6th Global CardioVascular Clinical Trialists Forum

Course Directors: Faiez Zannad, Nancy – FRA & Bertram Pitt, Ann Arbor – USA

3-5 December 2009
PARIS, Pullman Tour Eiffel, FRANCE

FINAL PROGRAM & ABSTRACTS BOOK

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SEYMOUR Nancy (Inverness, Biosite, USA)
SURUN Dominique (Ateroxav, FRA)
WENNHUSENE Ursula-Henrik (Roche Diagnostic, GER)
Endorsed by the European Society of Cardiology Working Group on Cardiovascular Pharmacology and Drug Therapy, CVCT Forum is a meeting specifically and totally dedicated to the discussion of clinical trials in cardiovascular disease.

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

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

The CVCT meetings are ‘grass root’ meetings, attended by individuals who are eager to communicate with one another and to share experiences with primary care physicians and the people that create and analyze major trials.

CVCT meetings are primarily oriented toward discussion between participants as opposed to lectures to a broad audience. Thought processes count and communication (during the meeting, but more importantly informal discussions outside the meeting) is an important agenda, as opposed to dictating doctrine. The format of the meeting is set to fulfill these aims. Beyond plenary sessions the meeting is structured with a variety of small interactive brainstorming workshops, expert discussions, how-to sessions and consensus building workshops.

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

CVCT Forum aims to:

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

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

Pr. Faiez ZANNAD  Pr. Bertram PITT
Synopsis

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ACCREDITATION
The "6th Global CVCT Forum" is accredited by the European Board for Accreditation in Cardiology for 17 hours of external CME credits (EBAC). Each participant should claim only those hours of credit that have actually been spent in the educational activity. EBAC works in cooperation with the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS).
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<td>10:00</td>
<td>Salon Orsay Nord</td>
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<td><strong>Workshop session</strong></td>
<td>Understanding the results of the MADIT-CRT. Key elements for an optimal implementation of CRT-D in clinical practice</td>
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<td><strong>Targeting the aldosterone pathway</strong></td>
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<td><strong>The future of anti-thrombotic therapy in coronary syndromes at the acute and post-acute phases</strong></td>
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<td><strong>Data Safety and Monitoring Committees (DSMC) in CV trials</strong></td>
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**FOYER ORSAY NORD**

**ESC WG on CV pharmacology and Drug Therapy**

Nucleus Business Meeting

Stefan AGEWALL, Stockholm - SWE – Angeles ALONSO, Madrid - SPA – Céline SERIO, Sophia Antipolis - FRA

Wiek VAN GILST, Groningen - NED – Finn GUSTAFSSON, Copenhagen - DEN

Keld KJELDSEN, Copenhagen - DEN – Luis RUILOPE, Madrid - SPA – Kurt STOSCHITZKY, Graz - AUT

Faiez ZANNAD, Nancy - FRA

**11:00-13:45**

**SALON ORSAY NORD**

**CVCT EXPERTS WORKSHOP**

Clinical trials in cardiovascular critical care

Chairmen: Alexandre MEBAZAA, Paris - FRA – Birhan Mehmet YILMAZ, Sivas - TUR

Format: Short presentations (no lecturing) in order to set the stage for a large expert panel discussion

- **What are the unmet needs?**
  - The clinician point of view: Alexandre MEBAZAA, Paris - FRA

- **Industry point of view**
  - Hemodynamic monitoring: Frederic MICHAUD, Edwards Lifesciences, Nyon - SWI
  - Trade off in heart failure: why clinical trial on ADHF should focus on quality of life
    Piero POLLESELLO, Orion Pharma, Espoo - FIN

- **What are the optimal endpoints?**
  - The emergentist point of view: Patrick RAY, Paris - FRA
  - The intensivist (ICU/CCU) point of view: Birhan Mehmet YILMAZ, Sivas - TUR
  - The cardiac surgeon point of view: Antonis PITSIS, Tessaloniki - GRE

Panellists: Xavier BAERMANN, Argenteuil - FRA – Abdel BELLOU, Rennes - FRA

Enrique CASALINO, Paris - FRA – Jean CASSAGNES, Clermont Ferrand - FRA – Bernard CHOLLEY, Paris - FRA

Alain COHEN SOLAL, Paris - FRA – Jean Emmanuel de la COUSSAYE, Nimes - FRA

Nicolas DEYE, Paris - FRA – Pierre GIBELIN, Nice - FRA – Corrina HEINISCH, Bâle - SWI

Guillaume JONDEAU, Paris - FRA – Said LARIBI, Paris - FRA – Alexandre MEBAZAA, Paris - FRA

Frederic MICHAUD, Edwards Lifesciences - SWI – Atul PATHAK, Toulouse - FRA

Antonis PITSIS, Tessaloniki - GRE – Patrick PLAISANCE, Paris - FRA

Piero POLLESELLO, Orion Pharma, Espoo - FIN – Patrick RAY, Paris - FRA


Eric WIEL, Lille - FRA – Birhan Mehmet YILMAZ, Sivas - TUR – Faiez ZANNAD, Nancy - FRA

**14:00-18:00**

**SALON ORSAY NORD**

**EXPERT WORKSHOP**

Understanding the results of MADIT-CRT.

Key elements for an optimal implementation of CRT-D in clinical practice

Objectives:

- Discussing the opportunities and challenges of an optimal implementation of the results of the device trials
- Discussing the strengths and limitations of the device trials in heart failure

Patient population and outcome issues: What is the clinical significance of the results of MADIT-CRT

Chairman: Karl SWEDBERG, Göteborg - SWE

- What are the patients eligible for CRT-D? How to estimate the size of the eligible population?
  Speaker: Mihai GHEORGHIADE, Chicago - USA
  Discussant: Aldo MAGGIONI, Florence - ITA

- The relative contribution of preventing death and preventing HF hospitalization
  Speaker: Frederic ANSELME, Rouen - FRA
  Discussant: Faiez ZANNAD, Nancy - FRA

- The Clinician point of view: Generalizability of the results of recent trials (MADIT-CRT)
  Gunter BREITHARDT, Münster - GER
Mechanistic issues: How does CRT-D work for the prevention of HF hospitalization?
Chairman: Daniel GRAS, Nantes - FRA

- Consistency within the trial subgroups, consistency with other CRT and ICD trials
  Cecilia LINDE, Stockholm - SWE

- Mechanistic plausibility. Insight from pathophysiology – importance of improvement of LV function across all trials
  Mark ESTES, Boston - USA

Registerability and implementation issues
Chairman: Faiez ZANNAD, Nancy - FRA

- Is “Prevention of HF events” in mild HF patients with large QRS and low EF an approvable new indication for CRT-D?
  Bernd LEMKE, Lüdenscheid - GER
  Discussant: Daniel GRAS, Nantes - FRA

- Updating the guidelines and overcoming implementation issues/barriers
  Karl SWEDBERG, Göteborg - SWE

Panellists: Kirkwood ADAMS, Chapel Hill - USA – Angeles ALONSO, Madrid - SPA
Frederic ANSELME, Rouen - FRA – Olivier BARTHEZ, Dijon - FRA – Gunter BREITHARDT, Münster - GER
Mark ESTES, Boston, USA – Mihai GHEORGHIADE, Chicago - USA – Daniel GRAS, Nantes - FRA
Jean-Yves LE HEUZEY, Paris - FRA – Bernd LEMKE, Lüdenscheid - GER – Cecilia LINDE, Stockholm - SWE
Faiez ZANNAD, Nancy - FRA

14:00-16:00
SALON VENDÔME BC
European Society of Cardiology
Working Group on Cardiovascular Pharmacology and Drug Therapy
Young CardioVascular Clinical Trialists (YCVCT) Course
Chairmen: Thibaut DAMY, Créteil - FRA – Patrick ROSSIGNOL, Nancy - FRA

- The young CVCT initiative: Time to rejuvenate CV clinical trialists
  Bertram PITT, Ann Arbor - USA

- Maximizing scientific knowledge from randomized clinical trials data. Opportunities for young CVCT fellows
  Gilles DAGENAIS, Quebec - CAN

- How to teach trial methodology to young clinicians?
  Eric VICAUT, Paris - FRA

- Responsibilities, role and functioning of trial committees (Steering committee, DSMC, Event committee)
  Sidney GOLDSTEIN, Detroit - USA
08:30-12:00  SALON ORSAY NORD
PLENARY SESSION
Biomarkers in clinical trials
Chairmen: Angeles ALONSO, Madrid - SPA – Kirkwood ADAMS, Chapell Hill - USA

- How evidence based is the current risk stratification guided CV preventive drug therapy?
  Luis RUILOPE, Madrid - SPA

- The challenge of designing a biomarker trial
  Faiez ZANNAD, Nancy - FRA

- Biomarker guided therapy: Trial design and interpretation issues
  Kirkwood ADAMS, Chapell Hill - USA

Debate: Design of Biomarkers for CV trials
The industry viewpoint.
Ursula-Henrike WIENHUES-THELEN, Roche Diagnostics - GER

The regulator viewpoint
Bruno FLAMION, European Medicines Agency - EMEA, Brussels - BEL

Panellists: Kirkwood ADAMS, Chapell Hill - USA – Enrico AGABATI-ROSEI, Brescia - ITA
Alain COHEN SOLAL, Paris - FRA – Finn GUSTAFSSON, Copenhagen - DEN – Wim HOUDIJK, Biomérieux - FRA
Patrick JOURDAIN, Paris - FRA – Alexandre MEBAZA, Paris - FRA
Patrick ROSSIGNOL, Nancy - FRA – Luis RUILOPE, Madrid - SPA – Nancy SEYMOUR, Invemess, Biosite - USA
Dominique SURUN, Aterovax - FRA – Wiek VAN GILST, Groningen - NED
Ursula-Henrike WIENHUES-THELEN, Roche Diagnostics - GER

08:30-12:00  SALON ORSAY SUD
PLENARY SESSION
Targeting the aldosterone pathway
Chairmen: Aldo MAGGIONI, Florence - ITA – Mihai GHEORGHIADE, Chicago - USA

- Aldosterone: a culprit hormone in cardiovascular disease
  Johann BAUERSACHS, Würzburg - GER

- Which is to blame? Is it aldosterone or mineralocorticoid receptor activation?
  Frederic JAISSER, Paris - FRA

- Pharmacology of agents interfering with the aldosterone pathways
  Michel AZIZI, Paris - FRA

- Update on aldosterone trials
  Faiez ZANNAD, Nancy - FRA

- Practical use of agents acting on the aldosterone system.
  Where to fit into the RAAS drug armamentarium?
  Bertram PIT, Ann Arbor - USA
08:30-12:00

**SALON VENDÔME BC**

**PLENARY SESSION**

**Cardiovascular Clinical Trials. Going Global**

Chairmen: Felipe MARTINEZ, Cordoba - ARG – Jean MORGAN, Quintiles

- Overview of international cardiovascular clinical trials and current regulatory requirements for clinical trials in Russia and Ukraine
  
  Vladimir POPOV, Moscow - RUS

- Middle East and the Arab world, emerging to CardioVacular trials. Cultural, organisational and regulatory aspects
  
  Mohamed SOBHY, Alexandria - EGY

- Regional Risk Factors and Cardiovascular trials: no influence or high impact?
  
  Felipe MARTINEZ, Cordoba - ARG

12:15-13:45

**SALON VENDÔME BC**

**MEET AND EAT WITH THE EXPERTS**

**Ventilatory therapy for sleep disordered breathing (SDB) in heart failure and CV disease. From proof of concept to evidence based medicine**

Chairmen: Luc HITTINGER, Paris - FRA – Guillaume JONDEAU, Paris - FRA

- Introduction and overview: Why does sleep disordered breathing deserve the cardiologist’s attention?
  
  Christiane ANGERMANN, Würzburg - GER

- Future clinical evidence needs? Design of the SERVE-HF protocol
  
  Luc HITTINGER, Paris - FRA

- How to screen and manage patients with SDB in the clinical cardiology routine?
  
  Olaf OLDENBURG, Bad Oeynhausen - GER

12:15-13:45

**SALON ORSAY SUD**

**TRANSATLANTIC TRIALISTS**

**Lunch Rountable**

**Non industry sponsored trials and the role of NHLBI and EU public institutions**

Chairmen: Michael LAUER, Bethesda - USA – Faiez ZANNAD, Nancy - FRA

- Cardiovascular clinical trials under the EU Research Framework Programmes? A good start or a missed opportunity?
  
  Faiez ZANNAD, Nancy - FRA

- National Heart Lung and Blood Institute cardiovascular drug trials - future directions?
  
