical or non-clinical data (depending on stage of development) showing the potential to address an unmet medical need. Features of Fast Track include frequent interaction with the review team and rolling review. The request for Fast Track designation may be submitted with the IND but no later than the pre-NDA meeting. The Division of Cardiovascular and Renal Products (DCRP) would not normally issue a FT designation unless the Sponsor commits to study an important aspect of the disease (e.g. mortality). The FDA will respond within 60 calendar days of the receipt of request.

The qualifying criterion for a Priority Designation is the demonstration of a significant improvement in safety or efficacy in the treatment, prevention, or diagnosis of a serious condition. The key feature of a Priority Designation is a 6-8 month review clock compared to a 10-12 month standard review. The request for priority designation may be submitted with the NDA, BLA, or sNDA. The FDA will respond within 60 calendar days of the receipt of request.

The qualifying criteria for a Breakthrough Designation are the treatment of a serious condition and preliminary clinical evidence (i.e. from human studies) demonstrating substantial improvement on clinically significant endpoints over available therapies. Key features of Breakthrough include intensive guidance on development, organizational commitment, rolling review, and possible co-eligibility for priority review pending data from the NDA. The request for breakthrough designation may be submitted with the IND but no later than the end-of-phase 2 meeting. Exceptions to this have occurred with oncology products (breakthrough designation upon receipt of NDA). The FDA will respond within 60 calendar days of the receipt of request.

The qualifying criteria for the Accelerated Approval Pathway are the treatment of a serious condition, provision of a meaningful advantage over available therapies, and demonstration of an effect on a surrogate endpoint likely to predict a clinical benefit, or on a short-term intermediate clinical endpoint likely to predict an effect on a long term irreversible morbidity or mortality (IMM) endpoint. Key features of the Accelerated Approval Pathway include the same statutory standards for safety and effectiveness as required for traditional approval, clinical data supporting a conclusion that a relationship between an effect on the surrogate endpoint or intermediate clinical endpoint to an effect on clinical outcome is reasonably likely, and a conditional Phase 4 confirmatory trial. The timeline for submission of a request for an accelerated approval pathway should be discussed with the review division during development. There is no specific timeline for an FDA response.

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Kaori Shinagawa (PMDA, Japan)

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

Dr. Shinagawa received Kimura Memorial Award from the Japanese Heart Rhythm Society in 2000.

Gérard Simonneau (Bicêtre, FRA)

Gérald Simonneau, MD, is Head of the Department of Pneumology and Intensive Care Medicine at Hôpital Kremlin Bicêtre, Paris-Sud University, France. In addition, Professor Simonneau is Director of the French National Reference Centre for Pulmonary Hypertension since 2004 and Director of Research Unit "New therapeutic approaches for Pulmonary Hypertension" INSERM U999, since 2010. He has published widely in the fields of pulmonary hypertension, pulmonary vascular diseases and pneumology in peer-reviewed Journals including New England Journal of Medicine, Lancet, Annals of Internal Medicine, and Circulation. He has been President of the working group on pulmonary circulation, of the European Society of Cardiology and has received the PAH research award of the European Respiratory Society in 2011.

ABSTRACT

Individual experiences and lessons learnt from recent trials: will outcome trials prevail?
Macitentan (SERAPHIN) Selexipag (GRIPHON)

Gérard Simonneau (Bicêtre, FRA)

Pulmonary arterial hypertension is a rare and fatal disease caused by functional and structural changes in the pulmonary vasculature. The rarity of the disease has elicited early investigators to run trials which were limited in terms of sample size and efficacy based on exercise capacity, mainly the 6 minutes walk test (MWT).

Based on 20 year experience in the field, there has been a shift on how to evaluate the efficacy of advanced PAH therapies, moving from the simple, inexpensive 6 MWT that was in the past considered enough for market access to PAH therapies, to the more robust long term efficacy endpoints. Today, there are many dedicated PAH therapies that have shown a positive effect on the 6MWT. While the 6 min walk test was initially considered to be a potentially reliable surrogate for disease progression in PAH, there is increasing evidence that this is not the case. Recent meta-analyses have shown that the change in 6 min walk distance poorly correlated long term outcome 1 . In addition, there are several limitations of the 6 min walk test including its reduced sensitivity in patients only

mildly symptomatic (WHO functional class II), in whom a ceiling effect is expected when new therapies are tested. In addition 6MWT has been a challenge to detect a treatment effect in non naïve patients, namely those already receiving background advanced PAH therapies. Because of those limitations and the growing need to better document long term efficacy of new PAH therapies, the PAH expert community have moved to morbidity and mortality endpoints, closer to the traditional cardiovascular endpoints which are routinely used in large indications with some adaptation due to the limited pool of available patients for clinical trials. This new type of endpoint are now recommended in current guidelines for clinical research on PAH as well as official Health Authorities guidelines for drug development in PAH2, 3. Specific recommendations have been made on the components of a composite endpoints which would clearly reflect an irreversible step in the disease progression. The SERAPHIN trial was the first registration trial in PAH which was event driven, it included a robust endpoint including time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension. These components need to be adjudicated by an independent group of experts in order to take into account the inherent subjectivity associated with some components of the composite endpoint, not forgetting the potential confounding effect triggered by the offered option for each patient who meets a morbidity event to receive free of charge the tested therapy in an open label study extension. Even with a composite endpoint, such trials need to recruit large numbers of patients, which is a challenge in a rare disease such as PAH. However, the SERAPHIN trial highlights that such trials can be conducted and other phase III, event driven, long-term morbidity and mortality trials in PAH were also successful in term of recruitment and outcome as was the more recently completed GRIPHON and AMBITION trials. When designing such an event driven study, a key factor or success is to have an estimate of the anticipated effect size. The postulated treatment effect of 40% reduction in hazard rate could at face value have been considered too optimistic because it is rarely observed in usual common cardiovascular indications. It is traditionally recommended that the number of events needs to be calculated to detect a more conservatively postulated treatment effect, e.g., 20%. A 20% risk reduction in a study adequately powered would not have been feasible in the context of PAH, because of the sample size in excess of few thousands of participants. Luckily, the 40% anticipated treatment effect was based on earlier data from previous clinical trials on other PAH therapies for which an impressive treatment effect was observed, although in limited number of patients, short observation times and in absence of background therapies. For a good planning of the study sample size, it is also important to upfront estimate the expected event rate in the planned control arm. In absence of previous similar clinical trials, consultation of international registries can be useful, keeping in mind the caveat that a disease registry population is not a clinical trial population. An alternative study design is when the event rate is not established in the control arm, one could continue to enroll patients until the specific number of event has been reached.

In conclusion the PAH field is moving towards event-driven trials and we expect in the future that all the new therapies will be approved based on robust outcome results.

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Olivier Sitbon (Paris, FRA)

Olivier Sitbon, MD, PhD, is Professor of Respiratory Medicine at University Paris-Sud, and consultant and specialist at the French Referral Centre for Severe Pulmonary Hypertension, Department of Respiratory and Intensive Care Medicine, Bicêtre University Hospital in Le Kremlin Bicêtre. He leads the team «Clinical Research» of the INSERM Unit U999 «Pulmonary Hypertension: Pathophysiology and Innovative Therapies». Pr. Sitbon has conducted extensive research in pulmonary arterial hypertension (PAH) and is responsible for the French registry of patients with PAH. His investigational activities include clinical studies on factors associated with PAH, such as HIV infection and portopulmonary hypertension, prognostic factors in PAH and the development of new strategies for the treatment of PAH. He has authored numerous peer-reviewed articles on pulmonary hypertension and related topics, and is a reviewer for the American Journal of Respiratory and Critical Care Medicine, Circulation, European Respiratory Journal and Chest, amongst other scientific journals.

ABSTRACT

Ambrisentan, from ARTEMIS, ARIES to AMBITION

Olivier Sitbon (Paris, FRA)

Ambrisentan is a highly selective ETA receptor antagonist that has been approved by the US FDA in 2007 and by the EMA in 2008 for the treatment of patients with pulmonary arterial hypertension (PAH). Selective ETA receptor inhibition has theoretical benefits in terms of preserving vasodilator and clearance functions specific to ETB receptors, while preventing vasoconstriction and cellular proliferation mediated by ETA receptors. Ambrisentan has a low potential for drug–drug interactions, explained by the small effect on hepatic CYP450 induction or inhibition. It can be safely administered with warfarin or sildenafil without dose adjustment.

Ambrisentan was studied in two phase III placebo-controlled trials, ARIES-1 (n = 202, doses of 5 mg daily or 10 mg daily for 12 weeks) and ARIES-2 (n = 192, doses of 2.5 mg daily and 5 mg daily for 12 weeks), in patients with idiopathic or heritable PAH or with PAH associated with connective tissue disease, anorexigen use, or HIV infection. The primary endpoint was change from baseline in 6-min walk distance (6MWD) at week 12. The 6MWD increased in all ambrisentan groups with mean placebo-corrected treatment effects of 31–59 m. Improvements in time to clinical worsening, functional class, quality of life (SF-36 score), Borg dyspnea score, and B-type natriuretic peptide (BNP) were also observed. No patient treated with ambrisentan developed aminotransferase concentrations greater than three times the upper limit of normal. In the extension phase of these studies (ARIES-E), 2-year treatment with ambrisentan was associated with sustained improvements in exercise capacity and a low risk of clinical worsening and death. Ambrisentan was generally well tolerated and had a low risk of aminotransferase serum level elevation over the study period (2 per cent patient-year). Another long-term study of ambrisentan in PAH reported similar sustained benefit in exercise capacity and pulmonary hemodynamics.

Recently, the randomized, double-blind, multi-center, AMBITION study showed that initial treatment with ambrisentan/tadalafil combination therapy in treatment naïve PAH patients was superior in terms of the primary endpoint (time to first clinical failure event) compared with monotherapy (ambrisentan or tadalafil). First-line treatment with the combination of ambrisentan 10 mg and tadalafil 40 mg reduced the risk of clinical failure by fifty percent compared to pooled ambrisentan and tadalafil monotherapy arm (hazard ratio = 0.502; p=0.0002). Statistically significant improvements were also observed for three of the secondary endpoints (6-MWD, percentage of patients with satisfactory clinical response, change from baseline in N-T pro-BNP). Rates of serious adverse events and events leading to discontinuation were similar across treatment arms. Occurrence of peripheral edema was the most frequent adverse event observed in the combination therapy arm. This result promotes arguments to treat de novo PAH patients with a combination therapy in order to improve clinical outcomes.

Endothelin-1 (ET-1) induces lung fibroblast proliferation and contractile activity via the ETA receptor. ET-1 receptor expression is increased in idiopathic pulmonary fibrosis (IPF) lung tissue, and data from preclinical models suggested that antagonism of ET-1 receptors may decrease the severity of pulmonary fibrosis. ARTEMIS was a randomized, double-blind, placebo-controlled, event-driven trial to determine whether ambrisentan reduces the rate of IPF progression. The study was prematurely terminated after enrollment of 492 patients (75% of intended enrollment) because an interim analysis indicated a low likelihood of showing efficacy for the end point by the scheduled end of the study. Ambrisentan-treated patients were more likely to meet the pre-specified criteria for disease progression (27.4% vs. 17.2% of patients; p = 0.010; HR 1.74 [95% CI, 1.14 to 2.66]). Respiratory hospitalizations were seen in 13.4% and 5.5% of patients in the ambrisentan and placebo groups, respectively (p = 0.007). Lung function decline was seen in 16.7% of ambrisentan-treated and 11.7% of placebo-treated patients (p = 0.109). Death occurred in 7.9% patients who received ambrisentan and 3.7% who received placebo (p = 0.100). In conclusion, ambrisentan was not effective in treating IPF and was associated with an increased risk for disease progression and respiratory hospitalizations. Ambrisentan is today contra-indicated in patients with IPF.

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Scott Solomon (Boston, USA)

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

Dr. Solomon's research interests have focused on changes in ventricular structure and function following myocardial infarction, modifiers of risk and influences of outcome in patients following myocardial infarction and with chronic heart failure, cardiovascular safety of non-cardiovascular therapies, factors that influence the transition from hypertension to heart failure, and heart failure with preserved ejection fraction. He has combined clinical trials with cardiac imaging, and has played a leading role in many international clinical trials in heart failure, hypertension and myocardial infarction, including the SAVE, HEART, VALIANT, CHARM, PEACE, OVERTURE, MADIT-CRT, ALOFT, ALLAY, TREAT, RED-HF, ALTITUDE, FREEDOM, TOPCAT trials. He chaired the VALIDD, EXCEED, ASPIRE. Dr. Solomon was a member of the executive committee for the PARADIGM-HF trial, led the phase II PARAMOUNT trial in heart failure with preserved ejection fraction (HFpEF), and chairs the PARAGON-HF outcomes trial in HFpEF.

Dr. Solomon has directed the Harvard Medical School Cardiovascular Clerkship and the echocardiography training program at Brigham and Women's Hospital for a decade. He has authored more than 300 peer-reviewed articles and reviews, two textbooks of cardiac imaging, an iphone atlas of echocardiography, and has written the echocardiography sections for the next edition of Braunwald's Heart Disease and Harrison's Principles of Internal Medicine. He is Cardiology Section Editor at UpToDate and serves as Associate Editor at Circulation.

ABSTRACT

Moving to HFPEF: PARAGON, the ultimate design?

Scott Solomon (Boston, USA)

Heart failure with preserved ejection (HFpEF) accounts for approximately 50% of patients with heart failure and to date no therapy has been found to definitively reduce morbidity and mortality in clinical trials. Of the four prior outcomes trials in HFpEF, none met their primary endpoint. LCZ696 is a novel dual acting angiotensin receptor neprilysin inhibitor that has recently been shown to reduce cardiovascular death, heart failure hospitalizations and all-cause mortality in patients with heart failure and reduced ejection fraction (HFrEF). In a parallel pilot trial in HFpEF, the PARAMOUNT trial, we showed that LCZ696 reduced NT-proBNP at 12 weeks, and improved left atrial size and NYHA class at 36 weeks compared with valsartan in 301 HFpEF patients. These findings were independent of blood pressure lowering and was associated with a reduction in high-sensitivity troponin. These hypothesis generating findings formed the rationale for the design of the PARAGON-HF outcomes trial. PARAGON-HF will test the hypothesis that LCZ696 can reduce cardiovascular death or total hospitalizations in 4300 patients with HFpEF. There are several unique aspects to the PARAGON design that distinguish this trial from other HFpEF outcomes trials, including the requirement that patients have evidence of structural heart disease and that they have a recent hospitalization for HF or elevation in natriuretic peptides, as well as a novel endpoint that takes into account multiple heart failure events. Finally, PARAGON-HF is the first outcomes trial in HFpEF with positive Phase II data, as well as positive phase III data in HFrEF. PARAGON-HF began enrollment in mid 2014 and will report in 2019.

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Stuart Spencer (London, UK)

Dr. Spencer 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.

Dr. Spencer's background is in research which started at the Brompton Hospital, London, looking at spinal curvature 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 an honorary doctorate of medicine from Umea University, Sweden. A broad biomedical research base in different settings (Universities, government and industry) in front-line research has given a clear understanding of principles in research and publications applicable across disciplines. Dr. Spencer is also a Trustee of the Scoliosis Association (UK), is on the British Scoliosis Research Fund grants committee and the steering Committee of the Swedish national GP Research School.

Norman Stockbridge (FDA, USA)

Norman Stockbridge received his MD and PhD (Physiology) from Duke University. He did basic research in cellular electrophysiology prior to joining FDA in 1991. Dr. Stockbridge has been serving FDA/CDER as Director of the Division of Cardiovascular and Renal Products since 2004.

Ahmad Tawakol (Boston, USA)

Dr. Tawakol obtained his medical degree from Stanford Medical School after which he completed training in Medicine, Cardiology, and Nuclear Cardiology at Harvard Medical School (at Brigham and Women's Hospital and Massachusetts General Hospital). He is Co-Director of the Cardiac MR PET CT Program and Director of Integrative BioImaging trials Program at the Massachusetts General Hospital, Harvard Medical School.

Dr. Tawakol is a pioneer in the field of PET/CT and PET/MR imaging of atherosclerosis. A hypothesis that is central to his research is that assessment of plaque biology and function provide an important supplement to the classical structural information. Dr. Tawakol's group provided the initial development and validation of molecular imaging as a tool to assess atherosclerotic plaques. Additionally, Dr. Tawakol played a prominent role in disseminating the approach and built an international network of collaborators to conduct multi-center trials. Within this paradigm, Dr. Tawakol has spearheaded several multi-center trials using this advanced imaging technology as a tool to learn about disease mechanisms and to identify new treatments in humans.

ABSTRACT

MRI imaging in clinical trials

Ahmad Tawakol (Boston, USA)

Phase III clinical endpoint trials evaluating treatments for atherosclerosis typically require very large sample sizes, cost hundreds of millions of dollars and historically have had very low success rates. Several cardiovascular imaging technologies have gone through evolutionary cycles of validation over the past decade and several have demonstrated promise as clinical tools and as clinical trial biomarkers.

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

Among the emerging imaging tools, the quantitative imaging of tissue activity with PET/CT and more recently with PET/MR has shown promise as a tool for gaining insight about cardiovascular biology and on the tissue effects of novel drugs. In this lecture, Dr. Tawakol will discuss applications of PET/MR and PET/CT in evaluation of PAH.

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John Teerlink (San Francisco, USA)

Dr. John R. Teerlink, FACC, FAHA, FESC, FRCP.(UK) 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 B.A. 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-LaRoche (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

Ongoing trials: therapies on the horizon? Serelaxin

John Teerlink (San Francisco, USA)

In humans, relaxin-2 is thought to be primarily responsible for the maternal adaptations to pregnancy, including improved renal function, increased arterial compliance, reduced afterload and protection against end-organ damage. Serelaxin is a recombinant form of human relaxin-2 that has been studied in animals, supporting these beneficial effects in multiple disease models.

Early studies in patients with heart failure (HF) suggested that serelaxin decreased central venous pressures, left ventricular filling pressures and pulmonary and systemic resistance. A Phase II, dose-finding study (Pre-RELAX-AHF) in 234 patients admitted with acute heart failure suggested that a 48-hour infusion of serelaxin at a dose of 30 mcg/kg/d improved the signs and symptoms of heart failure, decreased adverse clinical outcomes and possibly increased survival.

RELAX-AHF evaluated the effects of serelaxin compared to placebo in addition to standard of care therapy in 1,161 patients admitted for acute heart failure with normal to elevated systolic blood pressure, mild-to-moderate renal dysfunction and persistent symptoms despite an initial diuretic dose. In RELAX-AHF, serelaxin-treated patients had significantly greater improvement in the primary endpoint of dyspnea relief (AUC of change from baseline in visual analog scale assessment of dyspnea through 5 days; p=0.007), as well as significant improvements in signs and symptoms of heart failure, decreased use of rescue therapies (including diuretics, vasodilators and inotropes), decreased worsening heart failure events, reduced length of ICU/CCU and total index hospital stay, and a 37% reduction in cardiovascular and all-cause mortality. In addition, significant reductions in markers of end-organ dysfunction and damage, such as blood urea nitrogen, creatinine, cystatin-c, troponin, NT-proBNP, ALT, and AST were noted in the serelaxin-treated patients, each of which correlated with improved survival.

Subsequent analyses have demonstrated that these beneficial effects were evident across multiple subgroups, particularly those patients with heart failure with preserved ejection fraction or HFpEF. These findings from RELAX-AHF have been supported by other studies, including two mechanistic hemodynamic studies that demonstrate beneficial systemic and renal hemodynamic effects of serelaxin in patients with heart failure. The finding of improved cardiovascular survival in both Pre-RELAX-AHF and RELAX-AHF is being tested in RELAX-AHF-2, a trial with a targeted enrollment of over 6,300 patients admitted for acute heart failure, randomized to serelaxin or placebo with a primary endpoint of 180-day cardiovascular mortality.

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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.

Sam Tsimikas (ISIS Pharmaceuticals, USA)

Dr. Tsimikas is Cardiovascular Franchise Leader and Vice President of Clinical Development at Isis Pharmaceuticals and Professor of Medicine and Director of Vascular Medicine at the University of California San Diego. He obtained his MD degree in 1988 from the University of Massachusetts Medical School and completed his Internal Medicine training at the University of Massachusetts Medical Center in 1991. He completed separate fellowships in Cardiovascular Disease, Atherosclerosis and Interventional Cardiology at the University of California San Diego from 1992-1997. Dr. Tsimikas' clinical interests are focused in his role as Director of the Vascular Medicine Program that encompasses treating a wide variety of patients in the continuum of high-risk primary prevention to endovascular intervention. Areas of interest include evaluating and treating patients with elevated Lp(a) levels and percutaneous coronary and peripheral interventions. This program also functions as a key teaching venue for general and interventional cardiology fellows. Dr. Tsimikas has published over 195 articles and book chapters, including in NEJM, Cell, Nature, JACC, JCI, Circulation, Circ Res, ATVB, and EHJ. He is Fellow of the American College of Cardiology, the American Heart Association and the Society for Cardiac Angiography and Interventions.

ABSTRACT

Clinical trials with antisense therapy targeting triglycerides and Lp(a): geared for the big picture

Sam Tsimikas (ISIS Pharmaceuticals, USA)

Patients at high risk of or with established cardiovascular disease (CVD) accrue new events despite optimal medical therapy. Although LDL lowering therapies are effective in lowering CVD events, significant residual risk remains due to other lipoprotein disorders not addressed by LDL lowering alone. Strong genetic data exists that elevated triglycerides, mediated by elevated apolipoprotein CIII (ApoCIII), and elevated lipoprotein (a) [Lp(a)] levels contribute to this risk mechanistically through genetic causality. In that regard, clinical development of potent and specific therapies to lower ApoCIII and Lp(a) may reduce this risk further. Isis Pharmaceuticals has developed antisense oligonucleotides (ASO) targeting ApoCIII and Lp(a). These 2'-MOE chimeric ASOs are a second generation class of ribonucleic acid (RNA) therapeutics designed to specifically anneal to messenger RNA coding for specific proteins and mediate their degradation by the

nuclease RNase H1, ultimately reducing plasma levels. ApoC-III is a key regulator of plasma triglyceride (TG) levels. A randomized double-blind placebo-controlled dose-ranging phase 2 study was conducted to evaluate ISIS-APOCIIIRx vs. placebo once weekly for 13 weeks in untreated patients with fasting TG ≥350 mg/dL and ≤2000 mg/dL; and in patients on stable fibrate therapy with fasting TG ≥225 mg/dL and ≤2000 mg/dL. Mean baseline TG levels were 581 mg/dL (6.6 mmol/L) and 376 mg/dL (4.2 mmol/L) in each respective cohort. ISIS-APOCIIIRx produced dose-dependent, statistically significant and prolonged decreases in plasma apoC-III levels as a single agent (100 mg, -40±32%; 200 mg, -64±22%; 300 mg, -80±9%; vs placebo, 4±42%) and as an add-on to fibrates (200 mg, -60±13%; 300 mg, -71±13%; vs placebo, -2±25%). Concordant reductions were observed in TG levels (-31 to -71%). These results support further development of ISIS-APOCIIIRx for treatment of patients at risk for cardiovascular and pancreatic events due to severe hypertriglyceridemia. Lipoprotein(a) [Lp(a)] is an independent, causal, genetic risk factor for CVD and calcific aortic valve stenosis. A randomized, placebo-controlled, double-blind, ascending dose, phase 1 study was conducted in healthy volunteers to evaluate the safety, pharmacokinetics and pharmacological effects of ISIS-APO(a)Rx, a second generation antisense drug. Subjects received either a single (50, 100, 200, or 400 mg; n=4/cohort, 3 active:1 placebo) or six subcutaneous injections over four weeks (100, 200, or 300 mg; n=10/cohort, randomized 8 active:2 placebo). Lp(a) levels, apo(a) isoforms, lipid profile and oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB) and apolipoprotein (a) (OxPL-apo(a)) were measured. In the multiple ascending dose study, ISIS-APO(a)Rx treatment resulted in dose-dependent, mean percentage decreases in Lp(a) from baseline to Day 36 (two weeks after the last dose) of -39.6% (p=0.005), -59.0% (p=0.001), and -77.8% (p=0.001), in the 100, 200 and 300 mg groups, respectively. Similar reductions were present in OxPL-apoB and OxPL-apo(a). These changes were independent of baseline Lp(a) levels or apo(a) isoforms and there were no significant changes in other lipoproteins. This study provides a rationale for the clinical development of ISIS-APO(a)Rx to reduce CVD and calcific aortic valve stenosis.

Conclusion: ISIS-APOCIIIRx and ISIS-APO(a)Rx potently reduce plasma triglycerides and Lp(a). A Phase 3 trial in patients with Familiar Chylomicronemia Syndrome with elevated TG with ISIS-APOCIIIRx and a Phase 2 trial in patients with Lp(a) >125nmol/L (>50 mg/dl) ISIS-APO(a)Rx are ongoing.

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Freek Verheugt (Amsterdam, NED)

Freek W.A, Verheugt, MD, FESC, FACC, FAHA is Professor of Cardiology at the Heart-Lung Centre of the University Medical Centre of Nijmegen and Chairman of the Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam, The Netherlands. Professor Verheugt gradua¬ted from the University of Amsterdam in 1974 and wrote a thesis on platelet and granulo¬cyte antigens and antibodies. He trained in cardiology at the Thoraxcenter of the Erasmus University in Rotterdam. He has been a Professor at the University of Colorado Health Sciences Center in Denver, U.S.A., and at the Free University in Amsterdam. He was President of the Netherlands Society of Cardiology between 1999 and 2001.

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

ABSTRACT

A glimpse at the future: what space is left for new ant-IXas and for the actively controllable IXa blocker aptamer?

Freek Verheugt (Amsterdam, NED)

Parenteral anticoagulation is mandatory in patients undergoing percutaneous coronary intervention (PCI). Heparin, low molecular weight heparin and the specific thrombin blocker bivalirudin are currently used. Factor IX is part of the activation of the coagulation cascade via the intrinsic route.

REG1 is a two-component, actively controllable anticoagulant system consisting of the factor IX inhibitor, pegnivacogin and the control agent, anivamersen, which has a specific affinity for pegnivacogin.1,2 The RADAR trial3 evaluated REG1 versus heparin in NSTE-ACS patients undergoing femoral catheterization. At 30 days, ACUITY bleeding had occurred in 65.0%, 33.6%, 34.5%, 30.4%, and 31.3% of patients with 25%, 50%, 75%, and 100% reversal and heparin, respectively (Figure 1). At least 50% pegnivacogin reversal was needed to prevent bleeding. There were fewer ischemic events with REG1 (3.0%) versus heparin (5.7%).

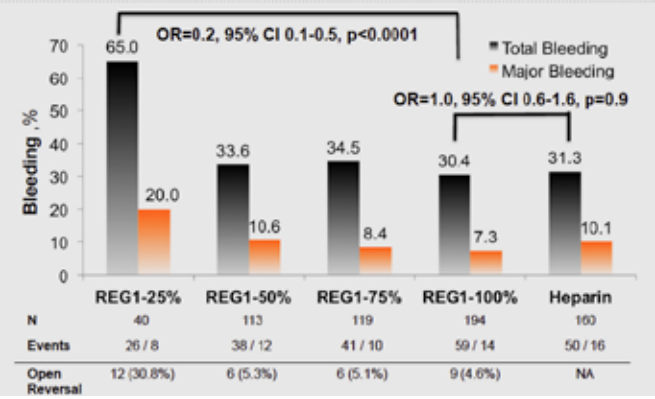

Fig 1. Bleeding outcome in the RADAR trial1

In 3 patients given pegnivacogin allergic reactions occurred. Thus, the RADAR study shows that factor IXa inhibition results in significantly more bleeding over UFH, but can be reversed. On the other hand, total reversal did not result in lower bleeding compared with UFH. Overall, the new treatment seemed to reduce recurrent ischemic events.

These findings warranted a Phase III study with this new anticoagulant with an effective reversal agent in patients undergoing PCI: the REGULAR-PCI study to include 13,200 patients. After about 3,200 patients included the Data Safety and Monitoring Board advised to halt the trail because of the occurrence of severe allergic reactions to REG1.

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Lars Wallentin (Uppsala, SWE)

Lars Wallentin is senior professor of Cardiology and founder and first head of the Uppsala Clinical Research Centre (UCR) at Uppsala University Hospital, Uppsala, Sweden. Pr. Wallentin has been President of the Swedish Cardiac Society, founder and first President of the Swedish Heart Association. He also founded and was the first chairman of the Swedish Cardiovascular Registries. The research group of professor Wallentin has developed many new concepts concerning pathogenesis, diagnosis, risk stratification, and antithrombotic and interventional treatments in acute coronary artery disease and stroke prevention in atrial fibrillation. Pr. Wallentin has published more than 500 manuscripts in peer-reviewed international journals and has received several prestigious research awards.

ABSTRACT

Prasugrel or Ticagrelor in ACS? A case study on how trial, comparative effectiveness and registry data may be used in conjunction, short of a head-to-head comparison

Lars Wallentin (Uppsala, SWE)

This presentation will review the currently available results from the phase III trials comparing respectively prasugrel and ticagrelor with clopidogrel when added to standard of care in patients with acute coronary syndrome. The main design features and outcomes are summarized in the table.