  Michael DOMANSKI, Bethesda - USA

**Debate:** Going global. Is an NHLBI-EU joint cardiovascular trial initiative at all feasible?

**Panellists:**

- Kirkwood ADAMS, Chapell Hill - USA – Enrico AGABATI-ROSEI, Brescia - ITA
- Christian BOITARD, Inserm, Paris - FRA – Gérard BRÉART, Paris - FRA
- Virginija DAMBRAUSKAITE, EU, Brussels - BEL – Jacques DESMOTES, ECRIN, Bordeaux - FRA
- Michael DOMANSKI, NHLBI, Bethesda - USA – Nancy GELLER, NHLBI, Bethesda - USA
- Mihai GHEORGHIADE, Chicago - USA – David GORDON, NHLBI, Bethesda - USA
- Michael LAUER, NHLBI, Bethesda, USA – Alexandre MEBAZAA, Paris - FRA
- Bertram PITT, Ann Arbor - USA – Philippe G. STEG, Paris - FRA – Faiez ZANNAD, Nancy - FRA
12:15-13:45

FOYER ORSAY NORD

MEET AND EAT WITH THE EXPERTS (2)

Management of atrial fibrillation: Trials that are rapidly changing the landscape
Chairmen: Dan ATAR, Oslo - NOR – Karl SWEDBERG, Göteborg - SWE

- Will new drugs and new trials shift the rate vs. rhythm control paradigm (Dronedarone, Vernakalant)?
  Gunter BREITHARDT, Münster - GER
- New anti-thrombotic trials in atrial fibrillation (RE-LY) and possible consequence on anti-thrombotic strategies
  Gregory LIP, Birmingham - GBR
- Ablation in atrial fibrillation: Reassessing the evidence
  Etienne ALIOT, Nancy - FRA

Debate: Revisiting the rate vs. rhythm control debate in the light of the new pharmacological environment

Panellists: Etienne ALIOT, Nancy - FRA – Angeles ALONSO, Madrid - SPA – Dan ATAR, Oslo - NOR
Gunter BREITHARDT, Münster - GER – Alain COHEN SOLAL, Paris - FRA
Finn GUSTAFSSON, Copenhagen - DEN – Patrick JOURDAIN, Paris - FRA – Keld KJELDSEN, Copenhagen - DEN
Gregory LIP, Birmingham - GBR – Aldo MAGGIONI, Florence - ITA
Kurt STOSCHITZKY, Graz - AUT – Karl SWEDBERG, Göteborg - SWE – Wiek VAN GILST, Groningen - NED
Faiez ZANNAD, Nancy - FRA

14:00-16:00

FOYER ORSAY NORD

CVCT EXPERT WORKSHOP

Arterial stiffness and central blood pressure as endpoints in hypertension trials
Chairmen: Enrico AGABATI-ROSEI, Brescia - ITA – Luc VAN BORTEL, Ghent - BEL

- Clinical significance of lowering central BP and arterial stiffness
  Athanas BENETOS, Nancy - FRA
- Central BP and arterial stiffness as clinical endpoints in large scale trials.
  Metrological and methodological issues
  Stéphane LAURENT, Paris - FRA
- Currently available drugs and new agents that decrease central BP and arterial stiffness.
  Insight from recent trials
  Luc VAN BORTEL, Ghent - BEL

Panellists: Enrico AGABATI-ROSEI, Brescia - ITA – Michel AZIZI, Paris - FRA
Athanas BENETOS, Nancy - FRA – Luc VAN BORTEL, Ghent - BEL – Alain COHEN SOLAL, Paris - FRA
Finn GUSTAFSSON, Copenhagen - DEN – Stéphane LAURENT - Paris - FRA – Atul PATHAK, Toulouse - FRA
Bertram PITT, Ann Arbor - USA – Patrick ROSSIGNOL, Nancy - FRA – Luis RUILOPE, Madrid - SPA
Michel SAFAR, Paris - FRA – Wiek VAN GILST, Groningen - NED – Charalambos VLACHOPOULOS, Athens - GRE
Ursula-Henrike WIENHUES-THELEN, Roche Diagnostics - GER

14:00-16:00

SALON ORSAY NORD

MAIN PLENARY SESSION

Coronary artery disease management: Breaking new grounds with ivabradine
Chairmen: Philippe G. STEG, PARIS - FRA – Ake HJALMARSON, Göteborg - SWE

- Introduction
  Ake HJALMARSON, Göteborg - SWE
- Heart rate reduction in clinical practice
  Ake HJALMARSON, Göteborg - SWE
- New results with Ivabradine
  Jeffrey BORER, New York - USA
- Coronary artery disease management: A step further with ivabradine
  Philippe G. STEG, Paris - FRA
16:30-19:00  SALON ORSAY NORD
MAIN PLenary SESSION
The future of anti-thrombotic therapy in coronary syndromes at the acute and post-acute phases
Chairmen: Nicolas DANCHIN, Paris - FRA – Dan ATAR, Oslo - NOR

- The pharmacology of modern anti-thrombotic drugs: how to maximize the benefit-to-bleed risk ratio?
  Tabassome SIMON, Paris - FRA

- Resistance to antiplatelet agents: biological fantasy or clinical reality?
  Gilles MONTALESCOT, Paris - FRA

- How the results of the most recent trials will change the anti-thrombotic strategy in acute coronary syndromes?
  Nicolas DANCHIN, Paris - FRA

- Post acute coronary syndromes. Risk and management of anti-thrombotic therapy in the ambulatory patient
  Philippe G. STEG, Paris - FRA

Debate: unclot with little bleed. Unravelling the Gordian knot

Panellists: Dan ATAR, Oslo - NOR – Nicolas DANCHIN, Paris - FRA
Efthymios DELIARGYRIS, Athens - GRE – Pascale GAUSSEM, Paris - FRA – Antoine LAFONT, Paris, FRA
Gregory LIP, Birmingham - GBR – Gilles MONTALESCOT, Paris - FRA – Bertram PITT, Ann Arbor - USA
Faiez ZANNAD, Nancy - FRA

16:30-19:00  FOYER ORSAY NORD
JOINT SESSION
The CardioRenal Forum - European Society of Cardiology (ESC) Working-Group on Pharmacology and Drug Therapy
Optimising Care at the Cardio-Renal Interface
Chairman: Alexandre MEBAZAA, Paris - FRA – Bengt FELLSTROM, Uppsala - SWE

- Cardiovascular outcomes in chronic kidney disease, Rationale for future clinical trials
  Faiez ZANNAD, Nancy - FRA

- Cardiovascular protection trials in end stage renal disease
  Bengt FELLSTROM, Uppsala - SWE

- Clinical trials targeting renal protection in heart failure and cardiovascular disease
  Marco METRA, Brescia - ITA

Debate: What endpoints for a renoprotective agent in cardiovascular disease?

Panellists: Kirkwood ADAMS, Chapell Hill - USA – Stefan AGEWALL, Stockholm - SWE – Angeles ALONSO, Madrid - SPA
Bengt FELLSTROM, Uppsala SWE – Mihai GHEORGHIADE, Chicago - USA – Felipe MARTINEZ, Cordoba - ARG
Alexandre MEBAZAA, Paris - FRA – Marco METRA, Brescia - ITA – Patrick ROSSIGNOL, Nancy - FRA
Wiek VAN GILST, Groningen - NED – Faiez ZANNAD, Nancy - FRA
1. Selecting the appropriate design

1.1. Positive control, placebo-controlled trials vs. non inferiority head-to-head comparative trials. Which way to go?
Speaker: Stuart POCOCK, London - GBR
Discussant: Yasser KHDER, Boehringer Ingelheim, Paris - FRA

1.2. Adaptive design. Strengths and limitation
Speaker: Sidney GOLDSTEIN, Detroit - USA
Discussant: Michael DOMANSKI, Bethesda - USA

2. Defining the appropriate patient population: ACS, AMI, STEMI/NSTEMI: terminology and definition matters
Speaker: David MORROW, Boston - USA
Discussant: Marteen SIMOONS, Rotterdam - NED

3. Study drug and comparator drug related issues: Clinical and Regulatory challenges

3.1. What is the optimal “reference” comparator?
Speaker: Gregory LIP, Birmingham - GBR

3.2. Timing of randomisation/dosing
Speaker: Philippe G. STEG, Paris - FRA
Discussant: Nicolas DANCHIN, Paris - FRA

4. Endpoint definition

4.1. Time to first event vs. cumulative events
Speaker: Christian TORP-PEDERSEN, Copenhagen - DEN
Discussant: Aldo MAGGIONI, Florence - ITA

4.2. Composite events
Speaker: John WARREN, London - GBR
Discussant: Edmond ROLAND, Paris - FRA

4.3. Balancing benefit vs. risk
Speaker: Edmond ROLAND, Paris - FRA
Discussant: Gregory LIP, Birmingham - GBR

5. Interpretation issues

5.1. Statistically significant vs. clinically meaningful results? A Statistical Interpretation of Recent Trials
Speaker: Stuart POCOCK, London - GBR

Faculty members Academy: Michael ANGIOI, Nancy - FRA – Vidal BENATAR, Saint-Cloud - FRA
Laurent BONELLO, Marseille - FRA – Jeffrey BORER, New York - USA – Jean CASSAGNES, Clermont-Ferrand - FRA
Gilles DAGENAIS, Quebec - CAN – Nicolas DANCHIN, Paris - FRA – Efthymios DELIARGYRIS, Athens - GRE
Gregory DUCROCOQ, Paris FRA – Sidney GOLDSTEIN, Detroit - USA – Antoine LAFONT, Paris - FRA
Gilles LEMESLE, Lille - FRA – Gregory LIP, Birmingham - GBR – Aldo MAGGIONI, Florence - ITA
David MORROW, Boston - USA – Bertram PITT, Ann Arbor - USA – Stuart POCOCK, London - GBR
Tabassome SIMON, Paris - FRA – Marteen SIMOONS, Rotterdam - NED – Philippe G.STEG, Paris - FRA
Faiez ZANNAD, Nancy - FRA

Faculty members EMEA / AFSSAPS: Eric ABADIE, Paris - FRA – Angeles ALONSO, Madrid - SPA
Faculty members NHLBI (NIH): Michael DOMANSKI, Bethesda - USA – Nancy GELLER, Bethesda - USA
David GORDON, Bethesda - USA

Faculty members Industry: Maria-Niki AIGYPTIADOU, Daiichi-Sankyo - GER
Gunnar BRANDRUP, AstraZeneca - SWE – Yasser KHDER, Boehringer Ingelheim - FRA
Stuart KUPFER, Takeda - USA – Guy LEREBOURS, Servier - FRA – Hubert POULEUR, Pfizer - USA
James REVKIN, Boehringer Ingelheim - USA – Magali SARTRAL, Eli-Lilly - FRA

Faculty members Industry and CROs: Michel ABITEBOUL, Quintiles - FRA – Bertrand BEAUX, Parexel - FRA
Robert CODY, Merck - USA – Amin KADI, MFF - FRA – Yasser KHDER, Boehringer Ingelheim - FRA
Stuart KUPFER, Takeda - USA – Michel LEVY, ADDS - FRA – Vladimir POPOV, Esmar - RUS
Hubert POULEUR, Pfizer - USA – James REVKIN, Boehringer Ingelheim - USA – Jorgen SELDRUP, Quintiles - FRA

Faculty members EMEA / AFSSAPS: Eric ABADIE, Paris - FRA – Angeles ALONSO, Madrid - SPA
Fernando De ANDRES, Trelles - SPA

13:45-16:45  
SALON ORSAY NORD  
CVCT EXPERT WORKSHOP  
Data Safety and Monitoring Committees (DSMC) in CV trials  
Chairmen: Stuart POCOCK, London - GBR – Bertram PITT, Ann Arbor - USA

1. Data access  
1.1. Data Cleaning issues  
Speaker: Jorgen SELDRUP, Quintiles - FRA  
Discussant: Robert CODY, Merck - USA

1.2. Adjudicating issues  
Speaker: Aldo MAGGIONI, Florence - ITA  
Discussant: Gilles DAGENAIS, Quebec - CAN

1.3. Unblinding issues  
Speaker: Nancy GELLER, Bethesda - USA  
Discussant: Philippe G. STEG, Paris - FRA

2. Stopping rules in adaptive design trials  
2.1. Methodological issues  
Speaker: Stuart POCOCK, London - GBR  
Discussant: Michael DOMANSKI, Bethesda - USA

2.2. Ethical issues  
Speaker: Sidney GOLDSTEIN, Detroit - USA  
Discussant: David GORDON, Bethesda - USA

2.3. Regulatory issue  
Speaker: Amin KADI, MFF, Paris - FRA  
Discussant: John WARREN, London - GBR

Faculty members Academy: Kirkwood ADAMS, Chapell Hill - USA – Jeffrey BORER, New York - USA
Jan CARLSEN, Lyngby - DEN – Gilles DAGENAIS, Quebec - CAN – Nicolas DANCHIN, Paris - FRA
Virginija DAMBRAUSKAITE, EU, Brussels - BEL – Jacques DESMOTES, ECRIN, Bordeaux - FRA
Bengt FELLSTROM, Uppsala - SWE – Mihai GHEORGHIADE, Chicago - USA
Sidney GOLDSTEIN, Detroit - USA – Luc HITTINGER, Paris - FRA – Guillaume JONDEAU, Paris, FRA
Stéphane LAURENT, Paris, FRA – Aldo MAGGIONI, Florence - ITA – Gilles MONTADECOT, Paris - FRA
Marteen SIMOONS, Rotterdam - NED – Chris TORP PEDERSEN, Copenhagen - DEN