	TRITON-TIMI 38	PLATO	TRILOGY-ACS Patients < 75 years
Study treatment	Prasugrel (60 mg LD + 10 mg od) Clopidogrel (300 mg LD + 75 mg od) up to 1h post PCI	Ticagrelor (180 LD+90mg bid + 90 mg at PCI) Clopidogrel (300 mg LD + 75 mg + 300 mg for PCI >24h)	Prasugrel (30 mg LD + 5–10 mg od) Clopidgorel (300–600 mgLD + 75 mg od)
Age median (yrs)	61	62	62
Female (%)	26	28	36
Type of ACS	ACS with PCI: NSTEACS 74%, STEMI 26%	Any ACS: NSTEACS 62%, STEMI 38%	NSTE-ACS
Symptom duration	NSTE <72h, PPCI <12h, other STE <14d	<24h	<10 days
Clopidogrel prior to coronary angiography	only at PPCI	allowed	allowed
CV-death, MI, stroke (%)	9.9 vs 12.1, P<0.001	9.8 vs 11.7, P<0.001	13.9 vs 16.0, p=0.21
Death	3.0 vs 3.2	4.5 vs 5.9, P<0.001	7.8 vs 8.1, p=0.63
Cardiovascular death	2.1 vs 2.4	4.0 vs 5.1, P=0.001	6.6 vs 6.8, p=0.48
Nonfatal MI (%)	7.3 vs 9.5, P<0.001	5.8 vs 6.9, P=0.005	8.3 vs 10.5, p=0.21
Stent thrombosis	1.1 vs 2.4, P<0.001	2.2 vs 2.9, P=0.02	Not stated
Nonfatal stroke	1.0 vs 1.0	1.5 vs 1.3	1.5 vs 2.2, p=0.08
Non-CABG major bleed (%)	2.4 vs 1.8, P=0.03	4.5 vs 3.8 (2.8 vs 2.2), P=0.03	2.1 vs 1.5, p=0.27
CABG-related major bleed (%)	13.4 vs 3.2 of CABG treated, P<0.001	7.4 vs 7.9 (5.3.vs 5.8)	Not stated
Life-threatening bleed (%)	1.4 vs 0.9 P=0.01	5.8 vs 5.8	0.9 vs 0.8, p=0.88
Intracranial bleeding (%)	0.3 vs 0.3 (non-CABG)	0.3 vs 0.2	0.7 vs 0.5, p=0.39
Fatal bleed (%)	0.4 vs 0.1 P=0.002	0.3 vs 0.3	0.5 vs 0.2, p=0.99

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Steve Winitsky (FDA, USA)

Dr. Steve Winitsky is a Medical Officer in the Office of Cellular, Tissue, and Gene Therapies (OCTGT) in FDA's Center for Biologics Evaluation and Research (CBER). As a Medical Officer on the General Medicine Team in the Division of Clinical Evaluation and Pharmacology/ Toxicology (DCEPT), he conducts primary clinical reviews and ongoing oversight of studies of cellular and gene therapy-based products, devices, or combination products that are conducted under IND (Investigational New Drug) and IDE (Investigational Device Exemption) applications, with a focus on therapeutics for cardiovascular indications.

ABSTRACT

Clinical considerations for early-phase cardiovascular cell and gene therapy studies

Steve Winitsky (FDA, USA)

The presentation will discuss clinical considerations for development programs for cellular therapies and gene therapies that are being studied for cardiovascular indications, with a focus on clinical considerations for early phase studies, including first-in-human studies.

Janet Wittes (Washington, DC, USA)

Janet Wittes, PhD, is President of Statistics Collaborative, Inc., which she founded in 1990. One of the main activities of Statistics Collaborative is to serve as the statistical reporting group for independent 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. Her research has focused on design of randomized clinical trials, capture recapture methods in epidemiology, and sample size recalculation. She has served on a variety of advisory committees and data monitoring committees for government (NHLBI, the VA, and NCI) 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). She received her PhD in Statistics from Harvard University.

Nadim Yared (CVRx, USA)

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

He had previously served as Vice President and General Manager of Medtronic Navigation, the leading supplier of integrated image-guided surgery products, from 2002 - 2006. He also held positions with GE Medical for ten years, where he was Vice President of Global Marketing for OEC Medical Systems and Vice President and General Manager of GE's European X-ray business based in Paris.

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

Mr. Yared is a member of the Board of Directors for AdvaMed and Chairman of AdvaMed EGCC Board. In addition, he is a member of the Board of Directors for MDIC, Hansen Medical and CVRx.

Faiez Zannad (Nancy, FRA)

Pr. Faiez Zannad is Professor of Therapeutics and Cardiology, Université de Lorraine, France and Director of the Clinical Investigation Center, Inserm-CHU of Nancy. www.cic-nancy.fr/cic
He is currently on annual sabbatical leave, acting as advisor to the Tunisian Ministry of Health, with a mission to structure health research.

In the last five years, his main professional activities have been in the following areas:

- Structuring of the clinical research infrastructure in France
- Roadmap of health research in Tunisia
- Contribution to clinical trial science and methodology in CV disease
- Significant contribution in advances in heart failure treatment, through major clinical trials, mainly with mineralocoticoid receptor antagonists (RALES, EPHESUS, EMPHASIS-HF, REMNDER, ARTS), but also with beta-blockers (CIBIS, CAPRICORN), Angio2 receptor blockers (VALIANT, HEAAL); Direct Renin Inhibitors (ASTRONAUT) and vasopressin antagonists (EVEREST), which has led to the approval of new drugs in this area and

change in international guidelines.

- Specific interest in mechanistic biomarkers in heart failure Results show that fibrosis biomarkers may predict outcome and describe one target mechanism of action of mineralocoticoid receptor antagonists.
- First randomized controlled trial of CV prevention in haemodialysis patients (FOSIDIAL). Results show a potential benefit of ACE inhibitor therapy to decrease CV morbidity and mortality in patients with ESRD and left ventricular hypertrophy. Follow up with the statin trial AURORA, which did not show benefit of Rosuvastatin in haemodialysis patients. On-going ALCHEMIST trial of spironolactone in haemodialysis high-risk patients (FOSIDIAL).

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

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

Among Pr. Zannad's current and anticipated research grant support

- 2010-14: EU 7th FP. Large scale integrating project The MEtabolic Road to DIAstolic Heart Failure (MEDIA) coordinating workpackage on biomarkers)
- 2013-2019 EU 7th FP Heart failure Omics and AGEing (HOMAGE), General Coordinator
- 2013-2017 EU 7th FP FIBRosis as a TARGET in Heart Failure (FIBROTAGERTS), General coordinator

He is chairman and organizer of several international meetings: "CardioVascular Clinical Trialists (CVCT) Forum and Workshop" (since 1998 in Cannes and Paris, with Bertram Pitt); "Heart Failure Trialists Workshop" (since 2010, for the ESC Heart Failure Association) and "Biomarkers in Heart Failure" (Since 2005 in Cannes, with Kirkwood Adams).

Pr. Zannad has received many honors during his career, the most recent in 2014, the Paul Milliez Award of the European Society of Hypertension.

ABSTRACT

Ongoing trials: therapies on the horizon?
Finerenone

Faiez Zannad (Nancy, FRA)

Although patients with severe renal dysfunction had been excluded from the mortality studies investigating MRAs in heart failure, there is growing interest not only from heart failure specialists, but also from nephrologists to treat these patients too with low dose MRAs to obtain cardiovascular but also potential renal benefits.
The so-called 'third-generation MRAs' are non-steroidal compounds with both high selectivity and high potency to inhibit the MR. The first compound of these novel MRAs undergoing clinical evaluation, Finerenone, appears, furthermore, to display a distinct tissue distribution different from that of first- and second-generation MRAs: while spironolactone and—to a somewhat lesser extent—eplerenone are enriched in the kidneys as compared with the heart, Finerenone appears to have an equal tissue distribution.

The first phase II clinical trial with Finerenone, The minerAlocorticoid-Receptor Antagonist Tolerability Study (ARTS) is a 4-week randomized, double-blind trial investigating increasing dosages of the finerenone compared with placebo or open-label spironolactone in patients with systolic heart failure NYHA class II/III and mild to moderate chronic kidney disease (eGFR) 30–60 mL/min/ 1.73 m^2]. The main results are very encouraging. Finerenone was associated with significantly less hyperkalaemia, worsening renal function, and blood pressure decrease in comparison with spironolactone (25–50 mg), while BNP and NT-proBNP as well as albuminuria were reduced by the Novel MRA at least as much as with spironolactone, thus providing reassurance that the lower incidence of side effects most probably does not come at the expense of lower efficacy.

Against this background, ARTS-Heart Failure (ARTS-HF) is a dose-finding study designed to investigate the effects of 90 days of finerenone (dose range, 2.5–20 mg/day) and eplerenone (dose range, 25 mg every other day to 50 mg/day) on plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in high-risk patients with worsening chronic HFrEF and concomitant T2DM and/or CKD.

ARTS-HF (ClinicalTrials.gov identifier: NCT01807221) is a multicentre, randomized, double-blind, active-comparator-controlled, five-parallel-group, phase 2b study. The trial is targeting adults with worsening chronic HFrEF (in the 7-day period following emergency presentation to hospital) requiring emergency presentation to hospital and treatment with intravenous diuretics, AND who have T2DM and/or CKD, a medical history of a left ventricular EF of 40% or less within the last 12 months. It is intended that 1510 patients will be enrolled and 1060 will receive treatment with study drug. The primary objective of the study is to investigate the safety and efficacy (measured as the percentage

of individuals with a decrease in plasma NT-proBNP of more than 30% relative to baseline at visit 9 [day 90±2]) of different oral doses of finerenone given once daily. The trial has an interesting adaptive design. Based on the safety profile of finerenone seen in the first 300 patients more treatment arms could be introduced into the study with finerenone at higher doses (7.5 mg, to 20.0 mg).

ABSTRACT

Ongoing trials: therapies on the horizon?
NOACS

Faiez Zannad (Nancy, FRA)

Thrombotic events occur frequently in patients with heart failure. These events may be precipitated by several mechanisms including hypercoagulability through enhancement of pro-coagulant reactions, impairment of the protein C pathway, protease activated receptor (PAR) activation, adenosine mediated thrombosis, or neurohormonal activation; stasis secondary to low cardiac output; and endothelial dysfunction from neurohormonal activation or systemic inflammation. Pathophysiologic evidence and analyses of retrospective data support the hypothesis that antithrombotic agents may improve outcomes in patients with heart failure. Warfarin has not been shown to reduce clinical events in patients with heart failure, although several of the completed randomized trials were underpowered, and the most recent was not placebo-controlled. Many unanswered questions remain that justify continued research in this area. There are conceptual opportunities and challenges of clinical investigative approaches with the newer anti-thrombotic agents in patients with heart failure. Although the results of previous studies with warfarin have demonstrated that anticoagulation is associated with reduced rates of important clinical events in patients with HF, results of these studies have not been conclusive. In a recent Phase 3 study of rivaroxaban in acute coronary syndrome (ACS), rivaroxaban was shown to reduce the incidence of the primary endpoint (cardiovascular [CV] death, MI, or stroke) in a subset of subjects with a history of HF. This supports the hypothesis that rivaroxaban may help reduce thrombotic events in patients with HF that can lead to death, MI or stroke. Thus, a large prospectively designed study with a novel anticoagulant is underway to adequately address whether or not rivaroxaban can reduce the risk of death, MI, and stroke in patients with chronic HF and significant coronary artery disease (CAD), following a hospitalization for exacerbation of their HF. The COMMANDER-HF trial is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven, superiority study of rivaroxaban with clinical outcome assessments in subjects with chronic symptomatic HF (3 months or longer) and significant CAD. The subject population comprises men and women age 18 and over who have a diagnosis of previous MI or significant CAD with a left ventricular (LV) dysfunction (left ventricular ejection fraction [LVEF]) ≤40%), and high BNP. Only subjects hospitalized for decompensated HF (known as the index hospitalization) will be eligible for enrolment at hospital discharge (and up to 30 days after discharge) if they are in stable condition. The primary efficacy outcome is the composite of ACM, MI, or stroke. The principal safety outcome is the composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability. Additional bleeding outcomes are bleeding events requiring hospitalization, and ISTH major bleeding events.

A total of 984 primary efficacy outcome events are targeted to demonstrate the superiority of rivaroxaban compared with placebo. A sample size of approximately 5,000 subjects will be enrolled. All subjects will also receive standard care based on international clinical guidelines for HF and CAD as prescribed by their managing physicians. Standard care is expected to include aspirin/acetylsalicylic acid (ASA) (or other antiplatelet agent as appropriate). The maximum dose of ASA will be 100 mg. Dual antiplatelet therapy is allowed where indicated.

ABSTRACT

Ongoing trials: therapies on the horizon?
Auto Serve Ventilation in sleep disordered breathing

Faiez Zannad (Nancy, FRA)

It is likely that new interventions will be targeted at specific subgroups of HF patients rather than the entire population. Treatment of sleep-disordered breathing (SDB) may be one such intervention. SDB is very common in patients with HF, with reported prevalence rates of 50-75%. The presence of SDB is associated with decreased survival in HF patients. Two types of abnormal breathing during sleep predominate in SDB, obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), which is often called Cheyne-Stokes Respiration (CSR) in the presence of HF. CSA/CSR prevalence is 25-40% of patients with chronic HF. CSR induces chemical, neural and hemodynamic changes similar to those seen in OSA, and is the most commonly SDB breathing pattern seen in the chronic HF population. It is an independent risk factor for death in these patients and one of the key mechanisms for this could be an increased risk for malignant ventricular arrhythmias. The only randomized controlled trial investigating mortality in patients with HF and CSA/CSR treated with CPAP was the CANPAP study. The trial was stopped prematurely after enrolment of 258 of the planned 408 patients, and data analysis did not show a beneficial effect of CPAP treatment (Bradley, NEJM 2005). However, a post-hoc analysis suggested that outcomes might be improved if SDB was well controlled (Arzt, circulation 2007).

ASV is a non-invasive respiratory therapy that provides positive expiratory airway pressure and inspiratory pressure support, which is servo controlled based

on the detection of respiratory events (hypopnoeas and apnoeas). Although clinical experience with ASV is extensive, there is a limited amount of published literature available. Several small studies have shown improvements in symptoms and measures of cardiac function, exercise tolerance and quality of life with ASV therapy.

Studies to date have not been of adequate size or duration to determine whether therapy with ASV is associated with significant reductions in morbidity and mortality in patients with HF and CSA/CSR.

SERVE-HF is a multinational, multicentre, randomised, parallel trial designed to assess the addition of ASV to optimal medical management compared with medical management alone (control group) in patients with symptomatic chronic HF, left ventricular ejection fraction ≤45%, and predominant central sleep apnoea (CSA). The trial is based on an event-driven design and the final analysis will be performed when 651 events have been observed or the study is terminated at one of the two interim analyses. The aim is to randomise approximately 1260 patients to one of the two treatment groups (with an estimated 20% of patients lost to follow-up). The first patient was randomised in February 2008 and the study is expected to end in early 2015. The primary combined endpoint is the time to first event of all-cause death, unplanned hospitalisation (or unplanned prolongation of a planned hospitalisation) for worsening chronic HF, or cardiac transplantation/resuscitation of sudden cardiac arrest/appropriate life-saving shock for ventricular fibrillation or fast ventricular tachycardia in implantable cardioverter defibrillator patients.

The SERVE-HF study is a randomised study that will provide important data on the effect of treatment with ASV on morbidity and mortality as well as the cost-effectiveness of this therapy in patients with chronic heart failure and predominantly CSA/CSR.

ABSTRACT

CV safety endpoints: the heart failure issue Insight from EXAMINE

Faiez Zannad (Nancy, FRA)

The FDA requires that a pooled analysis of MACE generate a reassuring risk ratio point estimate not to exceed 1.8 at the upper bound of the 95% confidence interval (CI). If the confidence interval excludes 1.8 but includes 1.3, then a separate, prospective, post-marketing safety study is required to rule out such a 30% increase in risk. Of note, the guidance did not specifically include heart failure hospitalization as a cardiovascular safety endpoint of interest, despite prior studies linking certain antidiabetic drugs (PPAR antagonists) with this adverse event. At the time the guidance was released, the impact on the field was uncertain. Two clinical trials that were designed to meet this regulatory requirement have been reported recently. The Examination of Cardiovascular Outcomes with Alogliptin versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) trial randomized patients with type 2 diabetes mellitus, HbA1c 6.5 to 11% and a recent ACS, to either alogliptin or placebo over a median of 18 months. The primary endpoint was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke. No difference was observed between groups in the primary endpoint (11.8% placebo versus 11.3% alogliptin, HR 0.96, upper bound of the one-sided repeated CI ≤1.16, P<0.001 for non-inferiority and P=0.32 for superiority). The findings were consistent across all components of the composite endpoint. The first occurrence of the composite of all-cause mortality, non-fatal MI, non-fatal stroke, urgent revascularization due to unstable angina, and hospitalization for heart failure was a pre-specified exploratory composite endpoint in EXAMINE. There was no difference between the alogliptin and placebo groups for this endpoint [16% alogliptin versus 16.5% placebo, HR 0.98 (95% CI 0.86-1.12), P=0.728]. When analysed individually, none of the components were different between alogliptin versus placebo; additionally, hospitalization for heart failure was not different between the alogliptin and placebo groups [3.1% vs. 2.9%, HR 1.07 (95% CI 0.79-1.46), P=0.657]. A post-hoc composite endpoint of cardiovascular death or heart failure hospitalization was also evaluated and showed no difference between alogliptin and placebo for the total cohort or by history of heart failure prior to randomization. In conclusion, in patients with T2DM and recent acute coronary syndrome, the EXAMINE trial demonstrates that alogliptin does not increase the risk of HF outcomes that included CV death and HHF. Additionally, reductions in NT-pro-BNP with alogliptin therapy and use of diuretics (both thiazide and loop) were similar to that observed with placebo at 6 months. These data, while interesting and hypothesis generating, should be interpreted cautiously because of the limitations of post-hoc analyses and the small number of events in patients without a history of heart failure.

These results are at variance with those reported with SAVOR, where saxagliptin was associated with an excess of HF events. Of note, heart failure is a pre-specified secondary endpoint in TECOS, which is important in light of the data that emerged from SAVOR-TIMI 53, recent meta-analyses, and observational studies that suggested an increased risk of heart failure hospitalizations with some DPP-4 inhibitors. TECOS may help elucidate whether the heart failure risk could be a group effect or limited to specific agents, at least in the population represented by the trial.

ABSTRACT

Heart failure
Lessons learnt post NECTAR-HF

Faiez Zannad (Nancy, FRA)

The NECTAR-HF (NEural Cardiac TherApy foR Heart Failure) was a randomized sham-controlled trial designed to evaluate whether a single dose of vagal nerve stimulation (VNS) would attenuate cardiac remodelling, improve cardiac function and increase exercise capacity in symptomatic heart failure patients with severe left ventricular (LV) systolic dysfunction despite guideline recommended medical therapy. The primary endpoint was the change in left ventricular end systolic diameter (LVESD) at 6 months for control versus therapy, with secondary endpoints of other echocardiography measurements, exercise capacity, quality of life assessments, 24-hour Holter, and circulating biomarkers. Change in LVESD, LVESV, LVEDV, LVEF, peak V02 and NTproBNP failed to show superiority compared to sham treatment. However, there were statistically significant improvements in quality of life for the MLHFQ (p = 0.049), NYHA class (p=0.032) and the SF-36 Physical Component (p=0.016) in the therapy group. Therefore, VNS as delivered in the NECTAR-HF trial failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodelling and functional capacity in symptomatic HF patients, but quality of life measures showed significant improvement.

Several characteristics of autonomic modulation devices pose challenges for clinical trial design. First, the introduction of bias can be problematic since these trials are difficult to blind. Actually in NECTAR-HF, although sham-controlled and blinded, many patients could guess the therapy they were receiving (On or OFF). Second, the mechanism of treatment effect is difficult to establish. Although a reduction in central sympathetic activity is the proposed mechanism of action, generating proof that sympathetic outflow is reduced either acutely after a procedure or long-term can be difficult. Third, the adequacy of surrogate endpoints (e.g. changes in blood pressure or cardiac dimensions) to reflect clinical outcomes in trials of autonomic modulation devices has been debated. Finally, safety assessments are of key importance because patients undergo invasive procedures, which may be irreversible (renal denervation) or may require a repeat invasive procedure when replacing a stimulator is necessary. Programmable autonomic modulation therapies offer a priori the theoretical advantage of adjustments to provide optimized and individualized therapy to patients. However, selecting the optimal "stimulation dose" of autonomic modulation therapies for clinical testing can be complex. Many parameters influence the stimulation "dose" and programming is highly individualized. Stimulation parameters are chosen on the basis of acute changes in blood pressure or heart rate, and/or occurrence of stimulation related adverse effects. Stimulation adjustments are not possible with some devices; such as vagal stimulation. They are either "on" or "off" or "dosed" only on the basis of non-target tolerance symptoms, or irreversibly destroy tissue. Finally, the number of patients with long-term follow-up is currently insufficient to provide robust assurance of safety. Autonomic modulation therapies hold promise for diseases that are resistant to multi-drug therapy (i.e. hypertension), or that progress despite optimized evidence-based therapies (i.e. heart failure). Overcoming the challenges of conducting trials in this field is critical to determine the true long-term effects of these device therapies, and to determine if the magnitude of their benefit is sufficient to justify their use from clinical and economic perspectives.

Nevine Zariffa (AstraZeneca, USA)

Névine Zariffa was born in Cairo, Egypt and was raised in Montréal, Canada. After her training at McGill University and at the University of Waterloo (Mathematics and Statistics), she began her career as a statistician supporting agricultural research before moving to Philadelphia to join SmithKline Beecham in 1991, which went on to become GlaxoSmithKline. She joined AstraZeneca in November 2011 and is currently VP and Head of Biometrics and Information Sciences in Global Medicine Development.

Over the last 20 years, Névine has amassed a wealth of experience in her specialist area and also in driving strategic programs. She has supported early & late-stage clinical development and marketed products - primarily in the area of Cardiovascular and Metabolism - and has led global teams of quantitative experts across many quantitative disciplines. Névine has also led, or played an integral part in numerous strategic initiatives, working with company colleagues, medical associations, academics and other groups (both PhRMA and FDA-sponsored) to enhance the value of quantitative sciences beyond the traditional role of designing, analysing and interpreting clinical trials. Névine has been a statistical Reviewer for The Lancet and is the (co-)author of over 25 publications in peer reviewed biostatistics and medical journals.

ABSTRACT

Methodological issues in analyzing big data

Nevine Zariffa (AstraZeneca, USA)

The big data concept deserves our full attention and careful evaluation. For many it is the inevitable consequence of the intersection of today's enhanced computing power and data access. For others it is a distant poor relative of the gold standard methods of evidence generation. And for most us, we declare quite humbly it is a mystery! We will use recent examples to review non-traditional 'Big Data' approaches to evidence generation and evaluate the strengths and limitations of the methodologies.

Bram Zuckerman (FDA, USA)

Dr. Bram Zuckerman is a graduate of the Boston University Medical School. He completed post-graduate training in internal medicine at Baltimore City Hospital and cardiology at the Johns Hopkins program. Prior to joining FDA in 1992, he was involved in basic research in hemodynamics at the University of Colorado Medical School and practiced noninvasive and invasive cardiology in Denver, Colorado and Northern Virginia. He joined the FDA Division of Cardiovascular Devices (DCD) as a Medical Officer in 1992 and has been actively involved in development and review of clinical trials for many new cardiovascular devices. In May 2001 he was appointed a Deputy Director in DCD. He was appointed to his current position as Director of the FDA Division of Cardiovascular Devices in September 2002.

Posters

Patiromer induced a rapid onset of action and sustained K^+ lowering throughout the dosing period in CKD patients with hyperkalemia

Authors: D. Bushinsky[1], G. Bakris[2], G. Williams[3], B. Pitt[4], M. Mayo[5], D. Garza[5], Y. Stasiv[5], E. Li[6], L. Berman[5].

[1] University of Rochester, Rochester, NY, USA
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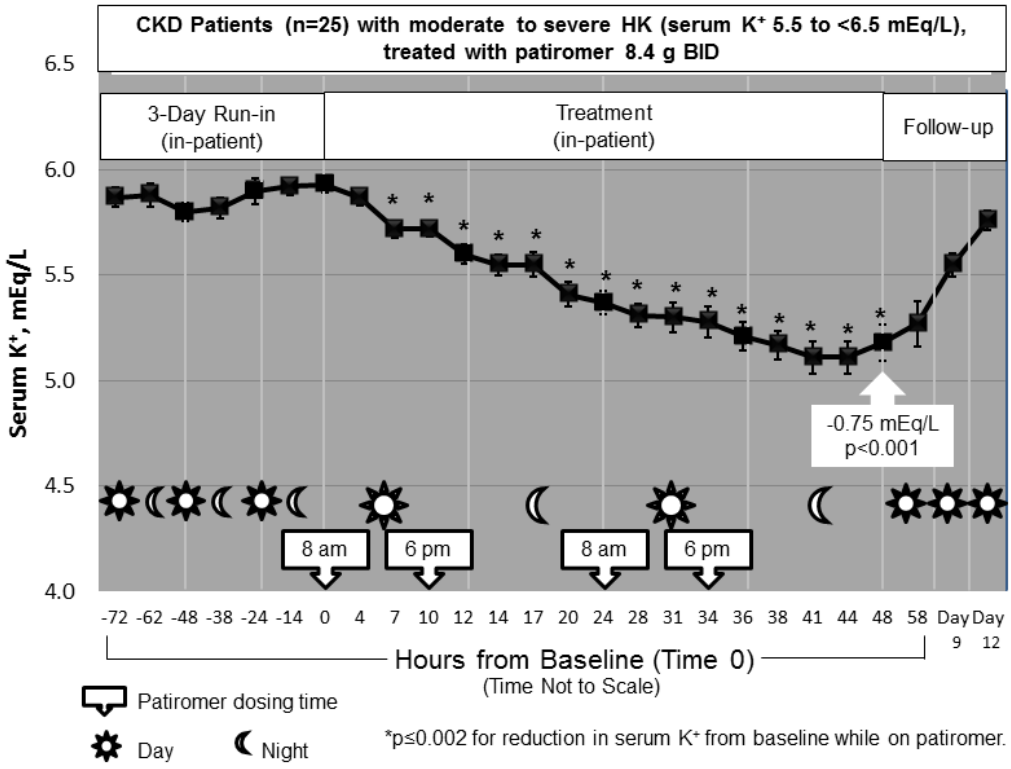
[3] Harvard Medical School, Cambridge, MA, USA
[4] University of Michigan, Ann Arbor, MI, USA
[5] Relypsa, Redwood City, CA, USA
[6] PharmaStat, Newark, CA, USA

Background: Patients (pts) with CKD on RAAS inhibitors (RAASi) have a high risk of hyperkalemia (HK), which increases mortality and can lead to RAASi dose reduction/discontinuation. Patiromer, a novel, nonabsorbed metal-free polymer with high K^+ binding capacity and good GI tolerability, has previously been shown to normalize serum K^+ in CKD pts with HK on RAASi. In this study, we determined the onset-of-action of patiromer in CKD pts with HK taking ≥1 RAASi.

Method: After a 3-day controlled diet (K^+ intake, 60 mEq/d) pts with serum K^+ ranging from 5.5 to less than 6.5 mEq/L received patiromer 8.4 g/dose with AM/PM meals for a total of 4 doses. Serum K^+ was assessed: at baseline (0 hr), 4 hr post-dose, then every 2-4 hr to 48 hr, and at Day 9 and 12.

Results: From a mean baseline serum K^+ of 5.93 mEq/L, a numerical reduction in mean K^+ occurred 4 hr after the 1st dose, with a significant reduction (p=0.002) at the next assessment (7 hr after 1st dose). Significant reductions occurred at all subsequent assessments through 48 hr (p<0.001; Figure). Mean serum K^+ <5.5 mEq/L was achieved within 20 hr (p<0.001). At 48 hr (14 hr after last dose), the reduction was -0.75 mEq/L (p<0.001). There was no rebound in mean K^+ levels overnight.



Patiromer was well tolerated, with no serious AEs and none leading to withdrawal. The most common AE was mild constipation (2 pts [8%]). No hypokalemia (K^+ <3.5 mEq/L) was observed.

Conclusion: Patiromer induced an early and sustained reduction in serum K^+ with no nighttime rebound and was well tolerated in CKD pts with HK on RAASi.

In-vivo carotid plaques characterisation using quantitative T2 map: histological validation and lipid quantification

Authors: J.T. Chai[1] *(joshua.chai@cardiov.ox.ac.uk)*, L. Biasiolli, L. Li, A. Handa, J. Perkins, L. Hands, E. Sideso, P. Jezzard, M.D; Robson, R.P. Choudhury

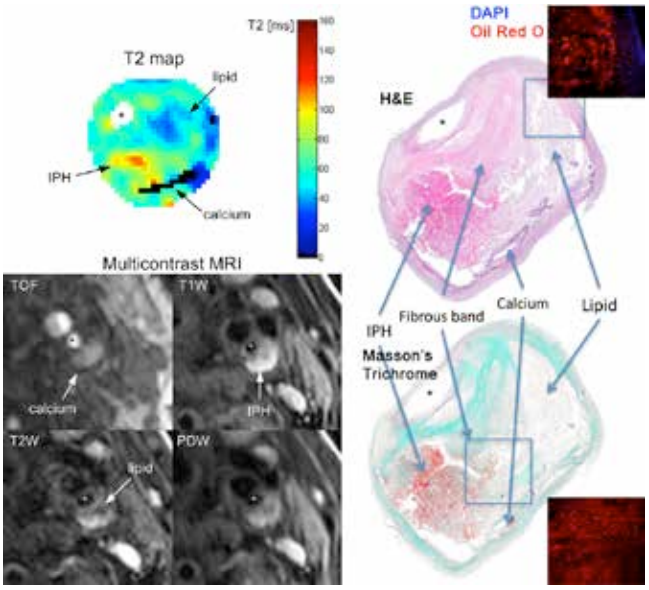
[1] RDM Division of Cardiovascular Medicine, University of Oxford, UK

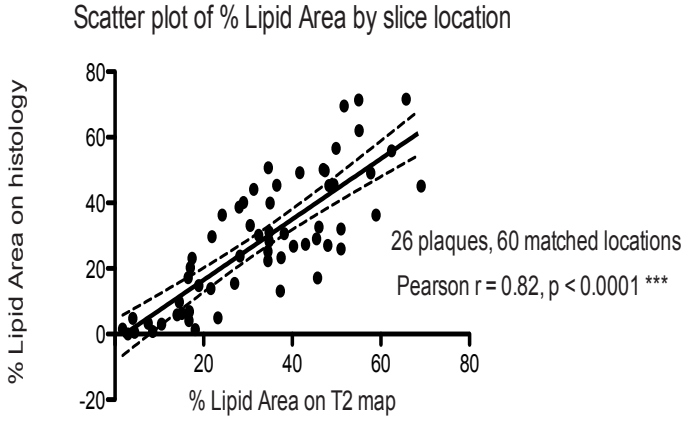
Background and objective: Multicontrast MRI has emerged as a powerful tool for plaque characterisation. While anti-lipid drugs might reduce plaque lipid measurable by MRI, the non-quantitative nature of multicontrast MRI and its need for extensive post-acquisition processing limited its clinical application. We recently reported the use of quantitative T2 map to measure the absolute physical properties of different plaque components. Here we sought to validate, at a tissue level, the agreement between T2 mapping and histology; and to evaluate the clinical potential of using T2 mapping in lipid quantification in human carotid atherosclerosis.