Faculty members: NHLBI (NIH): Michael DOMANSKI, Bethesda - USA
Nancy GELLER, Bethesda - USA –David GORDON, Bethesda - USA
Abstracts

6th Global CardioVascular Clinical Trialists Forum
Thursday December 3rd, 2009, 11 am - 1.45 pm

CVCT EXPERTS WORKSHOP
Clinical trials in cardiovascular critical care
Chairpersons: Alexandre Mebazaa, Birhan Mehmet Yilmaz

What are the unmet needs?
The clinician point of view

Alexandre MEBAZAA, Paris – FRA
Date et lieu de naissance: 21 mai 1960, Tunis – Tunisia
Adresse professionnelle: Département d’Anesthésie-Réanimation ; Hôpital Lariboisière, Tel : 01.49.58.80.85
Email: alexandre.mebazaa@ltb.ap-hop-paris.fr
A. Titres et Fonctions Universitaires
– Diplôme de Docteur en médecine, Université Strasbourg I, 1989
– Assistant Professor, Johns Hopkins University, Baltimore, États-Unis, de 1991 à 1994
– Président du Conseil Pédagogique de la Faculté de Médecine Paris 7 Denis Diderot, depuis Novembre 2005
– Professeur Associé Faculté de Médecine de Tunis, depuis juin 2006
B. Fonctions Hospitalières
– Staff Anesthésiologist : Anesthesiology and Critical Care Medicine, Johns Hopkins University, 1991-1993
– Praticien Hospitalier: Département d’Anesthésie-Réanimation, hôpital Lariboisière, 1994 à ce jour
– Vice-Président du CCM : depuis 2003
– Expert - rapporteur sur les recherches biomédicales portant sur les dispositifs médicaux AFFAPS, 2006
C. Scientifiques
– Guest Researcher, Gerontology Research Center, National Institutes of Health (NHI), Baltimore, 1992-1994
– Thèse de Sciences, Paris V, 1994
– Habilitation à Diriger les Recherches, Faculté Lariboisière-Saint-Louis, Université Paris VII, 1996
D. Principales publications

Industry point of view
Hemodynamic monitoring

Frederic MICHAUD, Edwards Lifesciences, Nyon – SWI

Trade off in heart failure: why clinical trial on ADHF should focus on quality of life:

Piero POLLESELLO, Orion Pharma, Espoo – FIN
Piero Pollesello has a Ph.D. in biochemistry (University of Trieste, Italy) and is adj.Prof. in biochemistry (Faculty of Medicine, University of Helsinki, Finland). Specialist in the application of Nuclear Magnetic Resonance Spectroscopy to bio- and medical sciences and to drug discovery, he worked on a broad range of research topics such as the characterization of human pathologies, the determination of the phosphorylation potential on perfused tissues and organs, the detection and quantification of metabolites, the determination of protein structure and protein-ligand interaction (e.g. on troponin C and phospholamban), and finally the pharmacological characterization of a new first-in-class cardiovascular drug. He has been head of cardiovascular pharmacology and drug discovery at Orion Pharma (Espoo, Finland), where he substantially contributed to the discovery, patenting, development, registration and launch of SMIAX® (Levosimendan), a novel inotrope for the treatment of acutely decompensated heart failure. In his publication list there are 65 peer-reviewed papers, several book chapters and ten patents. He has been a member of the Editorial Board of J.Cardiovasc.Pharmacol. from 2005. He cooperated as evaluator in the European Union framework FP6 in the years 2003-2005. In 2007 he was appointed Critical Care Global Brand Manager at Orion Pharma for the proprietary products Levosimendan and Dexametabolide. He is Knight of the Italian Republic (O.S.S.I.).

ABSTRACT
The incidence and prevalence of heart failure (HF), a pathologic condition associated with significant morbidity and mortality, are increasing in the Western population (1,2). Steward et al. (3) have shown that HF affects quality of life (QoL) more profoundly than many other chronic diseases. It is therefore straightforward that QoL should be taken into consideration when selecting the HF treatments and when developing new ones. New parameters such as health-related quality of life (HRQoL) and quality-adjusted life year (QALY) have been developed and used to measure reliably QoL (4). A distinction, however, should be made between HF and acutely decompensated HF patients, who are per definition hospitalised. An observation was recently made on the preferences of the patients after hospitalisation for AHF as it regards trading length of life for QoL (5). A bimodal distribution of the preferences was noticed making more difficult to prioritise the weight of one of the two when assessing the effect of therapies. Since it is objectively difficult to define and assess QoL in the acutization of HF some clinical studies included as end points some surrogate parameters such as patient self assessed symptoms, or even the “patient journey”, which is a composite consisting of repeated symptom assessments, worsening heart failure and mortality in a period of time of months after the event of decomposition (6). Other studies preferred a simpler “day alive and out of hospital” end-point (7). In a recent regulatory clinical study (8) on Levosimendan (REVIVE) the primary end point was on a composite with some Qol parameters (patient self assessment at different time points, in addition to doctor assessment of symptoms, biomarkers, etc.). The primary end-point in that study was successfully reached in front of a non significant neutral outcome on the mortality at 90 days. The open question is how to weight the success of Qol end-points over a long term mortality end-point in an ADHF clinical study. As a final consideration, it should be remembered that Qol parameters are often overlapping to health economic parameters, such as day-in-hospital and re-hospitalization (8), of paramount utility when planning clinical studies on new therapeutics in HF.
LIST OF SUGGESTED READINGS:


What are the optimal endpoints?
The emergentist point of view

Patrick Ray, Paris – FRA

The intensivist (ICU/CCU) point of view

Mehmet Birhan YILMAZ, MD
Associate Professor of Cardiology
He was born in Izmir in 1974. He graduated from Hacettepe University Faculty of English Medicine in 1998. He finished his residency in Türkiye Yüksek İhtisas Education and Research Hospital, Cardiology Clinic in 2003. He started Department of Cardiology of Cumhuriyet University School of Medicine as a consultant and as an academic staff in 2005. He has become Associate Professor of Cardiology in 2006. He has been academic staff and a consultant in the same department since then. He has been interested in valvular heart disease since 2003 and heart failure since 2005. He will be in INSERM U 942, in Laribosiere Hospital for one year with a grant from TUBITAK for research on biomarkers in heart failure. Dr.Yilmaz is a member of Working Group on Heart Failure of Turkish Society of Cardiology, and Working Group on Valvular Heart Disease of European Society of Cardiology.

ABSTRACT

Clinical trials in cardiovascular critical care: What are the optimal endpoints?
Cardiac Intensivist Point of View: Mehmet Birhan YILMAZ (Sivas, TUR)
Optimal end point is the one that takes every measurable impact of a therapeutic option into account. Every measurable means positive-negative impact both in the form of hard end points (mortality, disease-related mortality) and soft end points, which are quantifiable and comparable within different centres in a large trial. By saying optimal, there are at least two options: First is optimal endpoint during the critical care, the second is the optimal endpoint after the critical care, which is relatively well defined in many trials (hard endpoints: death, MI etc.)
A) After critical care: Shall we look at cancer studies? Possible candidates for soft end points: 1- Acceptably high quality life days, gained up on therapy, 2-How many days does the patient spend without dyspnea or without exacerbation of my dyspnea?, 3-How many days did the patient gain without significant angina (CCS II, or less than I), 4-How many days did the patient gain without palpitation?
5-How many days can the patient sleep without significant dyspnea? (sleep quality indices?), Though, half of the life is in sleep, sleep quality is not thoroughly considered among trials. HF significantly disturbs sleep, and sleep problems are unacceptably high among patients with HF.
6-Time to occurrence of specific-soft but relevant end-points (adjudicated):
   a) Time to occurrence of first attack which causes the patient to admit emergency department (there must be requirement of the ED physician to report this as a serious admission in order to adjudicate it as an event): For example for a patient with HF: if there is admission to ED, there must be at least one criterion proving that the patient was sicker than before. (BNP renal function, liver function, echocardiography, chestXray, questionnaires indicating worsening for HF), b) Admission free interval (any admission to health care facility), c) Combination of organ function end points with quality of life end points: If two are present or absent, 3 points, if one is present or absent 1 point in either direction. Organ function end-points could be in the form of natriuretic peptides, left ventricular remodeling, intima-media thickness, flow-mediated vasodilatation, creatinine, eGFR, liver dysfunction (enzymes). Organ function end points must be validated consistently before use in clinical trials.
B) During critical care: End points could possibly be focusing more specifically.
   1-Acute change in symptomatic status: both resting and with provocation,
   2-Acute change in critical-organ function: compared to baseline (at admission) or to levels during stable phase or to the best value before

SUGGESTED READINGS:

Anand IS. Surrogate end points in Heart Failure. J Am Coll Cardiol. 2002;39(9):1414-21

The cardiac surgeon point of view

Antonis A. PITSIS, Thessaloniki, GREECE
Antonis Pitsis is Head of the Department of Cardiothoracic Surgery of Aristotelian University of Thessaloniki Heart Institute (Thessaloniki, Greece). He is a British trained cardiothoracic surgeon. From 1992 – 1997 he undertook his residency in cardiothoracic surgery at Papworth Hospital (Cambridgeshire South - Cleveland Hospital (Middleborough), University Hospital of Wales (Cardiff). From 1997 – 1999 he served as a Consultant and Senior Lecturer in cardiac surgery at the Bristol Royal Infirmary and University of Bristol (Bristol). His thesis was on percutaneous ventricular assist devices. He was appointed in his current post at St. Luke’s Hospital in 1999. His main fields of interest are mechanical circulatory support and heart failure surgery.

ABSTRACT

The mortality of acute heart failure (AHF) remains high despite advances in treatment. Mechanical circulatory support (MCS) can be applied in AHF, refractory to conventional measures, to improve outcomes. This presentation aims to stimulate discussion on the current and the prospective role of MCS in the treatment of AHF. The support strategies and the indications of MCS are continuously evolving, including clinical scenarios considered as contraindications in the past.
Appropriate patient selection, advanced device technology and improved patient management have contributed to the substantially improved results. Evolution in device technology results in evolution of the clinical applications of MCS.

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Earlier application of MCS, with novel, flexible and individualized support strategies is now feasible. Bridging to recovery is the most intriguing support strategy and bridging to future treatments is feasible with long-term support. The progressively expanding role of MCS in the treatment of heart failure is not reflected in the existing guidelines. Being reserved for refractory heart failure, MCS has been applied to the sickest patients who were less amenable to randomization. This partly explains the lack of robust evidence, but also highlights the value of the progressively improving results. The anticipated wider application of MCS should be better defined, systematically recorded, and guided.3

LIST OF SUGGESTED READINGS:

Thursday December 3rd, 2009, 2 pm- 6pm
EXPERT WORKSHOP
Understanding the results of MADIT-CRT.
Key elements for an optimal implementation of CRT-D in clinical practice
Patient population and outcome issues: what is the clinical significance of the results of MADIT-CRT
Chairperson: Karl Swedberg, Göteborg – Swe

What are the patients eligible for CRT-D? How to estimate the size of the eligible population?

Mihai GHEORGHIADE, Chicago – USA
Dr Gheorghiade currently serves as Professor of Medicine and Surgery, Associate Chief of the Division of Cardiology, Chief of the Cardiomyopathy Clinical Service, and the Director of the Telemetry Unit at Northwestern University’s Feinberg School of Medicine and Northwestern Memorial Hospital. He was recently appointed Adjunct Professor of Medicine at Duke University and also Section Editor for Heart Failure Reviews Journal. He graduated Magna Cum Laude from the University of Rome Medical School in 1972 and did his residency and fellowship in cardiology at Brown University. He then moved to Virginia, where he was Chief of Cardiology at the Salem VA Medical Center and Associate Professor of Medicine at the University of Virginia. In 1985, Dr Gheorghiade became Chief of the Cardiac Care Unit at the Henry Ford Hospital in Detroit and Associate Professor of Clinical Medicine at the University of Michigan. During his tenures in Virginia and Michigan, he received numerous teaching awards from both medical students and residents. In 1992, he joined Northwestern University.

Dr Gheorghiade has served as a visiting professor in the United States and abroad. He has served as a visiting professor in the United States and abroad. He has chaired or co-chaired more than 150 national and international meetings and has given more than 500 invited lectures. He has served on the editorial board of several journals including The American Heart Journal, The American Journal of Cardiology, Journal of the American College of Cardiology, and Circulation Heart Failure Journal. He has also served as guest editor on several occasions for The American Journal of Cardiology, The American Heart Journal, and The American Journal of Medicine. He has chaired many international trials in heart failure including OPTIME-HF, ACTIV-HF, IMPACT, PRESERV/D, STEP-CHF and HORIZON Trials. He has co-chaired the global EVEREST Trial and the ECLIPSE Trial, and was a member of the Steering Committee of RADIANCE, FIRST, CASS, INIZ A, and EPESUS Trial. In addition, Dr Gheorghiade was an active member of the Steering Committee in the OPTIMIZE-HF and IMPACT-HF registries. He currently serves as Chair of the International ASTRONAUT, REENG-DEFEND, and Co-chair of the IGNITE trials. Dr Gheorghiade has authored more than 500 peer-reviewed publications and more than 300 abstract presentations at national and international meetings. He is the co-editor for two comprehensive textbooks on acute heart failure syndromes and has written several chapters in many textbooks including Kelsey’s Textbook of Internal Medicine, and Heart Failure: A Companion to Braunwald’s Heart Disease. He was recently invited to write a chapter on acute heart failure syndromes in the upcoming edition of Braunwald’s Heart Disease.

In 2004, Dr Gheorghiade founded the Acute Heart Failure Syndromes International Group, comprised of physicians, scientists, clinicians, and regulatory and governmental agencies from North America and Europe to advance the knowledge and care of patients with acute heart failure syndromes through clinical research. This group has met annually, producing several consensus documents published in Circulation, Journal of the American College of Cardiology, and European Heart Journal. At present, Dr Gheorghiade is actively involved in the management of patients undergoing solid organ transplantation at Northwestern Memorial Hospital, and remains actively involved in animal and human research for the development of novel compounds for acute heart failure syndromes. He dedicates significant time and energy to the mentorship of medical students, residents and junior faculty as attested by their primary authorship of more than 100 peer-reviewed publications in recent years. Improving outcomes of hospitalized patients with heart failure through research and education remains his top priorities.
The relative contribution of preventing death and preventing HF hospitalization

Frédéric ANSELME, Rouen – FRA

Date de naissance : 30 juin 1965  Nationalité : Française
Discipline : Cardiologie et Maladies Vasculaires
Numéro de l’Ordre des Médecins: 76/6002

Professeur d’Université- Praticien Hospitalier dans le service de Cardiologie du Pr Cribier depuis Septembre 2006
Responsable de l’unité de rythmologie dans le service du Pr Cribier à Rouen depuis 2000
Responsable du DIU de Rythmologie et de Stimulation Cardiaque à l’université de Rouen.

Activités administratives et responsabilités collectives:
Membre titulaire de la Société Française de Cardiologie
Membre du bureau du groupe de Rythmologie et de stimulation cardiaque de la Société Française de Cardiologie
Président de l’Association de Cardiologie de Haute Normandie (membre du conseil d’administration de la Fédération Française de Cardiologie).
Stage à l’étranger: Laboratoire d’Electrophysiologie du Pr M.E. Josephson, au Beth Israel Hospital of Boston, Harvard Medical School, Massachusetts, USA (1994-1995).

PUBLICATIONS RECENTES


The clinician point of view: generalizability of the results of recent trials (MADIT-CRT)

Gunter BREITHARDT, Münster – GER

Mechanistic issues: How does CRT-D work for the prevention of HF hospitalisation?

Chairperson: Daniel Gras, Nantes – FRA

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Consistency within the trial subgroups, consistency with other CRT and ICD trials.

Cecilia LINDE, Stockholm – SWE

Mechanistic plausibility. Insight from pathophysiology – importance of improvement of LV function across all trials

Mark ESTES, Boston – USA

Registerability and implementation issues.

Chairperson: Faiez Zannad

Is “Prevention of HF events” in mild HF patients with large QRS and low EF an approvable new indication for CRT-D?

Bernd LEMKE, Lüdenscheid – GER

Updating the guidelines and overcoming implementation issues/barriers

Karl SWEDBERG, Göteborg – SWE

Thursday December 3rd, 2009, 2 pm- 4 pm

EUROPEAN SOCIETY OF CARDIOLOGY

Working Group on Cardiovascular Pharmacology and Drug Therapy

Young CardioVascular Clinical Trialists (YCVCT) Course

Chairperson: Thibaud Damy, Patrick Rossignol

Thibaud DAMY, Créteil – FRA

Doctor Thibaud Damy qualified in medicine at the University of Paris XI in 1996. After a period of postgraduate cardiology training in several Parisian hospitals and a PhD on the effect of nitric oxide on heart failure at the University Paris VII, he was appointed first as a senior registrar at Paris V University (2004), then at Paris XI (2005-2006) and subsequently in 2007 as a senior lecturer in cardiology and honorary consultant cardiologist at Henri Mondor Hospital, Creteil, France. In August 2008, he obtained a secondment for 16 months as a senior research fellow at the Academic Cardiology Department of Professor John G Cleland at the University of Hull (UK). Doctor Damy’s main field of interest is heart failure, extending from its epidemiology and physiopathology through to its diagnosis and treatment. Particular current interests include the role of the nitric oxide pathway, neurohumoral systems, sleep apnoea syndrome, right ventricle function, and pulmonary artery pressure in heart failure.

Patrick ROSSIGNOL, Nancy – FRA

Born 15 April 1969, French

Professional address: Centre d’Investigation Clinique de Nancy

HOPITAL JEANNE D’ARC, BP 90303, F-54201 TOUL CEDEX

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Education (degrees, dates, universities)

Master degree in Biology and Pathology of the epithelia, 1998, University of Paris VI « Pierre et Marie Curie »

Medical Doctorate, specialty nephrology, 2000, University of Paris V « Necker-Enfants Malades »


Ph. D. "Biology and pharmacology of hemostasis": 2005, University of Paris VII "Denis Diderot"

Professional/research experience


11/2002-31/10/2003 : fellowship in vascular biology, Center for Molecular and Vascular Biology, Katholaecke Universiteit Leuven (Belgium) : Pr Lijnen, Pr Collen


05/2007 - : Assistant-Professor (Therapeutics), delegate physician of the Nancy University Hospital & INSERM Clinical Investigation Centre (Coordinating physician : Pr Zannad) ; associate researcher, INSERM 961, Dr Lacolley.

Main publications over the last 5 years

The young CVCT initiative: Time to rejuvenate CV clinical trialists

Bertram PIIT, Ann Arbor – USA
Professor of Internal Medicine
1949-53 B.S., Cornell University, New York.
1953-59 M.D., University of Basel, Switzerland
1959-60 Intern, Beth Israel Hospital, New York

Positions and Honors:
1960-62 Assistant Resident, Beth Israel Hospital, Boston, Mass
1961-62 Teaching Fellow in Medicine, Harvard, University Boston
1962-63 Chief Resident, Medicine, Beth Israel Hospital, Boston, Mass
1962-63 Assistant in Medicine, Harvard University Teaching Fellow in Medicine, Tufts University
1966-67 National Heart Institute Special Fellow, Department of Medicine, Division of Cardiology, Johns Hopkins University Academic Appointments
1967-68 Instructor in Medicine, Johns Hopkins University
1968-72 Assistant Professor Medicine, Johns Hopkins University
1972-77 Associate Professor of Medicine, Johns Hopkins University
1977-91 Professor of Internal Medicine, Director, Division of Cardiology, University of Michigan School of Medicine
1991-99 Professor of Internal Medicine, Associate Chairman for Academic and Industrial Programs, Department of Internal Medicine, University of Michigan School of Medicine
1999-Professor Internal Medicine, University of Michigan School of Medicine

Honors and Awards
1976-66 Bronze Award, American Heart Association – Maryland Affiliate
1977 Halifax Selassie Lecturer, British Heart Foundation
1978 Outstanding Cardiology Staff – University of Michigan
2000 Johns Hopkins University Society of Scholars
2001 Forest Dewey Dodd Award for Excellence – American Heart Association
2002 Paul Dukakis Lifetime Achievement Award – University of Michigan Research Support

Gilles DAGENAIS, Quebec – CAN
A graduate from the Medical School of the Université de Montréal, Dr. Dagenais pursued his training in research at McGill University and subsequently in Internal Medicine at the Université de Montréal. He did his training in cardiology and research at the Johns Hopkins Hospital and University and in clinical trial during a one-year sabbatical at the University of Oxford. From 1979 to 1987, Dr. Dagenais was the Director of the Quebec Heart Institute and the Cardiology Program at the Université Laval where he was a Professor of Medicine. From 1991 to 1999, he was Professor and Chairman of the Department of Medicine at the Université de Montréal. Professor emeritus at the Université de Montréal and at the Université Laval, he continues his career in clinical cardiology and research at the Quebec Heart Institute.

Dr. Dagenais’ main research interest is on ischemic cardiovascular diseases and their prevention. He is the principal investigator of the Quebec Cardiovascular Study, co-chair of the HOPE and HOPE TOO trials, and member of the steering committee of the DIG, DREAM/Epi-DREAM, ONTARGET-TRANSCEND, BARI-2D, ORIGIN, HOPE-3, TIDE clinical trials as well as the international epidemiological PURE study.

Dr Dagenais is involved in several national and international societies and professional associations. He has been President of the Canadian Cardiovascular Society, member of the College of Cardiology Board, Associate-editor of the Canadian Journal of Cardiology, President of the Canadian Association of Professors and Chairmen of Department of Medicine, President of the 4th International Conference on Preventive Cardiology and first Vice-president of the Inter-American Society of Cardiology.

ABSTRACT

It is what we think we know already that often prevents us from learning.

Claude Bernard

What we know and what we think that our fellows know about randomized clinical trials (RCTs) may be summarized as follows. Some RCTs have contributed to improving prevention and the quality of life of high-risk patients: GISS, ISIS-2, SOLVD and SAVE are good examples. Other RCTs have shown that despite encouraging surrogate findings and assumptions, the medications evaluated were deleterious (ILLUMINATE, CAST). Other RCTs have shown that the medication evaluated was not different from the placebo or the comparator agent (BARI 2D, HOPE-TOO). Some trials have generated hypotheses for example, ACE-inhibitors or angiotensin receptor blockers decreased the risk of type 2 diabetes; however, these trials were not designed to assess type 2 diabetes as primary outcome but they generated the hypothesis that was or is being tested (DREAM, NAVIGATOR).

A variety of methodologies have been used in RCTs alone or in pseudo-amalgams of RCTs-database registries. These different trials with their
methods constitute an extraordinary dataset covering a wide spectrum of information that is useful to improve knowledge on RCTs and beyond.1-4

Although several RCTs are model trials and others had limitations; did we, young and less young fellows, learn from these trials? Analyzing some of these trials in more details may enrich the training of fellows. For example raising questions such as: how relevant is the question to be answered by the trial? Was the question or the objective based on observational studies, mechanistic and/ or surrogate studies? Was the design of the study adequate to answer the question? Was the trial performed according to the submitted protocol? How was the interpretation of the data? The implications of such questions in the training of fellows will be highlighted during this presentation.

RCT analyses are important methods of improving knowledge of fellows in the field of clinical trials but they should be incorporated into a global training program including facilities for mentorship, basic epidemiological training, exchanges with colleagues in a productive milieu, the opportunities to generate a small or pilot clinical trial and if possible to participate in a large RCT.Finally, RCT knowledge facilitates critical appraisal and should be integrated at an early stage of the training such as in the curriculum of health care students.5-7

References

How to teach trial methodology to young clinicians?
Eric VICAUT, Paris – FRA

Responsibilities, role and functioning of trial committees (Steering committee, DSMC, Event committee).

Sidney GOLDSTEIN, Detroit – USA
Sidney Goldstein, M.D., is Professor of Medicine at Wayne State University and Division Head, Emeritus, of the Division of Cardiovascular Medicine at Henry Ford Hospital in Detroit, Michigan. Dr. Goldstein received his B.A. at Cornell University and his medical education at Cornell University Medical College. He completed both his internship and residency at the New York Hospital – Cornell Medical Center. Following this, he was a research fellow sponsored by the New York Heart Association at New York Hospital – Cornell Medical Center. Before going to Henry Ford Hospital, he was head of the cardiology division at Rochester General Hospital in Rochester, New York and Associate Professor of Medicine at the University of Rochester.

Dr. Goldstein’s major areas of basic and clinical research have been in the areas of ischemic heart disease, the mechanism and prevention of sudden cardiac death and the treatment of heart failure. He served as chairman of the steering committee of the Beta-Blocker Heart Attack Trial and was a principal investigator in the Aspirin Myocardial Infarction Study, the Cardiac Anhythmia Suppression Trial and the Asymptomatic Cardiac Ischemia Pilot Study. He has carried out extensive research on the mechanism and prevention of sudden death supported by the National Heart, Lung and Blood Institute. His current research interests are directed at understanding the basic mechanism of heart failure. He was Co-Principal Investigator of Metoprolol CR Randomized Interventional Trial in Heart Failure (MERIT-HF). Widely published, he is the author or co-author of more than 250 peer-reviewed articles, in addition to numerous editorials and book chapters. He is co-editor of Heart Failure Reviews, a journal examining the spectrum of research in heart failure from basic science to clinical research. He is medical editor of Cardiology News and currently serves on the editorial boards of the American Journal of Cardiology, American Journal of Geriatric Cardiology and Internal Medicine News.