Method: 40 adult patients with 50-99% carotid stenosis according to NASCET criteria, or 70-99% according to ECST criteria, who were either asymptomatic or whom had suffered a minor CVA or TIA on the culprit side, were recruited to participate in this study. Ethics were approved by national and local R&D committee. All patients were scanned using 3T-MRI within 1 week of their scheduled carotid endarterectomies as part of routine clinical care. Black-blood cross sectional 2D images of the carotid arteries were obtained using published imaging protocols. [Biasiolli L, Lindsay AC, Chai JT, et al. J Cardiovasv Magn Reson, 2013; Li L, Chai JT, Biasiolli L, et al. Radiology, 2014] One reviewer classified plaque types using T2 maps with TOF images using the AHA scheme and calculated %lipid area using segmentation algorithm. An independent reviewer processed and evaluated plaque histology and lipid content.

Results: High quality MRI and histology were obtained from 26 plaques with 60 matched slice locations (average 2.3 slices per plaque). First, in terms of AHA plaque type classification, T2 map (+TOF) and histology were shown to have excellent agreement (80.8%) with Cohen kappa = 0.73. In addition, calculated %Lipid Area from T2 maps was found to correlate with histology with a Pearson correlation coefficient of 0.82 (P=0.0001). The two techniques were found to have good agreement by Bland-Altman analysis with a small bias of 4.49%. To further evaluate its potential clinical application, we compared the %lipid area derived from T2 map alone in our symptomatic vs asymptomatic cohorts; we found that T2 map %lipid area in symptomatic patients were significantly higher compared to that in asymptomatic patients (P=0.013). If we use the conventional cut-off definition of large lipid-rich necrotic core as 25%, this difference was even more pronounced (P=0.0077). Finally, a ROC analysis confirmed that our T2 map %lipid area has a fair to moderate ability to discriminate between symptomatic and asymptomatic patients in our clinical cohort with an area under curve (AUC=0.76, P=0.024).

Conclusion: Our study showed that in-vivo T2 mapping can accurately discriminate plaque components and quantify lipid contents. It suggests great potential not only as a platform for evaluating the efficacy of lipid active drugs at the level of atherosclerotic plaques, but also help stratify risk / patient selection in future clinical trials.





Potassium levels and mortality in patients with CKD

Authors: A. Collins[1], N. Reaven[2], S. Funk[2], G. Bakris[3], B. Pitt[4], D. Bushinsky[5]

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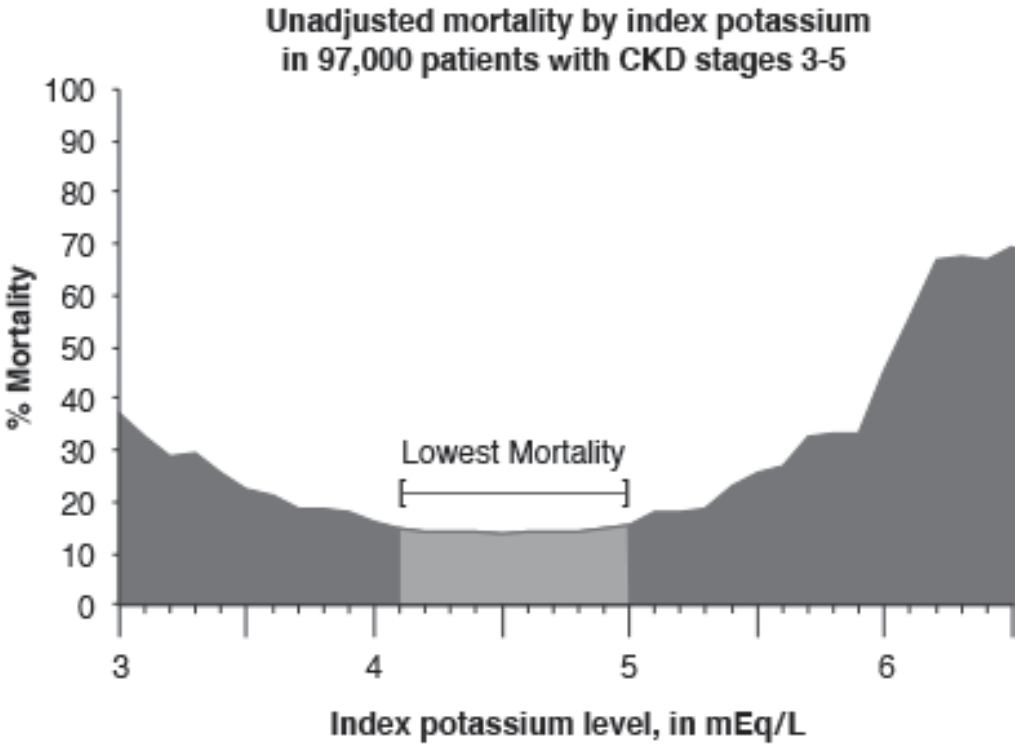
[2] Strategic Health Resources, La Canada, CA, USA
[3] University of Chicago, Chicago, IL, USA
[4] University of Michigan, Ann Arbor, MI, USA
[5] University of Rochester, Rochester, NY, USA

Background: Abnormal serum potassium levels are common in patients with advanced chronic kidney disease (CKD), yet the degree of mortality risk at different levels of potassium is not clear. We evaluated the odds of death in patients with CKD stages 3-5, stratified by potassium level.

Method: De-identified medical records (2007-2012) from a large US population of individuals ≥ 5 years of age with at least 2 potassium readings were evaluated. Patients with CKD stages 3-5 (n=97,415) were identified from ICD-9 codes and biochemical data, excluding those with acute kidney injury or end stage renal disease. Index potassium value was defined as the last reported value prior to pre-determined cut-off date. Mortality was evaluated through hospital discharge records and Social Security registry information.

Results: Unadjusted mortality rates are shown in the Figure. Patients with index potassium levels below 4.1 mEq/L and above 5.0 mEq/L show a significant increase in mortality, even at levels within the usual normal laboratory range. The increased mortality remained after adjustments for demographic characteristics (sex, age, race) and comorbidities, including heart failure, diabetes, hypertension, cardiovascular disease and acute myocardial infarction.



Conclusion: These findings suggest that there is a significant increase in mortality at serum potassium levels below 4.1 mEq/L and above 5.0 mEq/L in patients with CKD stages 3-5.

Translating preferences into action: design of a pilot clinical trial of shared decision-making in the cardiac catheterization laboratory

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Objective: Selecting a treatment strategy for patients with symptomatic coronary artery disease requires consideration of symptom burden, patient preferences, and practice guidelines. In many cases, treatment strategy is decided while the patient is undergoing angiography and cannot participate fully in the decision-making process. There is little guidance in the literature regarding strategies to improve patient participation in revascularization decisions. A shared decision-making tool that provides basic information about coronary disease and revascularization procedures could lead to improved patient knowledge and informed participation in these critical decisions.

Method: In this single center, pilot clinical trial, we will enroll 300 patients with planned cardiac catheterization to test the usability and clinical impact of a web-based shared decision-making tool. We will first test the tool using a pre-post design. The first 100 enrolled patients will undergo usual clinical care. The subsequent 200 patients will receive an interactive web-based tool prior to coronary angiography. The tool is designed to be brief but informative, require minimal assistance from clinical staff, and integrate into the electronic health record. We will survey all patients prior to angiography and at 3 months follow up. We will utilize validated instruments to assess patient knowledge, preferences regarding treatment for coronary artery disease, and decisional efficacy. Among the 200 patients receiving the tool, an embedded cluster randomized design will test the clinical impact of providing patient-reported preferences to interventional cardiologists at the time of angiography. Half of our interventional cardiologists will be randomized to receive the patient-reported information obtained by the tool, and half will continue usual care. We will assess the concordance between patient preferences and delivered treatments in these two groups.

Results and conclusion: Using a practical trial design, we will test a web-based shared-decision making tool at the time of coronary angiography. If this tool is found to be useful and efficient, it could be rapidly integrated into clinical practice.

Gender peculiarities of plasma interleukin -18 levels depend on the hypertri-glyceridemic phenotypeg

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Objective: It has been found that hypertriglyceridemic waist phenotype (HTGW) increase risk of coronary heart disease, and can be a matter of atherogenic metabolic triad. The presence of HTGW can predicts type 2 diabetes mellitus (T2DM) and increased visceral fat in patients with T2DM. The atm our study was to investigate cardiometabolic risk factors and plasma interleuktn-18 (01-18) levels in relationships with HTGW depend on gender of patients with arterial hypertension (AH).

Methods: Anthropometric parameters, carbohydrate and lipid metabolism, circulating IL-18 levels in 101 patients with AH (men (n=45-, 44.6%) and women (n=56: 55.4 %) aged 32-80 years) were examined. HTGW was defined as a waist circumference (WC) of 90 cm and more in male. and 85 cm and more in female.: and a trigl)ceride level of 1.7 mmo1/1. or more. Patients were categorized into phenotype groups: ['group (n=10) with hypertriglyceridemia and normal WC. 2rd, group (n=25(with normal triglyceride level and increased WC, 3' group (n=66) with HTGW.

Results: Our results showed that HTGW phenotype was associated with statistically higher SOP, DBP levels; increased body mass, BMI; and highest glucometabolic risk and atherogenic metabolic risk profile.
The patients of 3rd group characterized by maximum blood pressure levels (SBP-166.50 ±1.83 mmHg. DBP-102.89±0.94 mmHg) as compared with group (SBP-142.91,0.99 mmHg, DBP-91.64,0.93 mmHg, $p<0.05$) and 2»4 group (SSP-159.44,3.23 mmHg, DBP-100.32±1.48 mmHg, 100.05). Body mass index (Mil) in 3' group was also highest (31.050.61 kg/m-) vs 1' (23.95,0.91 kg/m-) and 2' one (30.21,1.00 kg/m). Fasting insulin levels were elevated in patients of 3rd group with HTOW (14.66,0.95 mkU/m1), and same in 1» (12.52,2.79 mkl.i,ml(and 2'112.31,1.41 mkU/m1) groups.

IL-18 — pro-inflammatory cytokine levels in 3' group were 176.97, 2.38 pg/ml. that was statistically higher in comparison with (167.73,7.21 pg/m1). and 2' group (172.40,5.61 pg/ml: p<0.05). Plasma IL-18 in 204 group was higher in men (172.40,5.61 pg/mg) vs women (169.53,7.04 pg/ml; p<13.05); whereas in 1' group women characterized by significantly higher IL-l8 content (169.00,1.11 pg. ml) compared with men (160.83,9.35 pg/ml; p<0.05). The same tendency was found in group 3 with HTGW phenotype presence where IL-18 content in ;omen (180.62,2.93 pg/ml) exceed cytokine level in men (167.76,3.5' pg/ml: p<0.051).

Association of dyskalemia and prognosis in acute heart failure: results from the GREAT registry

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Objective: Both hypo- and hyper-kaliemia are frequent in acute heart failure (AHF). The mechanism is often multifactorial, related either to diuretic effect, aldosterone agonist effect or kidney dysfunction. Dyskalemia have bathmotropic effects that could affect morbidity and mortality in acute heart failure (AHF). Accordingly, the aim of this study was to assess the association between dyskalemia and prognosis in AHF.

Method: We studied 12,367 patients with AHF from 15 prospective observational cohorts followed in 14 countries across 4 continents. Primary outcome was all-cause mortality at one year. Cox proportional hazards models described associations of dyskalemia with all-cause mortality. Hypokalemia and hyperkalemia were defined as a potassium concentration below 3.5 mmol/l and above 4.5 mmol/l, respectively. The effect of dyskalemia on all-cause mortality was studied without and with adjustment for potential confounding factors. The confounders included in the multiple model were age, sex, comorbidities (history of chronic HF, diabetes mellitus, chronic atrial fibrillation, coronary artery disease, history of hypertension) and impaired renal function (estimated glomerular filtration rate <60 ml/min/1.73 m^2).

Results: In the studied population, median age was 72 years, median left ventricular ejection fraction was 40%, 52% of patients presented de novo AHF and median blood potassium concentration on admission was 4.1 [3.9 – 4.7] mmol/L. 62% of patients had a normal level of potassium although 9% were hypokalemic and 29% hyperkalemic. After one year, 21% of patients had died. The death rates of patients with normo-, hypo- and hyper-kalemia were 18.2%, 19.4% and 24.2% (p<0.0001). After adjustment for potential confounders, hazard ratios (HR) of hypo- and hyperkalemia compared to normo-kalemia were 1.13 [1.02 - 1.26] (p=0.03) and 1.12 [1.01 - 1.24] (p=0.03) respectively.

Conclusion: Dyskalemia appears to be independently associated with one-year mortality in AHF. Although it is usual to supplement in potassium patients with or at risk of hypokalemia, it might be important to also strike for correcting hyperkalemia in AHF patients.

Patients hospitalized for heart failure have difficulties managing medications despite self confidence

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Background: The ability of a hospitalized patient to manage heart failure (HF) medications is not routinely assessed. We hypothesized that hospitalized HF patients have under-recognized poor medication self-management skills.