Dr. Goldstein is a fellow of the American College of Cardiology and a past member of its board of trustees and chairman of the Workforce and Credential Committees. He is a member of the Council of Clinical Cardiology and Epidemiology of the American Heart Association and a fellow of the American College of Physicians, and a member of the American Federation for Clinical Research and the Central Society for Clinical Research and the Association of University Cardiologists.
Friday December 4th, 2009, 9.00 am – 12.00 am

PLENARY SESSION

Biomarkers in clinical trials

Chairpersons: Angeles Alonso, Kirkwood Adams

Angeles ALONSO, Madrid – SPA
I was born and raised in Madrid, Spain. In 1979 I graduated from the School of Medicine at the Universidad Autónoma de Madrid and later in 1991 I successfully completed my Ph.D at the Faculty of Medicine. I began my clinical experience with as a resident doctor in the Intensive Care Unit at the Hospital La Paz (Madrid) and then in the Department of Cardiology at the Academic Hospital Puerta de Hierro (Madrid) where I went on to become a member of staff of the Department of Cardiology in 1987 to the present date (Coronary Care Unit, Hospitalisation Unit). In 2000 I became a member of the Committee for Ethics and Clinical Investigation and a Member of the Committee for Mortality. Two years later I was promoted to Senior Consultant of the Cardiology Department at the Hospital Universitario Puerta de Hierro (Majadahonda). I am an Honorary Professor at the Department of Medicine in Cardiology at the Faculty of Medicine, Universidad Autónoma de Madrid and have also been Coordinator, Chairman and speaker of several post-degree Ph D Courses at the Academic Hospital Puerta de Hierro Madrid on Cardiovascular Topics: Hipertensión, Cardiac Emergencies, Heart Failure and Cardiac pacing. I have been a member of the Spanish Society on Cardiology (SEC) since 1986, a member of the Heart Failure, Ischemic Diseases, Women and CV Disease, Pharmacology Working Groups of the Spanish Society of Cardiology, General Vice-Secretary elect of the Spanish Society of Cardiology: 1999-2001, General Secretary of the Spanish Society of Cardiology: 2001-2003 and President of the International Relations Department of the Spanish Society of Cardiology and Member of the Editorial Committee of the Spanish Heart Journal. I have also been a Fellow of the European Society of Cardiology since 2001, a member of the WG of Heart Failure and Acute Heart Diseases of the European Society of Cardiology ESC, a member of the Heart Failure Committee of the European Society of Cardiology ESC from 2002-2004, National Coordinator of the Euro Heart Survey Program of the European Society on Cardiology 2000-2004, a member of the Clinical Practice Guidelines Committee of the European Society of Cardiology ESC 2000-2004, a member of the Task Force of Stable Angina Guidelines of the ESC 2006, a member of the Regulatory Committee of the ESC until the present date and a member of the General Coordinating Committee of The Euro Heart Survey Program until the present date. In terms of regulatory experience, I am a member of the Cardiovascular Group of the Efficacy Working Party of the European Medicines Agency EMEA (2000 to date) and a member of the Scientific Advice Working Party of the EMEA (2005 to date).

How evidence based is the current risk stratification guided CV preventive drug therapy?

Luis RUILOPE, Madrid – SPA
Luis Rulope is currently Associate Professor of Internal Medicine at Complutense University and Head of the Hypertension Unit at the 12 de Octubre Hospital in Madrid, Spain. Dr Rulope received his MD degree from the University of Madrid and completed his residency and fellowship in nephrology at the Jiménez Díaz Foundation in Madrid. His principal area of interest is hypertension and the kidney. Dr Rulope is a member of the editorial boards of several journals including Journal of Hypertension, Blood Pressure, Hypertension and The Journal of Human Hypertension. In addition, he was President of the Spanish Hypertension Society and Chairman of the 16th European Society on Hypertension in Madrid. Between 1998 and 2009, Dr Rulope was a member of the Scientific Committee of the European Society of Cardiology. He is also an International Fellow of the Council for High Blood Pressure Research and the Council of the Kidney in CV Disease for the American Heart Association.

ABSTRACT
Clinical evidence is required in order to develop guidelines of treatment in different areas in medicine. In CV disease evidence is usually based in trials where differences in outcome is obtained while comparing different therapeutic attitudes. In the particular case of arterial hypertension, evidence was firstly obtained in studies where active therapy was compared to placebo and later obtained comparing different therapies in most cases monotherapies. Nowadays an adequate risk stratification is required to initiate the adequate type of therapy which will always consist of an adequate life-style accompanied by physical activity and who required by pharmacological therapy. This scheme is used by the ESH-ESC Guidelines for the treatment of hypertension and contributes to facilitate not only BP control but also the correction of the very frequently associated CV risk factors other than elevated BP.

References-
2- Zanchetti A. Bottom BP or bottom CV risk? How far can CV risk be reduced. J Hypertens 2009, 27: 1509-1520

The challenge of designing a biomarker trial.

Faiez ZANNAD, Nancy – FRA

Biomarker guided therapy: Trial design and interpretation issues

Kirkwood ADAMS (Chapell Hill, USA)

Debate: Design of biomarkers for cardiovascular trials

The industry viewpoint

Ursula-Henrike WIENHUES-THELEN, Roche Diagnostics – GER

Ursula-Henrike Wienhues-Theelen’s background is a molecular biologist. She obtained her PhD in the Institute of Genetics at the University of Cologne. After a three years postdoctoral fellowship in the Institute of Physiology at the University of Munich she moved to the R&D Department of Boehringer Mannheim Diagnostics, thereafter Roche Diagnostics in Penzberg. She is now involved as a senior scientist in the early assessment of novel diagnostic marker candidates.

ABSTRACT
Recent progress yielded in the availability of large databases as tools for biomarker identification. Several transcriptomic and proteomic profiling experiments concern progressive heart failure. Targeted biomarker extraction to filter candidates for development of assays for CV trials is discussed.

LIST OF SUGGESTED READINGS:
Circ Res 2006 (98) 309
J Am Coll Cardiol 2006 (48) 1733
Molecular and Cellular Proteomics 2008 (7.3) S20
The regulator viewpoint

Bruno FLAMION, European Medicines Agency-EMEA, Brussels – BEL

Bruno Flamion, MD, PhD, is a Belgian national. He graduated from the Medical School of the University of Brussels and specialized in internal medicine and nephrology, then obtained a PhD in Physiological Sciences in 1992 and worked at the National Institutes of Health (USA) in Bethesda, MD, between 1998 and 1999 and for the Belgian National Fund for Scientific Research, 1992-1996. He is now Full Professor in Physiology and Pharmacology at the University of Namur, Belgium where he heads the Laboratory of Physiology and Pharmacology. His main research interest is in hyaluronidases.

Since 1999 Bruno Flamion has been a medical and pharmacological expert for what has become the Belgian Federal Agency for Medicinal and Health Products (FAMHP). At the European Medicines Agency (EMEA) in London, he has been a member of the CHMP, the Efficacy Working Party and the Pharmacogenetics Working Party, as well as vicechairman of the new Committee for Advanced Therapies (CAT) which started its activities in January 2009.

Bruno Flamion was appointed chairman of the Scientific Advice Working Party (SAWP) of the CHMP in April 2005 and was reelected in April 2008 for another 3-year term. Through SAWP, the CHMP gives more than 300 scientific advices per year to large and small companies on drug development in all therapeutic areas.

Bruno Flamion is also a member of the Regulations Advisory Board of the Centre for Medicines Research (CMR), International Institute for Regulatory Science. His continued activities in basic research and teaching make Bruno Flamion a strong supporter of increased scientific interactions between pharma leaders, regulatory bodies and the academia.

Friday December 4th, 2009, 9.00 am – 12.00 am

PLENARY SESSION

Targeting the aldosterone pathway

Chairpersons: Aldo Maggioni, Mihai Gheorghiade

Aldosterone: a culprit hormone in cardiovascular disease

Johann BAUERSACHS, Wurzburg – GER

Medizinische Klinik und Poliklinik I Universitätsklinikum Würzburg

Josef-Schneider-Str. 2, 97080 Würzburg

E-Mail: jbauersachs@medizin.uni-wuerzburg.de

Curriculum vitae

13.12.1993 Thesis (M.D.) at the University of Freiburg, Department of Physiology

1993-1995 Residency and Fellowship in Internal Medicine, University Hospital Frankfurt

1995-1996 Postdoctoral / Research Associate, Center of Physiology, University of Frankfurt

1996-1999 Residency and Fellowship in Internal Medicine, University Hospital Mannheim

1999-2003 Residency and Fellowship in Internal Medicine and Cardiology, Department of Medicine, University of Würzburg

1999-2004 Scientific Secretary DFG Special Research Program SFB 355

23.06.00 Board of Internal Medicine Certification

2001 Habilitation, Member of the Faculty, senior lecturer, Dept. of Medicine, Division of Cardiology, University of Würzburg

31.01.2002 Board of Cardiology Certification

since 2003 Consultant Internal Medicine/Cardiology, University Hospital Würzburg

since 2006 Scientific Secretary DFG Special Research Program SFB 688

since 2008 Associate Professor, Dept. of Medicine, Division of Cardiology, University Hospital Würzburg

Special achievements/honors

2001 Oskar-Lapp- Award of the „Deutsche Gesellschaft für Kardiologie”

2004 Albert-Fraenkel- Award of the „Deutsche Gesellschaft für Kardiologie”

2006 Parmley-Award of the American College of Cardiology

ABSTRACT

Activation of the renin-angiotensin-aldosterone system plays an important role in the pathogenesis of cardiovascular disease. High levels of aldosterone impair cardiac and vascular function and predict mortality risk of patients with acute myocardial infarction or heart failure. Patients with primary hyperaldosteronism display a higher incidence of myocardial infarction and stroke. Large clinical trials (RALES, EPHESUS) have shown mineralocorticoid receptor (MR) blockade to decrease mortality in heart failure with reduced ejection fraction (Greenberg et al., 2006). While numerous studies suggest that MR blockade is also effective in heart failure with preserved ejection fraction, definitive evidence will come from ongoing randomised, placebo-controlled studies. In a large proportion of patients with resistant hypertension MR blockade reduces blood pressure even in the absence of primary hyperaldosteronism (de Souza et al., 2009).

In contrast to the classical notion that mineralocorticoids were only involved in body electrolyte and water homeostasis mediated by the kidney, aldosterone exerts important direct (patho)physiological effects on the cardiovascular system. MR expression has been repeatedly documented in cardiovascular cells such as cardiomyocytes, cardiac fibroblasts, endothelial cells and smooth muscle cells leading to cardiac hypertrophy, fibrosis and vascular injury. MR expression in the heart is increased in heart failure explaining detrimental effects of aldosterone even in the absence of markedly elevated circulating levels of aldosterone. MR activation increases cardiomyocyte as well as vascular endothelial and smooth muscle cell reactive oxygen species formation (Lombes et al., 1995; Fracarollo et al., 2003).

Under certain pathophysiological circumstances, also glucocorticoids may act...
as agonists on the MR (Mihailidou et al., 2009). In the Würzburg heart failure registry including consecutive heart failure patients with either preserved or reduced LV function, higher serum levels of both cortisol and aldosterone were independent predictors of increased mortality risk controlling complementary and incremental prognostic value. (Guder et al., 2007). The predictive value of cortisol in heart failure has recently been confirmed by Yamaji et al. (Yamaji et al., 2009).

Evidence has also been accumulated linking aldosterone levels/MR activation to the metabolic syndrome and its single components, especially abdominal obesity and insulin resistance, which may be driven by renin-independent stimulation of aldosterone secretion (Guo et al., 2008; Sowers et al., 2009).

LIST OF SUGGESTED READINGS


Which is to blame? Is it aldosterone or mineralocorticoid receptor activation?

Frederic JAISSER, Paris – FRA

Frédéric Jaisser is Research Director at the Unit 872 of INSERM (Institut National de la santé et de la Recherche Médicale). He is Professor at the Faculty of Medicine of REIMS where he coordinates different courses such as Animal Models and Physiopathological Mechanisms. He is MD, specialist in Nephrology, has a University degree in Biological and Medical Engineering. He joined the INSERM in 1996. His fields of expertise are mainly renal and cardiovascular pathophysiology, development of transgenic or animal models for pathophysiological studies of human disease models, mainly in the field of aldosterone pathophysiology. He is also the coordinator of several multicentric projects. He is an Editorial Board Member of Endocrinology and an expert for several others peer-review journals such as Circulation or Hypertension. He is currently the President of ESAC-France (European Section of the Aldosterone Council).

Pharmacology of agents interfering with the aldosterone pathways.

Michel AZIZI, Paris – FRA

Dr Azizi received his MD from René Descartes University and his PhD from Pierre et Marie Curie University, Paris, France. He is Professor in Vascular Medicine in Paris Descartes University and Head of the Clinical Investigation Center at the Hôpital Épiphané Georges Pompidou of Paris. Dr Azizi was member of the Clinical Research Commission of INSERM (Institut National de la Santé et de la Recherche Médicale) and of AFPH (Assistance Publique des Hôpitaux de Paris) until 2008. He has received the Jean Hamburger prize for Medical Research in 2007. His main research interests include the physiology, genetics and pharmacology of the renin-angiotensin-aldosterone system, and of the haematological peptide, AcSDKP. Dr Azizi is a member of the French Society of Cardiology and of the European Society of Hypertension. He has published more than 100 papers in peer reviewed journals.

Selected publications:

ABSTRACT

Up to now, blockade of the biological effects of aldosterone has been achieved with the two available mineralocorticoid receptor (MR) antagonists, spironolactone and eplerenone which are effective in the treatment of congestive heart failure, proteinuric nephropathies and hypertension. Both drugs are especially effective in those forms of hypertension where aldosterone is the main participant, such as in primary hyperaldosteronism, low-renin hypertension, and resistant hypertension. Their use may however be limited by two facts. First, spironolactone has a low tolerance profile as long term treatment with is associated with a large, dose-related incidence of gynecomastia in males, sexual dysfunction and menstrual irregularities that is not shared by eplerenone at marketed doses. Second, both drugs induce a counter-regulatory rise in plasma renin and aldosterone concentrations which may limit the efficacy of MR blockade and stimulate the MR-independent effects of aldosterone. Aldosterone synthase inhibition has thus emerged as a new option aiming at decreasing hormone concentrations in both plasma and tissues and consequently at reducing both MR-dependent and –independent effects at the level of the renal epithelial cells and other target organs. The consequences of this very specific and targeted pharmacological approach have not yet been tested in humans, although the use of various adrenal inhibitors of steroidogenesis, such as aminogluthethimide (P450 side chain cleavage enzyme inhibitor), metapyrone (11β hydroxylase inhibitor) and triostane (3 ß hydroxysteroid dehydrogenase inhibitor) has been reported in small series of hypertensive patients with or without primary aldosteronism. These drugs have potential safety drawbacks due to inhibition of early steps of steroidogenesis involved in both the glucocorticoid and mineralocorticoid axis and are usually not efficient in controlling BP in the long-term. More recently, the availability of facao, an aromatase inhibitor with inhibitory properties against 11 ß-hydroxylase and corticosterone methyloxidase type II enzymes and its dextroenantiomer, in animal models have shown that the neutralization of aldosterone’s effects with its beneficial consequences is achievable by two different methods: the inhibition of its synthesis and the blockade of its action at the receptor level, as it has become shown with the aldosterone synthase inhibition and angiotensin II antagonism. New drugs derived from the initial structure
of FAD286A are currently under development. When available for human use, aldosterone synthase inhibitors by specifically decreasing aldosterone exposure should contribute for neutralizing on the long term the genomic and non-genomic direct effects of aldosterone at the level of the heart, the blood vessels and the kidneys.

LIST OF SUGGESTED READINGS


Friday December 4th, 2009, 9.00 am – 12.00 am

Cardiovascular Clinical Trials
Going Global

Chairpersons: Felipe Martinez, Jean Morgan

Felipe MARTINEZ, Cordoba – ARG

POSITIONS
-Professor of Medicine, Cordoba National University (since 1994)
-Director, Instituto Damic and Fundacion Rusculleda. (since 1993)

OUTSTANDING ACHIEVEMENTS
-Former President, Argentinean Federation of Cardiology (2002-2003)
-Co Chairman, Scientific Program, World Congress of Cardiology (2008)

-Advisor to Argentina International Society of Cardiovascular Pharmacology (since 2007)

SCIENTIFIC SOCIETIES/ COMETEES
-Board Member, World Heart Failure Society
-Fellow, American College of Cardiology
-Member of 16 Steering Com. Of International Trials

SCIENTIFIC ACTIVITIES
-Publications 129

Jean MORGAN, Quintiles

Jean received her undergraduate degree (Health Information Management) from Cumberland College of Health Sciences in Sydney Australia and her post graduate diploma in marketing from the University of Technology, Sydney Australia. Her career started as a data manager, running clinical trials at the Royal North Shore Hospital Radiation Oncology Unit in Sydney prior to moving over to work in the pharmaceutical industry as a clinical research manager.

After several years working in clinical research for Pharmacia and Lederle, Jean joined Quintiles in 1993. Working in Australia as well as Asia, Jean has personally managed or had senior oversight of clinical trials across a diverse range of therapeutic areas including oncology, cardiovascular, infectious diseases, rheumatology and respiratory medicine. Currently Jean is Vice President in the Cardiovascular & Diabetes Unit where she is responsible for project oversight and delivery for projects.

Jean received her undergraduate degree (Health Information Management) from Cumberland College of Health Sciences in Sydney Australia and her post graduate diploma in marketing from the University of Technology, Sydney Australia. Her career started as a data manager, running clinical trials at the Royal North Shore Hospital Radiation Oncology Unit in Sydney prior to moving over to work in the pharmaceutical industry as a clinical research manager. After several years working in clinical research for Pharmacia and Lederle, Jean joined Quintiles in 1993. Working in Australia as well as Asia, Jean has personally managed or had senior oversight of clinical trials across a diverse range of therapeutic areas including oncology, cardiovascular, infectious diseases, rheumatology and respiratory medicine. Currently Jean is Vice President in the Cardiovascular & Diabetes Unit where she is responsible for project oversight and delivery for projects.

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Overview of International cardiovascular clinical Trials and Current regulatory requirements for clinical trials in Russia and Ukraine

Vladimir POPOV, Moscow – RUS

Vladimir Popov MD, Dr Sc Med Leading Researcher of Cardiology Department, Moscow Medical Academy named after I.M. Sechenov, Head of Clinical Pharmacology, Central Hospital No. 6 of Russian Railways JSC, Moscow, Russia

Dr Popov was awarded an MD with an honorary degree, a Master of Internal Medicine and PhD in Cardiology by the Kharkiv State Medical University, Ukraine. In 2007 he was awarded an Dr Sc Med in Cardiology by the Moscow University of Medicine and Dentistry.

He completed postgraduate training in Clinical Pharmacology and Internal Medicine at the Russian Medical Academy in Moscow.
Dr. Popov has over 15 years of experience in cardiovascular multinational clinical trials, in roles as a co-investigator, principal investigator and project leader.

Dr. Popov is a recognized leader in cardiovascular drug research and development. He has coordinated national and international clinical trials in the following therapeutic areas: Hypertension, CHF, Angina, Pulmonary Arterial Hypertension.

He is Active Member of the Cardiovascular Pharmacology and Drug Therapy working group of the European Society of Cardiology, the British Association of Research Quality Assurance (BARQA GCP), and of the Russian Society of Pharmacoeconomics and Outcome Research (RSPQR). Scientific Expert of Romualdo Del Bianco Foundation, Florence, Italy.

He has published more than 140 articles and abstracts, directed numerous symposia, and co-authored 3 books.

ABSTRACT

More and more industry-sponsored cardiovascular clinical trials (CVCTs) are conducted in emerging regions, especially in Russia and Ukraine. At the moment cardiovascular diseases represent the widely spread pathology in the structure of common morbidity and mortality in Ukraine and Russia. According to the recent data (2008) the general mortality rate due to cardiovascular diseases is 66.1 % in Ukraine and 56.6 % in Russia.

The aim of the presentation is to review the development of CVCTs and regulatory requirements for clinical trials in Russia and Ukraine over the last years.

Data from the US clinical trials register (www.ClinicalTrials.gov on the 1st of November 2009) and Federal Service on Surveillance in Healthcare and Social Development trials register (www.rozdraznadzor.ru) analyzed to study the magnitude of contribution by Russia and Ukraine to the Global CVCTs arena, based on registered industry sponsored phase I-IV trials.

Over the period from 2005 up to the 3rd quarter of 2009: 342 industry-sponsored CVCTs conducted in Russia. The major contribution to the total number of CVCTs was made by international multi-center phase II-III clinical trials (MCT). Largest number of MCTs conducted in 2007-2008 years (48 and 43 trials, respectively).

Within 5 years, pharmaceutical companies from 23 countries sponsored clinical trials in Russia. International multi-center phase II-III clinical trials in Russia sponsored mainly by the world’s top pharmaceutical or biotech companies. Trials came from the USA – 16 %, Germany – 8 %, France – 8 %, UK – 6 %, Switzerland – 5 % and Japan – 3 %.

Seven phase I trials were initiated over the period 2005-2009, 5 of them in 2008. The number of the Phase II trials made 28% of the all CTs, the peak of the CVCTs was in 2007 (22 CT). The situation with Phase III MCT trials was stable (In 2005 - 22 CVCTs, in 2006 - 31 CVCTs, in 2007 and 2008 – 32 and by the 3rd quarter of 2009 – 24 CVCTs).

It is well known that Russia and Ukraine belong to the world leaders in patient enrollment. The average patients recruitment rate in 2006 exceeded 4.7 patients per site per month. For some indications the figures were 10 times higher than in Western Europe and in the USA. For example for hypertension, this ratio amounted to 10.2. In Phases II-IV CVCTs launched in 2009, 8752 patients have been planned to be enrolled.

According to the analysis of the number of CVCTs sponsored by international companies over the period 2005–2009, the first place took Novartis which had 24 approved studies. Astra Zeneca was the leading company in patients recruitment (6324 patients). Main cardiovascular trials were: Hypertension, Dyslipidemia, Acute coronary syndrome, CHF. By the 1st of November 2009 99 and 42 CVCTs were ongoing in Russia and Ukraine respectively.

Clinical Centers of Excellence leading by the number of trials investigators sites were selected: the Russian Cardiology Scientific Complex (www.cardioweb.ru), the Moscow University of Medicine and Dentistry (www.msmsu.ru) and the State Research Center for Preventive Medicine (www.gnicpm.ru).

Since 1995, the FDA has carried out 36 audits of the activities of Russian clinical study centers. In 50 % of cases no shortcomings has been discovered (no action indicated (NAI)). Seventeen audits resulted in a positive grade (VAI), and only in one case a negative grade was obtained (official action indicated (OAI)).

Middle East and the Arab world, emerging to CardioVacular trials. Cultural, organisational and regulatory aspects

Mohamed SOBHY, Alexandria – EGY

ABSTRACT

Though Egyptian medicine dates from about 2900 B.C, the best-known and most important pharmaceutical record is the “Papyrus Ebers” (1500 B.C.), a collection of 800 rx, mentioning 700 drugs.

In the last 200 years medical research has been hindered in the Middle East yet the Middle East has great potential for clinical trials. The latest epidemiological data on the Middle East shows clearly the evident diversity in the populations type and characters. A number of 14 countries form the Middle East with a total population of 280 million with some of the richest & poorest countries in the world. Each country holds its diversified political, economic and health care environment.

The Middle East has a reasonable pharmaceutical market valued annually at 6 billion dollars in 2006 but this number will increase dramatically in the next 10 years. The reason for that is a dramatic change that is occurring in the epidemiological pattern of disease in most countries of the Middle East.

Changing from the traditional infectious disease to the Non-Communicable Diseases (NCDs) including cardiovascular diseases, diabetes, obesity and cancer. By the year 2020, NCDs are expected to account for 7 out of every 10 deaths in the developing regions compared with less than half today.

Egypt is the biggest country in the Middle East in terms of population (75 million) with 48 % of the population between 15 and 45 years. These current demographics with the increased life expectancy from around 50 in 1960 to around 70 in 2006 and the prevalence of hypertension (30%), diabetes mellitus (7.2%) and hypercholesterolemia (20%) can predict an epidemic of cardiovascular disease in Egypt.

The infrastructure of research in the Middle East needs remedies and this is obvious from the low publication rate yet there is a good foundation to build on in some countries. This foundation is mainly based on well-educated Physicians (Academics, Consultants, etc.) with post graduate experience in Europe or USA, big & diverse patient population covering various disease areas, various ethnic groups (e.g. Expats in Gulf countries), relatively low cost of medical and clinical investigations and university hospitals, institutions and private Hospitals, well equipped, partnering with International Organizations/Reputable Universities.

The culture of the Middle East is quite different from the West in terms of population and patient understanding and acceptance for the concept of clinical trials is not yet established. The patients still are hesitant about there enrollment and there acceptance is mainly based on their believe in there doctor. Patient compliance in follow up visits and adherence to study protocol is pretty good based on previous trials. Within the present culture and understandings the phase III trials will be most easily accepted.