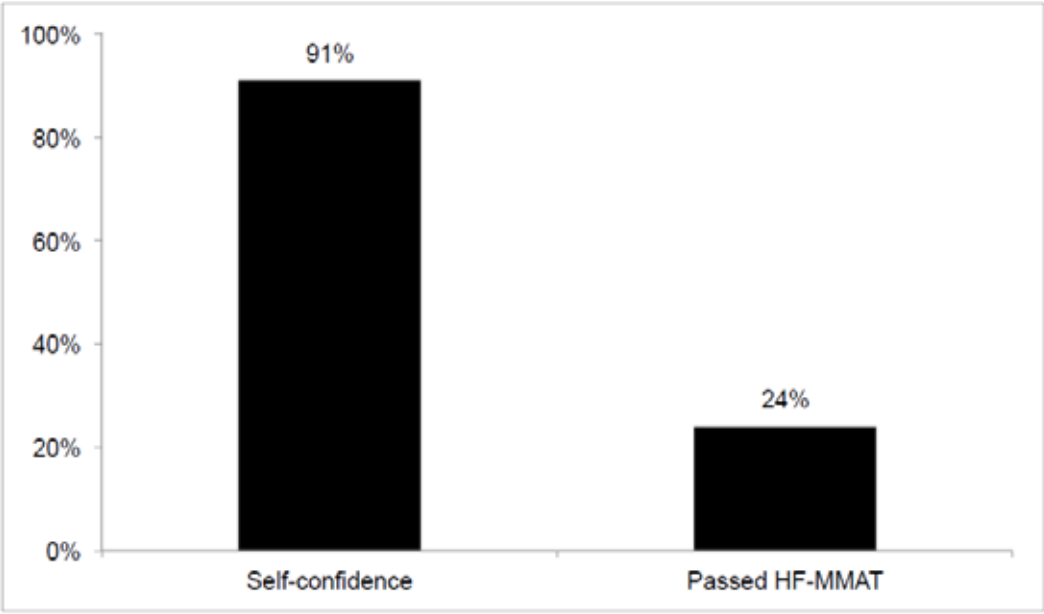
Method: We developed a novel HF medication management assessment tool (HF-MMAT) which consisted of (1) reading a pill bottle label, (2) opening a pill bottle, and (3) allocating heart failure pills from pill bottles into a pillbox. We validated HF-MMAT in a cohort of high-functioning medically oriented individuals (n=30, physicians and pharmacists). We performed a prospective cohort study of patients hospitalized for HF (n=55) with anticipated discharge to home. All patients completed HF-MMAT.

Results: We found that despite 50 (91%) patients indicating confidence in managing medications, performance on HF-MMAT was poor (5% of patients unable to read pill bottle label, 9% unable to open pill bottle, and 81% with ≥1

quantitative pill allocation errors most commonly due to failures in comprehension) (Figure 1). Overall, only 13 (24%) patients "passed" HF-MMAT.

Conclusion: Patients hospitalized for HF have difficulties managing medications despite self-confidence. HF-MMAT is a simple tool that objectively measures literacy skills, physical coordination, and executive function related to medication self-management. Routine screening with HF-MMAT prior to hospital discharge may identify HF patients at increased risk for making medication errors at home.

Figure 1. Patient self-confidence managing medications compared to HF-MMAT results



Long-term prognostic significance of coronary artery calcium scores in women and men

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Objective: It is well established that the Framingham Risk Score (FRS) underestimates risk in women. Coronary artery calcium (CAC) scoring improves risk reclassification beyond the FRS in women and men. The primary aim of this analysis was to compare 15-year mortality by CAC in a cohort of 2,363 asymptomatic women and men with a low-intermediate FRS (6-9.9% 10 year predicted risk).

Method: We estimated all-cause mortality (n=159) using Cox proportional hazards models; hazard ratios (HR) with 95% confidence intervals (CI) were calculated.

Results: There were 1,072 low-intermediate risk women who were older (55.6 years) as compared to the 1,291 low-intermediate risk men (46.7 years, p<0.0001). In this cohort, a greater prevalence and extent of CAC was observed among women; 18.9% of women and 15.1% of men had a CAC score ≥100 (p=0.029). Women had a 1.44-fold higher 15-year mortality as compared to men (p=0.022). For women, CAC scores had 15-year mortality ranging from 5.8% for CAC score of 0 to 30.5% for a CAC score ≥400 (p<0.001). For men, CAC scores had 15-year mortality ranging from 4.0% for CAC score of 0 to 14.0% for a CAC score ≥400 (p<0.001). For CAC scores ≥400, women had a 2.77-fold (95% CI 1.04-7.38) higher mortality as compared to men (p=0.04).

Conclusion: Women with low-intermediate FRS scores have a sizeable burden of CAC that accelerates risk. Clinical practice guidelines should be revised to reduce the threshold for screening to include low-intermediate risk women (6-9.9% FRS)

Obesity and hypertension: prevalence and association in the population of the city of Marrakech

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Objective: The aim of this study was to estimate the prevalence of high blood pressure and obesity and their association in adults in the city of Marrakech in Morocco.

Method and results: This is a cross-sectional study conducted in 2014 among a representative sample of adults in the city of Marrakech. A questions about the social, dietary habits and physical activity was used. The prevalence of obesity (body mass index ≥30 kg/m^2) and abdominal obesity (waist circumference >102 cm in males or >88 cm in females) was determined and associations between both types of obesity and other cardiovascular risk factors specialy high blood pressure were investigated. A total of 1198 adults (18-75 years) were included in this study of which 634 were women. The prevalence of obesity was 46% (20% has BMI > 40 kg/m^2), The prevalence of abdominal obesity was 37% and it was higher in women at 54,1% than in men. The prevalence of hypertension was higher in obese (39% of obese against 19,6% of non-obese).

Conclusion: Obesity and hypertension are common among adults, hence the need to expand the detection of hypertension and obesity by practitioners and raise awareness about the importance of good eating habits and sports.

Keywords: Obesity; abdominal obesity; Cardiovascular disease; hypertension

METformin in DIastolic Dysfunction of MEtabolic Syndrome Trial: rationale and study design

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Objective: Insulin resistance plays a central role in the pathophysiology of metabolic syndrome (MS). Its cardiac deleterious effects are characterized by an increase in fibrous tissue that increases myocardial stiffness and contributes to subclinical left ventricular diastolic dysfunction (LVDD) and heart failure with preserved ejection fraction. In addition to lifestyle counseling (LC), metformin treatment may attenuate or even reverse diastolic dysfunction in these patients. This trial aims to evaluate if treating non-diabetic patients with MS and LVDD with metformin in addition to LC improves diastolic function and assess its impact in functional capacity and health-related quality of life (HRQoL).

Method: MET-DIME is a phase II prospective, randomized, open-label, blinded-endpoint trial with a scheduled follow-up of 24 months. Fifty-four patients (adults 40-65 years old with AHA/NHLBI criteria of MS and rest LVDD) will be randomized by minimization to LC only or LC plus metformin (target dose of 1,000mg twice daily). The primary endpoint will be change in mean of early diastolic mitral annular velocity, an echocardiographic parameter highly correlated with myocardial fibrosis (serial measurements will be performed at 6, 12 and 24 months). The secondary endpoints will include change in diastolic parameters at rest; metabolic, inflammatory and remodeling biomarkers; functional capacity; adipose tissue volumes and HRQoL.

Conclusion: MET-DIME is a pragmatic trial designed to evaluate if adding metformin to the standard treatment of patients with MS improves diastolic dysfunction, assessing its impact in metabolic homeostasis, proinflammatory state, functional capacity and HRQoL.

IVC measurement by ultrasound in acute decompensated heart failure prevents readmissions

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Background: Previous work demonstrates that patients discharged from the hospital after admission for acute decompensated heart failure (ADHF) are more likely to be readmitted if they leave with an inferior vena cava (IVC) that is plethoric. We propose that IVC diameter and collapsibility, as measured by Focused Cardiac Ultrasound, can help guide inpatient management of ADHF and prevent hospital readmission.

Method: Patients presenting with ADHF to a single tertiary academic medical center between February and November 2013 were enrolled. Exclusion criteria included the need for hemodialysis or admission to an intensive care unit. IVC diameter and collapsibility were measured upon admission, the following 4 days, and the day of discharge. Measurements were performed by housestaff trained in ultrasound IVC measurement who were blinded to all clinical data. Clinicians on 1 of the 4 cardiology services (intervention group) were provided IVC data, to integrate into their clinical care plan. Patients were contacted by telephone to determine if hospital readmission or emergency department visits occurred in the 30 days following discharge.

Results: 70 patients were enrolled. The 30-day hospital readmission rate was decreased in the intervention group (4% vs 30%, p=0.006.) The combined rate of emergency room visits and hospital readmission was also decreased (7% vs 42%, p=0.002.) Both intervention and control groups had the same average length of stay (5 days). Control group patients seen in the emergency department, or readmitted, had a smaller absolute change in IVC size during their admission (-0.2 vs –0.5 cm, p=0.03,) when compared to controls who were not readmitted or seen in emergency department.

Conclusion: The use of IVC diameter and collapsibility, as measured by Focused Cardiac Ultrasound, is associated with decreased readmission rates in patients with ADHF. Use of bedside assessment of the IVC with a focused cardiac ultrasound exam is an effective tool to guide management and prevent hospital readmissions.

Association of ACE discontinuation, renal dysfunction and prognosis in acute heart failure: results from the GREAT registry

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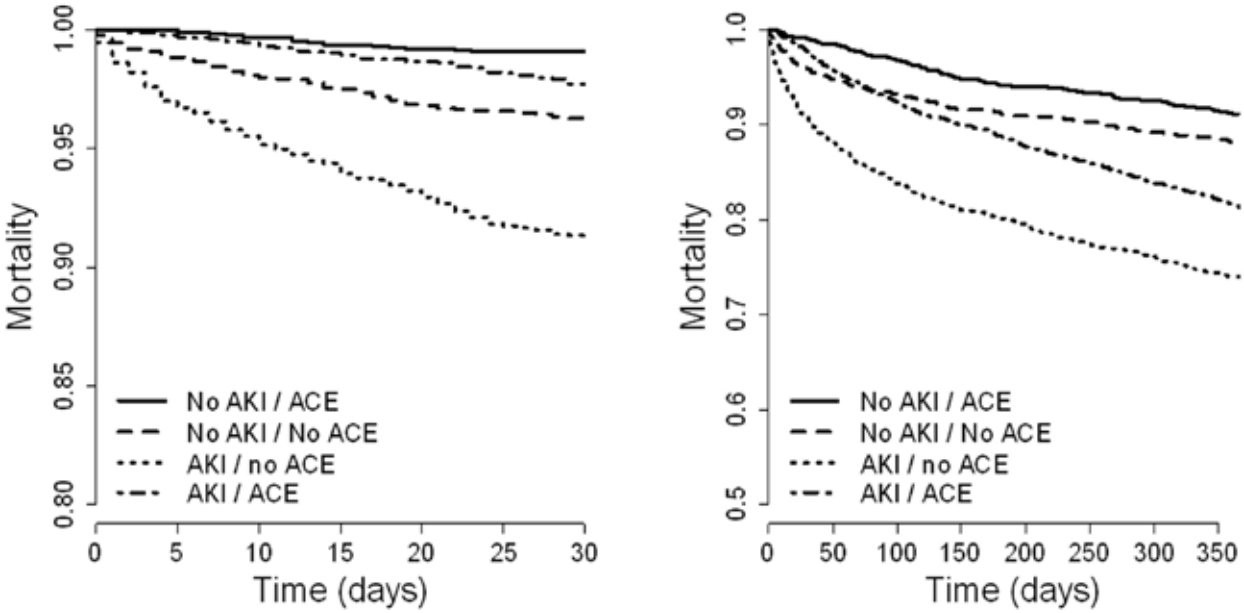
Objective: Angiotensin converting enzyme (ACE) inhibitors are considered as a key therapeutic option to improve outcome of patients with heart failure. Due to the risk of worsening of renal function and/or hyperkalemia after ACE inhibitors introduction, physicians may be reluctant to introduce ACE inhibitors in patients with renal dysfunction. This may negatively affect outcome. The aim of the study was to evaluate the influence of renal dysfunction on admission on the risk of being not treated with ACE inhibitors at discharge.

Method: We studied 10,113 patients with AHF from 11 prospective observational cohorts followed in 10 countries across Europe, Asia and North America. Primary outcome was all-cause mortality at one year. We considered four groups of patient according to occurrence of kidney dysfunction at admission (defined by an estimated glomerular filtration rate [eGFR] below 60 ml/min/m²) and the prescription of ACE inhibitor at discharge. Comparison of survival among groups was performed using Cox proportional hazards models. Associations were studied without and with adjustment for potential confounding factors. The confounders included in the multiple model were age, sex, comorbidities (history of chronic HF, diabetes mellitus, chronic atrial fibrillation, coronary artery disease, history of hypertension).

Results: In the studied population, median age was 74 years, median left ventricular ejection fraction was 40%, 56% of patients presented de novo AHF and median eGFR at admission was 54 [38 – 71] ml/min/m². Patients with kidney dysfunction at admission were significantly less frequently treated by ACE inhibitor at discharge (53% vs 45%, p<0.0001). Using group of patients without kidney dysfunctin at admission and treated by ACEi (KD-/ACEi+)

at discharge as reference, hazard ratios (HR [95% CI]) of the three groups were 1.27 [0.82 – 1.96] for KD-/ACEi-, 2.33 [1.46 – 3.74] for KD+/ACEi-, 1.69 [1.45 – 1.97] for KD+/ACEi+, after adjustment for potential confounders.

Conclusion: This preliminary data from a large multi-center international cohort, patients with renal dysfunction at admission for acute decompensated heart failure were less likely to be treated with ACE inhibitor at hospital discharge. Among patients with renal dysfunction, ACE inhibitors at discharge were associated with survival benefit. Further investigation should determine the respective contribution of ACE and renal dysfunction on this outcome.



Prognostic impact of number of controlled risk factors in patients achieved target LDL cholesterol

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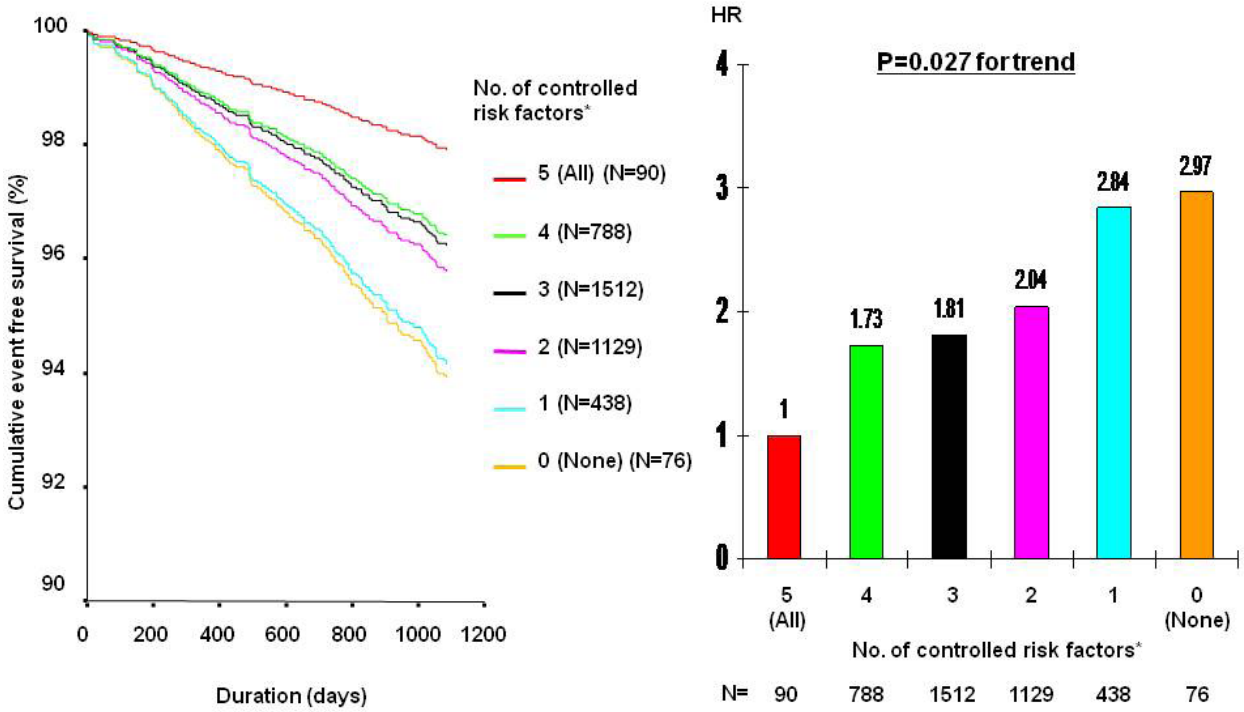
Objective: It is reported that after achieving target LDL cholesterol (LDL-c) level, patients with accumulated residual risk factors (i.e. low HDL cholesterol, high triglyceride, high blood pressure, high blood glucose, and obesity) still have a high incidence rate of cardiovascular (CV) events. However, it remains unknown whether a reduction in the number of such residual factors can affect the incidence of CV events. The Heart Care Network (HCN) registry consists of registered data from 62 sites in Japan with the help of general practitioners treating lifestyle diseases. We examined the relationship between the number of controlled residual risk factors and the incidence of CV events among subjects who achieved target LDL-c level using data of HCN registry.

Method: The Heart Care Network Group collected data on lifestyle diseases including investigations and medication use during 3-year follow-up period in 14064 high-risk patients (i.e. patients having ≥2 lifestyle risk factors or a history of myocardial infarction). Additionally, incidence of fatal/non-fatal CV events was also recorded. The event-free survival and hazard ratios (HR), after adjusting for age, sex, history of myocardial infarction, smoking, and alcohol intake, and stratified according to the number of controlled risk factors such as HDL cholesterol level, triglyceride level, blood pressures, blood glucose and obesity, were assessed in subjects who achieved target LDL-c level.

Results: Overall, 4033 subjects who achieved target LDL-c level were included in the analysis. Among them, 166 CV events occurred during the follow-up period. Cumulative event-free survival increased and adjusted HR decreased in association with decrease in the number of controlled residual risk factors (HR for patients with 4 controlled residual risk factors, 1.73; HR for those with 3 controlled residual risk factors, 1.81; HR for those with 2 controlled residual risk factors, 2.04; HR for those with only 1 controlled residual risk factor, 2.84; and HR for those with no controlled residual risk factors, 2.97; compared with patients of whom all 5 residual risk factor were controlled; P for trend, 0.027).
Conclusion: The management for residual risk factors and reduction in their numbers in high-risk patients who have achieved target LDL-c level may reduce CV morbidity and mortality.



*Controlled risk factors:
achieving target levels in any of 1) HDL cholesterol; 2) triglycerides; 3) blood pressure; 4) hemoglobin A1c; 5) BMI

Patiromer lowers serum potassium and prevents recurrent hyperkalemia in patients with heart failure and chronic kidney disease when treated with renin angiotensin Aldosterone system inhibitors : results from a two-part phase 3 trial

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Hyperkalemia (HK) affects patients with heart failure (HF) and chronic kidney disease (CKD), especially when treated with renin angiotensin aldosterone system inhibitors (RAASi). Patiromer (RLY5016 for oral suspension), a novel, metal-free polymer with good gastrointestinal tolerability, was previously shown in clinical trials to lower serum potassium (K^+). This multicenter international study in 243 hyperkalemic subjects with an eGFR 15 to < 60 mL/min/1.73m^2 with/without HF on RAASi medication, was a two-part study: Part A, the 4-week single-blind treatment study, assessed patiromer for the treatment of HK; Part B, the 8-week placebo-controlled randomized withdrawal study, assessed whether chronic treatment with patiromer prevented recurrent HK. This analysis presents the findings in CKD subjects with and without HF.

The Part A primary outcome was change from baseline in serum K^+. The Part B primary outcome was the between group difference in the change in serum K^+ from Part B Baseline to Part B Week 4. Secondary outcomes included the proportion with a serum K^+ in the target range in Part A and the proportion with recurrent HK in Part B. An additional outcome to be presented was the proportion requiring RAASi modification due to recurring HK.

Table 1: Part A Primary Endpoint Result

	Change in Serum K^+ (mean ± SE; p-value)	Interaction p-value
ITT Population (n=237) (Baseline mean ± SE = 5.58 ± 0.033 mEq/L)	-1.01 ± 0.031 mEq/L; p < 0.001	
Heart Failure present (n=100, 42%)	-1.06 ± 0.052 mEq/L; p < 0.001	0.22
Heart Failure absent (n=137, 58%)	-0.98 ± 0.039 mEq/L; p < 0.001	

Table 2: Part B Primary Endpoint Result

	Median Change in Serum K^+ from Part B Baseline to Part B Week 4 (quartiles)		Between-Group Difference in Medians (p-value)	Interaction p-value
	Placebo	Patiromer		
ITT Population (n=107) (Baseline mean [SD]= 4.47 [0.39])	0.72 mEq/L (0.22, 1.22)	0.00 mEq/L (-0.30, 0.30)	0.72 mEq/L; p < 0.001	
Heart Failure Present (n=49, 46%)	0.74 mEq/L (0.44, 1.04)	0.10 mEq/L (-0.30, 0.30)	0.64 mEq/L; p < 0.001	0.50
Heart Failure Absent (n=58, 54%)	0.78 mEq/L (0.08, 1.23)	-0.05 mEq/L (-0.25, 0.30)	0.83 mEq/L; p < 0.001	

All primary and secondary outcomes were statistically significant for subjects with and without HF.
A substantial majority of subjects had their serum K^+ controlled at the end of Part A and significantly more placebo subjects developed recurrent HK during Part B.

Patiromer was well tolerated with mild to moderate GI symptoms being the most frequently reported adverse events. Frequencies of other AEs in the patiromer group were similar to, or lower than, placebo.

Patiromer provided effective serum K^+ control and significantly decreased recurrence of HK compared to placebo in CKD subjects with and without HF with a well-tolerated safety profile that may allow continuous management of serum K^+ inml hyperkalemic HF patients on RAASi therapy.

Effect of cardiovascular comorbidities on the mortality risk associated with serum potassium

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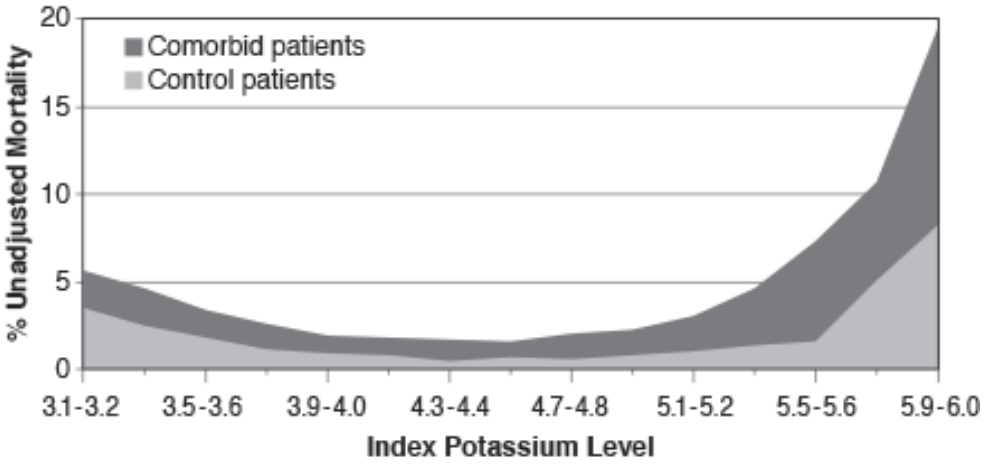
Background: Both hypokalemia and hyperkalemia are known to be associated with an increased mortality risk. The serum potassium (K^+) levels associated with these risks and the relationships to comorbidity, however, are not well defined. We therefore evaluated the odds of death in patients with and without comorbid conditions, stratified by K^+ level.

Method: De-identified medical records (2007-2012) from a large US population of persons ≥ 5 years of age with at least 2 K^+ readings were evaluated. Patients 45-64 years of age with comorbidities defined as CKD stages 3-5, heart failure, diabetes, hypertension, and cardiovascular disease (n=231,070) were identified from demographic data, ICD-9 codes and biochemical data, excluding those with acute kidney injury or end stage renal disease, and compared with controls having none of these conditions (n=146,645). A separate analysis of patients ≥ 65 years of age was performed. Index K^+ value was defined as the last reported value prior to a pre-determined cut-off date. Mortality was evaluated through hospital discharge records and Social Security registry information.

Results: Among patients aged 45-64 with comorbid conditions, index K^+ levels below 4.1 mEq/L and above 4.6 mEq/L demonstrate a significant increase in mortality (Figure). This finding was similar in patients ≥ 65 years of age. The general pattern remained after adjustments for demographic characteristics (sex, race) and subgroup analyses controlling for comorbidities associated with the propensity to develop hypo- and hyperkalemia.

Mortality by Potassium Level, ages 45-64 years



Conclusion: These results indicate that the level of potassium and the risk of mortality in patients with hypokalemia or hyperkalemia is highly associated with underlying disease; is significantly greater in patients with comorbid illness; and is independent of demographic characteristics. The increased mortality in patients with comorbidity occurs even at K^+ levels within the usual normal laboratory range.

Outcomes and biomarker expression in diabetics with heart failure: insights from the COACH study

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Objective: Studies have generally suggested adverse outcomes in diabetic patients but results regarding risk of readmission or mortality are conflicting. Our understanding of the underlying pathophysiology of heart failure with diabetes is limited but novel biomarkers reflecting several pathophysiological processes in heart failure may provide insights in underlying differences between patients with and without diabetes. These studies are often limited in numbers, extent of follow up and breadth of biomarkers analyzed. We characterized the clinical outcomes and biomarker expression of diabetics during admission for acute heart failure and 6 months after discharge.

Method: This is a post hoc analysis of the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) study. COACH was a multicentre, randomized, controlled, nurse-led disease management intervention trial testing whether follow-up by a cardiologist or basic or intensive additional support by a heart failure nurse improved outcomes in patients hospitalized with heart failure conducted between 2002 and 2007 in The Netherlands. The COACH study included 1023 patients shortly before discharge following a heart failure hospitalization regardless of left ventricular ejection fraction (LVEF). \ All patients provided written informed consent for the main study. Baseline clinical information was assessed at the index hospitalization. Diabetic status was assessed at hospital admission and was based on prior history of diabetes and need for anti-diabetic medication.

The following outcomes were assessed: hospitalization for heart failure or death after discharge, cardiovascular hospitalization after discharge, all cause hospitalization after discharge, and all-cause mortality after 3 years. These outcomes were assessed by an adjudication committee. Biomarkers were measured at discharge and at 6 months.

Results: Compared with non-diabetics (n = 752), diabetics (n = 297) were older, more often female, and had more previous myocardial infarctions, peripheral arterial disease, hypertension, stroke, and renal failure. Biomarker levels in diabetics (n=147) and non-diabetics (n=349) at discharge revealed significant differences relating to inflammation (pentraxin-3, GDF-15, TNF-R1a), angiogenesis (VEGFR) and renal function (cystatin-c). At 6 months, differences were seen in inflammatory (GDF-15, TNF-R1a), renal (cystatin-c, NGAL), cardiomyocyte stretch (BNP) and atherosclerosis (ESAM) markers. In diabetics, univariate and multivariate analysis revealed a higher risk of rehospitalization for heart failure or death (multivariate hazard ratio 1.69, 95% confidence interval 1.16-2.47, p-value 0.007), all-cause rehospitalization (multivariate hazard ratio 1.68, 95% confidence interval 1.23-2.29, p-value 0.001), and all cause 3 year mortality (multivariate hazard ratio of 1.69, 95% confidence interval 1.23-2.29, p-value 0.001).

Conclusion: Diabetics have a distinct clinical and biomarker profile and experience adverse outcomes during and after discharge for acute heart failure. These results provide insights into the underlying differences in diabetics with heart failure.

Prediction of reduced kidney function in patients with acute coronary syndrome

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Development of cardiorenal syndrome (CRS) significantly worsens the prognosis of patients with acute coronary syndrome (ACS), low renal function is a predictor of worsening myocardial revascularization. Stress-induced marker growth differentiation factor 15 (GDF 15), a member of the transforming growth factor-β cytokine superfamily is being actively studied.

Objective: to determine prognostic significance of GDF 15 and other clinical and biochemical markers in prognosis of development of CRS in patients with ACS.
Method: 70 patients with different forms of ACS were included in the study, they were admitted to National Institute of Therapy from 2012 to 2013 years, signed the informed consent: 77% men and 23% women, mean age was 61, 8 ± 1, 3 years. Among them, 54% patients with Q-wave myocardial infarction (Q-wave MI), 20% - with non-Q-wave myocardial infarction (non-Q-wave MI), 26% - unstable angina (UA). All patients underwent a baseline investigation which includes: standard electrocardiography, echocardiography, angiography, determination of marker of myocardial necrosis – cardiac troponin T, marker of inflammation – C-reactive protein (C-RP) GRACE score has been used for risk stratification. The glomerular filtration rate (GFR) was estimated by Cockcroft-Gault formula. All patients have divided into groups, according to level of GFR: ≤ 30 ml/min, 30-45 ml/min, 45-60 ml/min, ≥ 60 ml/min. In addition, the level of GDF 15 was determined during the first day of hospitalization via ELISA test.

Results: The effect of 60 variables of clinical, instrumental and laboratory status were assessed on formation of CRS in patients with different level of GFR. We calculated the GFR, the average was 73,7±5,7 ml/min. Statistical analysis shows the mean value of GDF 15 3000 pg/ml, the mean value of C- RP 8 mg/l. For identification of the main risk factors for CRS, we have used logistic regression (LR): CRP (area under curve (AUC) 0.817; p<0.0057; 95% confidence interval (CI): 0.592 – 1), GDF 15 (AUC 0.754; p<0.017; 95% CI: 0.546 – 0.962) were main risk factors for predicting development of CRS. We have developed a prognostic model for predicting CRS formation (AUC 0.839; p <0.0007). This model with 88% of sensitivity and 76% of specificity can predict development of CRS in patients with different level of GFR after ACS.

Conclusion: The prognostic multifactor model was the best for predicting the risk formation of CRS after admission and could be used in clinical practice to improve risk stratification in patients with ACS to prevent formation of CRS.

ONO-4232, a novel lusitropic agent for HF: safety and tolerability results in the first human study

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Objective: ONO-4232 is a novel, first in class EP4 selective agonist with a dual lusitropic and venodilatory action, being developed for the treatment of acutely decompensated heart failure (ADHF; hospitalised for heart failure). This healthy volunteer study is part of the clinical development plan for ONO-4232 and its results are being implemented into a proof-of-principle study in heart failure patients. The primary objective was to evaluate the safety and tolerability of ONO-4232, across single ascending doses, in healthy adult male and female subjects. Secondary objectives were to measure the dose-dependent responses of ONO-4232 on blood pressure (BP) and heart rate (HR).