The regulatory aspect ranges in the Middle East from very well established in Jordan to well established in Lebanon and Egypt and a plan to implement new rules in Saudi Arabia. The average approval timelines is about 3-5 months in most countries. There is some regulatory problems as for example the clinical trials law still in evolving phase, and documentation system not well developed and not comprehensive enough.

To some up the Middle East is a promising region for cardiovascular research trials and with proper engagement we can yield very good results. This notion of course will be supported by the performance of the clinical trials already taking place in the Middle East.

Regional Risk Factors and Cardiovascular trials: no influence or high impact?

Felipe MARTINEZ (Cordoba, ARG)

ABSTRACT

Global approach is expanding to Medicine, and the cardiovascular therapeutics are not the exception. Multicentric international trials with new therapeutic interventions are being performed in the five continents. However, baseline characteristics and in many cases regional risk factors are not exactly the same all over the planet. This is the justified interest on the

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It may also be useful for local Public Health Authorities. Trialists to prepare, design and better understand multinational clinical studies. An accurate analysis of such observations may help Cardiologists, and also fever in some areas. cardiovascular system like Chagas, or the still mild incidence of rheumatic disease and heart failure, some "regional" differences appear in Registries with "real world" patients.

Interventions in the RAAS show higher numbers compared with the rest of the world. The opposite is observed with beta blockers and different dosing of statins.

The impact of the above characteristics may result not only in some variation of results, but obviously in drug use for the management of different disorders along the cardiovascular continuum. Despite the recommendations of international guidelines, for the treatment of hypertension, coronary artery disease and heart failure, some "regional" differences appear in Registries with "real world" patients.

Another "Risk factor" is the impact of some endemic diseases affecting the cardiovascular system like Chagas, or the still mild incidence of rheumatic fever in some areas.

An accurate analysis of such observations may help Cardiologists, and also Trialists to prepare, design and better understand multinational clinical studies. It may also be useful for local local Public Health Authorities.

**ABSTRACT**

Sleep provides regular periods of physical and mental rest and covers a large proportion of our life time. Heart rate, cardiac output and vascular resistance decrease during sleep. This physiologic cardiovascular relaxation is disrupted in sleep-disordered breathing (SDB), when frequency and/or depth of breathing are deficient. With a prevalence of up to nine percent, obstructive sleep apnea/hypopnea (OSA) is the most common form of SDB; this condition results from complete or partial collapse of narrowed upper airways. Due to close and complex interrelations between the respiratory and the cardiovascular system sequelae of SDB include hypertension, arrhythmias, atrial enlargement and myocardial hypoxemia and hypertrophy. Postulated pathophysiological mechanisms comprise hemodynamic, neuro-vegetative, immuno-modulatory and metabolic aspects.

Intermittent hypoxemia and increased respiratory work during hyperventilation induce a mismatch between oxygen supply and demand that may impair cardiac function and trigger myocardial remodelling. In this context, OSA is suspected to induce nocturnal symptom onset in acute coronary syndromes as well as nocturnal sudden death. Regarding breathing mechanics, inefficient inspiratory efforts against an occluded pharynx result in abrupt intrathoracic pressure changes which may reach values over 100 mmHg. This translates into substantial increases in transmural left atrial and ventricular pressure and leads to structural and functional cardiac alterations such as wall thickening, diastolic dysfunction and atrial enlargement. In severe SDB, cycles of apnoea and arousal may occur several hundred times per night. The resulting high-amplitude oscillations in central and peripheral sympathetic nerve traffic impact may trigger loss of myocardial contractility, cardiomyocyte apoptosis and necrosis. SDB leads to elevated morning plasma norepinephrine concentrations which contributes to an increased mortality risk. Analogous to ischemia-reperfusion injury, hypoxemia-reoxygenation injury leads to significant oxidative stress. In sleep-apneic cardiovascular patients, production of free radicals in injury, hypoxemia-reoxygenation injury leads to significant oxidative stress. As all these pathophysiological sequelae of SDB contribute cardiovascular risk factors, predispose to heart failure development, SDB per se must which be considered a risk factor. Correspondingly, prevalence of SDB in heart failure populations is high, amounting to 50% or more. While OSA is 4 – 10 times more common in heart failure patients and is frequently diagnosed in earlier disease stages, central sleep apnea/hypopnea (CSA) occurs more...
often in advanced heart failure stages. CSA is caused by a reduced central respiratory drive; its prevalence amounts to 35-66% depending on disease severity. Prevalence in the community is unknown, but is supposed to be rare. Respiration is highly susceptible to PaCO2-changes during sleep, and patients with pulmonary congestion fail to decrease respiratory rate. Relative hyperventilation induces hypocapnia, which attenuates the central respiratory drive thus inducing hyperventilation. Rising PaCO2 levels precipitate another period of compensatory hyperventilation. Alternating periods of hypo- and hyperventilation induce the typical crescendo-decrescendo oscillation of tidal volumes in CSA while the cycle length depends on circulation time.

The multifaceted relations between SDB and cardiovascular diseases seem part of a cardio-sleep-respiratory disease continuum: OSA contributes to cardiovascular disorders which result in cardiac dysfunction and heart failure. Vice versa, heart disease by itself predisposes to CSA. Heart failure as the final common pathway of all cardiovascular diseases represents one of the greatest contemporary socioeconomic challenges. Today, we begin to understand the role of SDB in the cardiologist’s domain, but SDB has remained under-diagnosed in all heart failure stages. Symptom overlap of SDB and heart failure as well as lack of physicians’ awareness may be possible explanations. Although impaired survival rates have been reported for both types of SDB in heart failure, only for OSA evidence-based treatment options are available, and sufficient knowledge about CSA is lacking.

LIST OF SUGGESTED READINGS


Future clinical evidence needs? Design of the SERVE-HF protocol

Luc HITTINGER, Paris – FRA

How to screen and manage patients with SDB in the clinical cardiology routine?

Olaf OLDENBURG, Bad Oeynhausen – GER

PhD, Doz, Dr. med. Olaf Oldenburg studied medicine at the Westfälische Wilhelms University of Münster, Germany and University of Southern California, Los Angeles, USA. He finished his medical thesis with magna cum laude in 1997 in the Department of Cardiology and Angiology of Münster’s medical school. He started his cardiology rotation at the Center of Internal Medicine, Department of Cardiology at the University Hospital Essen, Germany. From 2001 to 2002 he spent 2 years as a post-doctoral fellow in cardiovascular physiology at the University of South Alabama, Mobile, USA. In 2003 he took a position in the department of cardiology at the Heart and Diabetes Center North-Rhine Westphalia, University Hospital, Ruhr-University Bochum, Bad Oeynhausen, Germany. As a senior cardiologist he is the head of cardiorespiratory diseases and sleep-disordered breathing as well as for the heart failure programme at this institution.

ABSTRACT

Sleep-disordered breathing (SDB) is associated with various cardiovascular diseases. By now, not only statistical association but pathophysiological concepts are linking obstructive (OSA) and central sleep apnoea (CSA) to hypertension, arrhythmias and heart failure. For heart failure the prognostic impact has been proven and specific treatment is recommended by current ESC guidelines. Besides an emerging interest, a routine screening of cardiology patients is not adequately established and cardiac patients suffering from SDB are not getting sufficient therapy. Since 2003 we have developed an in hospital screening program using several screening devices. The best experiences we have are achieved by using 6-channel-cardiorespiratory polygraphy devices with software-based analyses and manually review of each recording. With these unattended recordings of our in-hospital patients, a definitive diagnosis and graduation of CSA and OSA is possible. However in ambulatory patients even simpler devices with fully automatically analysis might be used to exclude SDB in most cases. In some cases however, full cardiorespiratory polysomnography is needed to adequately diagnose, characterise and graduate SDB even in cardiology patients. Traditionally, treatment of SDB is initiated by respiratory physicians in most cases. With identification of SDB in patients with severe cardiac diseases like advanced heart failure, a good cooperation of cardiologists and respiratory physicians in daily clinical routine is needed to adequately treat these patients in a reasonable time. However, if such cooperation can not be achieved, cardiologist themselves should take care of their cardiac patients and screen, diagnose and treat these patients themselves.

LIST OF SUGGESTED READINGS


Friday December 4th, 2009, 12.15-1.45 pm

TRANSATLANTIC TRIALISTS

Lunch Roundtable

Non industry sponsored trials and the role of NHLBI and EU public institutions

Chairpersons: Michael Lauer, Faiez Zannad

Michael LAUER, Bethesda – USA

Michael Lauer, MD, FACC, FAHA, joined the National Heart, Lung, and Blood Institute (NHLBI) in July 2007 as Director of the Division of Prevention and Population Science; he now serves as the Director of the Division of Cardiovascular Sciences. A board certified cardiologist, he received his MD from Albany Medical College in 1985 and underwent postgraduate training within the Harvard University system at Massachusetts General Hospital, Boston Beth Israel Hospital, the Harvard Graduate School of Education, and the Harvard School of Public Health. After completing specialized research training in Cardiovascular Epidemiology at the Framingham Heart Study, he joined the cardiovascular medicine staff of the Cleveland Clinic in 1993. During 14 years at the Clinic, he established a world-renowned clinical epidemiology research program with primary focus on diagnostic testing and comparative effectiveness. His research led to over 200 publications in major medical journals (including New England Journal of Medicine, JAMA, Lancet, and Annals of Internal Medicine), grant support from the American Heart Association and the NIH, and election to the American Society of Clinical Investigation. Dr. Lauer has served as Contributing Editor for JAMA, co-Director of the Cleveland Clinic Coronary Care Unit, Director of Cardiac Clinical Research, and as first Vice-Chair of the Cleveland Clinic IRB. He achieved distinction in medical education, leading the development of an award-winning clinical research curriculum at the newly founded Cleveland Clinic Lerner Medical College at Case Western Reserve University, where he was Professor of Medicine, Epidemiology, and Biostatistics. In November, 2008, he was awarded the prestigious Ancel Keys lectureship at the annual meeting of the American Heart Association. In his current position at NHLBI, Dr. Lauer is leading a $1.7 billion per year research division that oversees major programs in cardiovascular biology, translation, clinical research, comparative effectiveness, epidemiology and prevention.

Faiez ZANNAD, Nancy – FRA

Cardiovascular clinical trials under the EU Research Framework Programmes? A good start or a missed opportunity?

National Heart Lung and Blood Institute cardiovascular drug trials – future directions?

Michael DOMANSKI, Bethesda – USA
Friday December 4th, 2009, 12.15- 1.45 pm

MEET AND EAT WITH THE EXPERTS (2)

Management of atrial fibrillation: Trials that are rapidly changing the landscape

Chairpersons: Dan Atar, Karl Swedberg

Dan ATAR, Oslo – NOR
Professor and Head of Cardiology, Oslo University Hospital, Aker University of Oslo, Norway. Email: dan.atar@online.no

Dan Atar, MD, (50) is Head of Cardiology at Oslo University Hospital Aker, Oslo, Norway, and holds a full Professorship in Cardiology at the University of Oslo, Norway, along with a Visiting Associate Professorship in the Johns Hopkins University, Baltimore, Maryland, USA.

Dan Atar trained in Denmark, Switzerland, and the United States before receiving his board certification in Internal Medicine and Cardiology in 1996. His research focuses on myocardial biomarkers, myocardial function, heart failure and cardiovascular pharmacology. He has written >100 articles and book chapters and holds the fellowship-titles FESC, FACC, and inaugural FAHA. Dan Atar is the past-Chairman of the ESC Working Group-3 (Cardiovascular Pharmacology and Drug Therapy), and Associate Editor of the international peer-reviewed journal “Cardiology” (Karger). He was on the writing committee for the 2007 ESC “Cardiovascular Disease Prevention Guideline” and the 2008 ESC “Guideline on acute and chronic Heart Failure”, and serves on the “2010 ESC Guideline on Atrial Fibrillation”, as well as the ESC/AHA/ACC guideline “New Definition of Myocardial Infarction”. He was chairing the FIRE-Trial, a multicenter study in patients with STEMI to reduce ischemia/reperfusion injury, published in 2009.

Will new drugs and new trials shift the rate vs. rhythm control paradigm (Dronedarone, Vernakalant)?

Gunter BREITHARDT, Münster – GER

New anti-thrombotic trials in atrial fibrillation (RE-LY) and possible consequence on anti-thrombotic strategies.

Greg LIP Birmingham – GBR

Professor Lip is an academic clinical cardiologist based in a busy city centre teaching hospital, and leads a large multidisciplinary research group (including clinical and laboratory-based components) at the Centre for Cardiovascular Sciences, University of Birmingham (United Kingdom), where he is Professor of Cardiovascular Medicine. He is also Visiting Professor of Haemostasis, Thrombosis, and Vascular Science in the School of Life & Health Sciences at the University of Aston in Birmingham (United Kingdom).