Method: Healthy male and female subjects were randomised to receive a 3-hour iv infusion of ONO-4232 or placebo. 15 cohorts were planned in a single escalating dose design to explore 15 doses of ONO-4232 in the range 0.001 to 3.075 ng/kg/min.

Result: Out of total 76 subjects, 57 received ONO-4232 as a continuous iv infusion and 19 received placebo. Ten out of the planned 15 cohorts (ONO-4232 doses ranged from 0.001 to 0.27 ng/kg/min) were conducted and dose escalation was terminated at 0.27 ng/kg/min due to orthostatic effects. ONO-4232 was generally well tolerated. A total of 34 treatment emergent adverse events (TEAEs) were reported in 23 subjects. Overall, the majority of TEAEs were mild. No subjects discontinued due to AEs and no serious TEAEs or deaths were reported. More AEs were reported by subjects who received the higher doses of ONO-4232 and more of the AEs reported at these higher doses were considered related to study treatment. No AEs were considered related to study treatment in subjects who received placebo or ONO-4232 at 0.001, 0.003, 0.01, 0.02 and 0.04 ng/kg/min. Following treatment with ONO-4232, the most frequently reported TEAE was infusion site erythema, occurring at doses of 0.08 ng/kg/min and above. Other TEAEs reported by more than one subject in any cohort were headache and, at the higher doses, orthostatic hypotension. Three subjects who received placebo reported AEs of headache (one subject), presyncope (one subject) and musculoskeletal chest pain (one subject). There were no clinically relevant findings on ECG monitoring during the study.
There was evidence of a trend to a dose dependent elevation from baseline in HR during the infusion. In some subjects this correlated with a reduction in systolic and diastolic BP. There was evidence of a trend to a dose dependent decrease from baseline in systolic and diastolic BP.

Conclusions: ONO-4232 was generally well tolerated in healthy male and female volunteers. There was a trend to dose related changes in vital signs and infusion site erythema which were both consistent with a venodilatory effect and possible evidence for the pharmacological effects of ONO-4232. These study results support further evaluation of the cardiovascular effects of this first-in-class lusitropic drug in heart failure patients.

Patiromer lowers serum K^+ and prevents recurrent hyperkalemia in patients with diabetes and CKD on RAAS inhibitors: subgroup results of a phase 3 trial

Authors: M. Weir[1], G. Bakris[2], D. Bushinsky[3], M. Mayo[4], D. Garza[4], Y. Stasiv[4], Y. Hou[5], H. Christ-Schmidt[5], L. Berman[4].

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Background: RAAS inhibitors (RAASi) have proven cardiorenal benefits in patients (pts) with CKD and Type 2 diabetes (T2DM), yet hyperkalemia (HK) often limits RAASi therapy. Patiromer, a nonabsorbed polymer with high K^+-binding capacity and good GI tolerability, normalized serum K^+ (s-K^+) and prevented HK recurrence in a large study in CKD pts with HK on RAASi. Here we present results in pts with T2DM.

Method: Pts with BL s-K^+ 5.1 to<6.5 mEq/L received patiromer (4.2 or 8.4 g BID to start) in a 4-wk Initial Treatment Phase; pts with BL s-K^+ 5.5 to <6.5 mEq/L were eligible to continue into an 8-wk placebo (PBO)-controlled Randomized Withdrawal Phase. Primary and secondary endpoints, respectively, were: change in

s-K^+ from BL to Wk 4 and % of pts with s-K^+ within target at Wk 4 [Initial Treatment Phase]; between-group difference in s-K^+ change over the 1st 4 wk of the phase and % of pts with recurrent HK [Randomized Withdrawal Phase].

Results: Of pts treated in the 1st and 2nd phases, respectively, 57% and 63% had T2DM. Consistent with overall results, primary endpoints were significant for pts with T2DM (Table). Overall and in pts with T2DM, >75% of pts had normalized s-K^+, and significantly ($p<0.001$) more PBO pts developed recurrent HK.

Table. Primary Endpoint Results in Both Study Phases

Primary Endpoint Results in the Initial Treatment Phase			
Population	Mean ± SE Baseline Serum K+, mEq/L		Mean Change ± SE in Serum K^+ (95% CI), mEq/L [p value]
Overall (n=237)	5.58 ± 0.03		-1.01 ± 0.03 (-1.07, -0.95) [p < 0.001]
Diabetes (n=138)	5.61 ± 0.05		-1.00 ± 0.04 (-1.08, -0.92) [p < 0.001]
Primary Endpoint Results in the Randomized Withdrawal Phase			
	Median Change (25^{th}, 75^{th} Percentile) in Serum K^+ from Baseline to Week 4 of Phase, mEq/L		Between-Group Difference in Median Change in Serum K^+ (95% CI), mEq/L [p value]
	Placebo	Patiromer	
Overall (n=107)	0.72 (0.22, 1.22)	0.00 (-0.30, 0.30)	0.72 (0.46, 0.99) [p < 0.001]
Diabetes (n=67)	0.69 (0.19, 1.29)	0.03 (-0.20, 0.30)	0.66 (0.28, 1.03) [p < 0.001]

Overall, patiromer was well tolerated; mild to moderate GI symptoms were the most common AEs. Rates of other AEs with patiromer were similar to, or lower than, placebo.

Conclusion: After controlling s-K^+, patiromer significantly decreased HK recurrence compared to PBO in CKD pts with T2DM on RAASi, with a tolerability profile that may allow continuous management of s-K^+ in these pts.

Patiromer reduced RAASi dose discontinuations in CKD patients with moderate-to-severe hyperkalemia

Authors: M. Weir[1], G. Bakris[2], D. Bushinsky[3], B. Pitt[4], M. Mayo[5], D. Garza[5], Y. Stasiv[5], J. Wittes[6], H. Christ-Schmidt[6], L. Berman[5].

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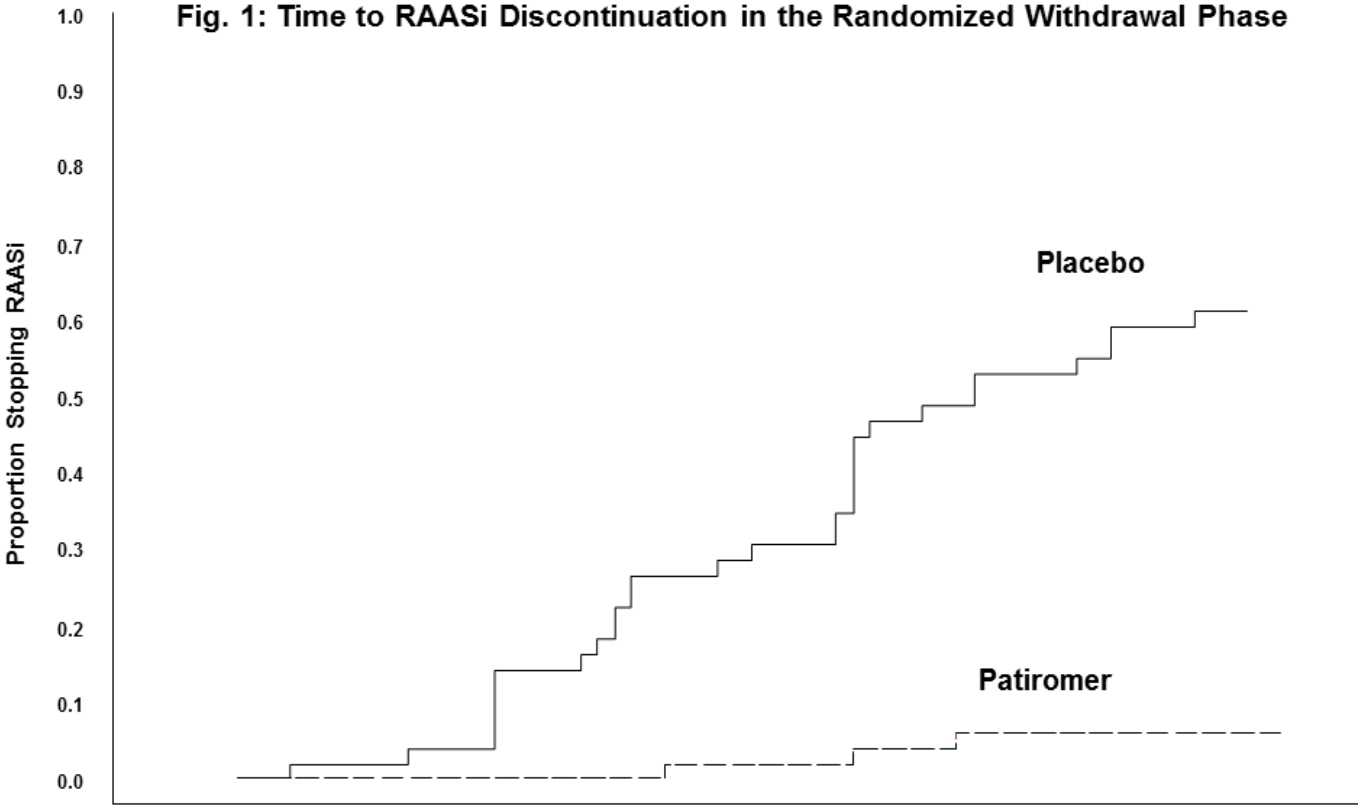
Background: RAAS inhibitors (RAASi) have proven cardiorenal benefits in patients (pts) with CKD, yet hyperkalemia (HK) often limits RAASi therapy. Patiromer, a nonabsorbed, metal-free polymer with high K^+-

binding capacity, controlled serum K^+ ($s\text{-}K^+$) and decreased recurrent HK vs placebo (PBO) with good GI tolerability in a two-part Phase 3 trial in CKD pts with HK on RAASi. Here we present additional endpoints from the PBO-controlled Randomized Withdrawal Phase.

Method: Pts with $s\text{-}K^+$ 5.1 to <6.5 mEq/L received patiromer (4.2 or 8.4 g BID to start) in a 4-wk Initial Treatment Phase; pts with BL $s\text{-}K^+$ 5.5 to <6.5 mEq/L were eligible to continue into an 8-wk PBO-controlled Randomized Withdrawal Phase. Additional endpoints included % of pts requiring an intervention for recurrent HK (RAASi dose ↓/discontination [PBO]; patiromer dose ↑/RAASi discontinuation [patiromer]) and time to RAASi discontinuation.

Results: Overall (n=237) after having controlled $s\text{-}K^+$ in the Treatment Phase (BL mean $s\text{-}K^+$ = 5.58 ± 0.03 mEq/L, Δ from BL = -1.01 ± 0.03 mEq/L, p<0.001), 55 pts were randomized to continue patiromer and 52 were switched to PBO in the 2nd phase. As a result of recurrent HK ($s\text{-}K^+$ Δ 5.5 mEq/L; PBO = 60%, patiromer = 15%; p< 0.001) more PBO (62%) than patiromer (16%) pts required an intervention to manage $s\text{-}K^+$. By Wk 8, significantly (p<0.001) more patiromer (94%) than PBO (39%) pts were still on RAASi therapy. Figure 1 shows time to RAASi discontinuation.

Fig. 1: Time to RAASi Discontinuation in the Randomized Withdrawal Phase



Conclusion: After controlling their $s\text{-}K^+$ in this Phase 3 study, significantly fewer CKD pts with moderate-to-severe HK on patiromer had recurrent HK and more stayed on RAASi therapies vs PBO.

Effects of combined DPP4 and ACE inhibition on sympathetic activity and anti-hypertensive response

Authors: J.R. Wilson[1] (*jessica.r.wilson@vanderbilt.edu*), C.E. Ramirez, J.K. Devin, N.J. Brown

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Objective: Two thirds of patients with type 2 diabetes mellitus (T2DM) also have hypertension. Often patients with both T2DM and HTN are prescribed angiotensin converting enzyme (ACE) inhibitors for blood pressure control. Dipeptidyl peptidase-4 (DPP4) inhibitor therapy is a class of medications used to treat T2DM. Combined ACE and DPP4 inhibition may lead to altered degradation of DPP4 substrates substance P, neuropeptide Y (NPY), and peptide YY (PYY), to cause blood vessel constriction and sympathetic activation (norepinephrine release). Our group has previously shown that subjects with the metabolic syndrome treated with combined DPP4 and acute ACE inhibition had increased heart rate and norepinephrine concentrations. The current randomized double-blind placebo-controlled cross-over trial is designed to test the hypothesis that DPP4 inhibition increases sympathetic activation and attenuates the anti-hypertensive effect of chronic ACE inhibition in a clinically relevant study population: subjects with T2DM, hypertension, and obesity. We will also investigate the contribution of substance P, NPY, and PYY to these effects.

Method: We plan to enroll a total of 50 subjects per arm. Subjects enrolled will undergo a 3-week washout period off antihypertensive medications (4 weeks if previously on spironolactone). They will be randomized to therapy with ramipril (ACE inhibitor), valsartan (angiotensin receptor blocker or ARB), or amlodipine (calcium channel blocker) for a total of fifteen weeks per arm. After 4 weeks of therapy, subjects will be randomized to one of three 1-week concurrent interventions, in a cross-over fashion, separated by at least a 4-week washout: placebo + placebo, placebo + sitagliptin, sitagliptin + aprepitant. On the 7th day of each cross-over treatment, each subject will present to the clinical research center for laboratory collection and hemodynamic monitoring. Data analysis will be primarily using mixed-effects models to evaluate differences in treatment groups, with the primary endpoints of blood pressure (mean arterial pressure, systolic and diastolic blood pressure), heart rate, and norepinephrine concentration between groups. In particular we will focus on the ramipril arm +/- sitagliptin and with or without aprepitant, and compared to alternative anti-hypertensive therapy (valsartan or amlodipine). Secondary endpoints will include concentrations of vasoactive peptides, glucose homeostasis markers, urinary catecholamines and electrolytes, measurements of drug activity levels, and levels of renin-angiotensin hormones.

Conclusions: This topic is particularly relevant to better understand the possible interaction of combined DPP4 and ACE- inhibition to affect blood pressure and sympathetic activity, contribution of the metabolism of NPY, PYY, and substance P to vasoconstriction and the sympathetic response, and possible future targets for therapy of cardiovascular disease and diabetes. These underlying mechanisms may also provide insight into the mechanism for increased rates of admissions for heart failure seen with dipeptidyl peptidase-4 (DPP4) inhibitor therapy in recent trials.

GENERAL INFORMATION

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Participant registration fee includes

- Access to all scientific sessions
- Access to the Clinical Gathering Space
- Congress materials
- Lunches on 5 and 6 December 2014
- Daily coffee breaks
- Networking Reception on 5 December 2014 upon invitation only. Please ask as the congress desk.

Opening hours of the welcome desk

- Thursday 4 December, 4.00pm-6.30pm
- Friday 5 December, 8.00am-6.30pm
- Saturday 6 December, 7.30am-6.30pm
- Sunday 7 December, 8.00am-12.00 noon

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.

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