Half of his time is spent as a clinician, and he practises the full range of cardiovascular medicine, including outpatient clinics (with large atrial fibrillation and hypertension specialist clinics) and coronary care units. He also undertakes coronary intervention, and assists in a 24/7 primary angioplasty rota for ST elevation MIs.

As an academic, he provides strategy and research direction for his group, with many local/national/international collaborations in progress. He has been involved in national and international guidelines and working groups (see later section), mostly at European level.

Professor Lip sits on the cardiovascular research strategy committee of the university, and has taught/examined at undergraduate/postgraduate level both nationally and internationally. More recently, he has been external examiner to the University of Hong Kong and University Putra Malaysia.

Professor Lip is a member of the scientific documents committee of the European Heart Rhythm Association (EHRA), and serves on the board of the Working Group on Hypertension of the Heart of the European Society of Cardiology (ESC). He is a member of the Working Groups of Thrombosis and Cardiovascular Pharmacology of the ESC. He is also a member of EHRA and the European Association of Percutaneous Coronary Revascularisation.

Professor Lip has acted as Clinical Adviser for the UK National Institute for Health & Clinical Excellence (NICE) guidelines on atrial fibrillation (AF) management. He was on the writing committee for the 8th American College of Chest Physicians (ACCP) Antithrombotic Therapy Guidelines for Atrial Fibrillation, as well as various guidelines and/or position statements from EHRA including the EHRA statement on defining endpoints for AF management. EHRA guidelines for antithrombotic therapy during ablation. He has acted as peer reviewer for recent ESC guidelines e.g. on cardiac resynchronisation therapy, hypertension, ST elevation myocardial infarction, etc. He is currently Chairing an ongoing ESC Task Force writing a Working Group of Thrombosis Position Statement on Antithrombotic therapy use in atrial fibrillation patients presenting with an acute coronary syndrome and/or undergoing percutaneous coronary intervention/ stenting (due 2009). He is also on the writing committee of the next version of the ESC Guidelines on Atrial Fibrillation (due 2010) and will be Deputy Editor for the 9th ACCP guidelines on antithrombotic therapy for AF.

He has acted as senior editor for major international textbooks (e.g. Lip GYH, Hypertension: A comprehensive Guide, Mosby 2007) and section editor on hypertension (e.g. Crawford, DiMarco, Paulus Cardiology – now in 3rd edition), as well as contributed to major textbooks (e.g. the European Textbook of Cardiovascular Medicine (chapter on atrial fibrillation – this serves as the core curriculum for ESC cardiology trainees), Crawford’s Cardiology textbook chapter on atrial fibrillation, etc.

Professor Lip is involved at senior editorial level for major international journals e.g. Journal of Human Hypertension (Editor in Chief), Thrombosis & Haemostasis (Editor in Chief (Clinical Studies) designate), Thrombosis Research (Associate Editor), Europace (Associate Editor), Circulation (Guest Editor), etc.

He has acted as grant peer reviewer for national/international grant giving bodies e.g. Medical Research Council (UK), Hong Kong Research Grants Council, Canadian institutes of Health Research, etc.

Professor Lip has acted as Chairman or served as member of steering committees of major international trials and has also acted as Chairman or member of trial Clinical Events Committees.

ABSTRACT

Atrial fibrillation (AF) is the commonest sustained cardiac rhythm disorder, and is encountered in everyday clinical practice. Irrespective of a rate-control or rhythm-control strategy, stroke prevention with appropriate thromboprophylaxis still remains central to the management of this common arrhythmia. Indeed, AF is also a major contributor to stroke and thromboembolism, but stroke risk is not homogeneous. Thus, a crucial part of AF management requires the appropriate use of thromboprophylaxis. New data from trials such as RE-LY with the oral direct thrombin inhibitor dabigatran, would overcome the limitations of warfarin and allow reexamination of thromboprophylaxis recommendations. High risk patients should have anticoagulation therapy, and are those with previous stroke or thromboembolism and those age ≥75, as well as those with 2 or more of the following risk factors: diabetes, hypertension, age 65-74, heart failure (or moderate-severe left ventricular dysfunction) – and probably, female gender and vascular disease. Low risk patients are those with no risk factors, and treatment with aspirin or no antithrombotic therapy is recommended, given the data for aspirin in this category of patients is poor, with little demonstrable effect on reducing thromboembolism but increasing the risk for bleeding.

Unfortunately, many stroke risk assessment schema classify a large proportion of subjects into the ‘moderate risk’ category where treatment guidelines recommend either oral anticoagulation or aspirin, and only have modest predictive value for thromboembolism. Given the availability of new oral anticoagulant drugs, risk schema need to evolve to be better at identifying the ‘low risk’ category of patients where no antithrombotic therapy may be an option. A simple, novel risk factor based approach involving a simple scoring system (CHA2DS2-VASc; denoting Cardiac failure or dysfunction, Hypertension, Age over 75 years (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65-74 and Sex category (Female)), whereby 2 points are assigned for a history of stroke or transient ischemic attack or age ≥75, 1 point each for age 65-74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque and peripheral...
arterial disease (PAD), including prior revascularization, amputation due to peripheral artery disease or angiographic evidence of peripheral artery disease, etc.) and female gender), demonstrates improvement over previous schemes in identifying high-risk subjects, whilst those designated ‘low risk’ rarely developed thromboembolism and only a small proportion are classified as ‘intermediate risk’.

**LIST OF SUGGESTED READINGS**

Lip GY, Lim HS. Atrial fibrillation and stroke prevention. Lancet Neurol. 2007;6:981-93


Ablation in atrial fibrillation: Reassessing the evidence.

Etienne ALIOT, Nancy – FRA

**Friday December 4th, 2009, 2 pm - 4 pm**

**CVCT EXPERT WORKSHOP**

**Arterial stiffness and central blood pressure as endpoints in hypertension trials**

Chairpersons: Enrico Agabati-Rosei, Luc Van Bortel

Luc VAN BORTEL, Ghent – BEL

Luc Van Bortel studied medicine at Ghent University and specialized in internal medicine and clinical pharmacology. He graduated in tropical medicine at the Institute of Tropical Medicine (Antwerp). As a research fellow he was on mission in Zaire for 2 years. He obtained a Ph.D. in Medicine in 1993. He spent a 6-month intensive collaboration with Prof. dr. M. Safar and S. Laurent at Broussais Hospital Paris (Université Pierre et Marie Curie). For more than 20 years he is involved in research on arterial stiffness and in phase-I clinical drug research. He was associate professor Clinical Pharmacology and Pharmacotherapy at Maastricht University (The Netherlands). From 2000 he is appointed full professor clinical pharmacology and pharmacotherapy at Ghent University (Belgium). He is currently head of Drug Research Unit Ghent, the phase-I drug research unit at Ghent University Hospital and is the leading professor of the hypertension excellence center at Ghent University Hospital. His unit is still involved in arterial stiffness research and has national and international collaboration.

Professor Van Bortel is author/co-author of more than 300 publications in the field of arterial stiffness, quality of life, clinical pharmacology and pharmacotherapy. He is chairman of the Working Group on arterial structure and function of the European Society of Hypertension. He is president of the Belgian Hypertension Committee and is treasurer of the Artery Society. His research team was awarded in 2007 as the best research team on hypertension in Belgium.

Clinical significance of lowering central BP and arterial stiffness.

Athanas BENETOS, Nancy – FRA

Central BP and arterial stiffness as clinical endpoints in large scale trials. Metrological and methodological issues.

Stéphane LAURENT, Paris – FRA

Currently available drugs and new agents that decrease central BP and arterial stiffness. Insight from recent trials

Luc VAN BORTEL, Ghent – BEL

**ABSTRACT**

Objective: To summarize the available evidence from clinical studies and trials for the effect of drugs on arterial stiffness and central blood pressure (cBP) beyond lowering peripheral (brachial) blood pressure (pBP).

Methods: We searched for all-scale clinical trials and studies in humans, accessible through Medline (Pubmed) and hand-searching through cited references. No language restrictions were applied. Data are presented according drug classes in two parts: arterial stiffness and cBP.

Results:

Drug effects on cBP: None of the 4 retrieved studies supported a reduction in cBP beyond pBP with diuretics.
Concerning beta-blockers (BB), 6 studies evaluated atenolol, 1 bisoprolol and 1 nebivolol. Atenolol and bisoprolol seem to decrease pBP more than cBP. This more pronounced effect on pBP with classical BBs was much less with nebivolol which may be related to its vasodilator properties.

In the group of calcium channel blockers (CCBs) 3 studies showed evidence for dihydropyridine CCBs to reduce cBP beyond pBP. These results were also supported by large clinical trials i.e. the CAFE-study.

The majority of studies (8 out of 11) with angiotensin converting enzyme inhibitors showed a reduction in cBP beyond pBP. Three studies showed a neutral effect. In these studies lisinopril, captopril and enalapril were used as ACEI, respectively. Both the CAFE and REASON trials confirmed the effect of ACEIs on cBP.

Two studies with angiotensin receptor blockers (ARBs) studying eprosartan and valsartan supported a reduction in cBP beyond pBP while 2 other studies showed a neutral effect with the ARB eprosartan and telmisartan, respectively. Three studies showed a reduction in cBP beyond pBP with nitrates.

Drug effects on arterial stiffness: A large number of studies have been reported on the effect of different classes of antihypertensive drugs on arterial stiffness. Results of studies with diuretics were heterogeneous. Some studies using spironolactone, indapamide or bendrofluazide showed a decrease in arterial stiffness, while others with hydrochlorothiazide and amiloride did not. The combination diuretic hydrochlorothiazide/amiloride decreased arterial stiffness but less than the ACEI perindopril.

Like diuretics, results on the effect of BBs on arterial stiffness are also quite heterogeneous. Noneselective BBs like propranolol did not improve arterial stiffness, selective beta-1 blockers were not conclusive, while selective beta-1 blockers with vasodilating properties like nebivolol improve arterial stiffness.

The large majority of studies with ACEIs, ARBs, CCBs show that these agents improve arterial stiffness. Based on reports of older studies, the effects of nitrates on large artery stiffness is minimal or absent. As a decrease in blood pressure will decrease passively arterial stiffness, it is not always clear whether the improvement of arterial stiffness with an antihypertensive drug is due to the decrease in blood pressure or whether also a direct effect of the drug on the arterial wall is present.

Conclusions: Overall, it seems that the newer antihypertensive drugs (ACEIs, ARBs, dihydropyridine CCBs and BBs with vasodilating properties) as well as nitrates reduce cBP more than diuretics and classical BBs. Noneselective BBs do not improve arterial stiffness. The effect of beta-1 selective blockers, diuretics and nitrates on arterial stiffness appear to be small or absent. ACEIs, ARBs, CCBs and beta-1 selective BBs with vasodilating properties may improve arterial stiffness.

LIST OF SUGGESTED READINGS

Friday December 4th, 2009, 2 pm - 4 pm
MAIN PLENARY SESSION
Coronary artery disease management: Breaking new grounds with ivabradine
Chairpersons: Philippe G Steg, Ake Hjalmarson

Ake HJALMARSON, Göteborg – SWE
Åke Hjalmarson, M.D., Ph.D, Professor of Cardiology
Born June 21, 1937 In Skövde, Sweden
Swedish Nationality
Education at Göteborg University, M.D. 1968, Ph.D. 1969
Specialist in: Cardiology 1975, Internal Medicine 1980
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Major Research interests: Cardioprotection, Adrenergic regulation and signal transduction; Cardiomypathy and CHF; Beta-blockers; Myocardial receptor autoantibodies
Academic and Professional
1960-1964 Junior Res. Assistant of Physiology, Göteborg Univ.
Positions:
Senior Res. Assistant of Physiology, Göteborg Univ.
Assoc.Professor of Physiology, Göteborg University
Assoc.Professor of Medicine and Physiology, Penn. State University, Hershey, USA
Assoc.Professor of Physiology and Medicine, Göteborg Univ.
1974-1987 Assoc. Professor of Internal Medicine, Göteborg Univ.
Visiting Professor, Div. of Cardiology, Dept.of Medicine
University of California at San Diego, USA
1989- 2003 Professor of Cardiology, Sahlgrenska University Hospital, Göteborg University
Chairman and Head, Institute of Heart and Lung Diseases, Göteborg University
2004-present Professor of Cardiology, Wallenberg Laboratory, Sahlgrenska University Hospital, Göteborg University
Supervisor Ph.D. theses: 30 doctors
Steering Committees: Chairman: Göteborg Metoprolol Trial, MIAMI Trial, MDC Trial, MERIT, CORONA (EC)
Member: RESOLVE, PICO, PRISC I, ACTION
Board Member: Cardcon Ltd, Anatomeica Ltd, A+Science
Number of Publications : 500

Heart rate reduction in clinical practice
Ake HJALMARSON, Göteborg – SWE

ABSTRACT
There is a strong evidence that heart rate has a central role in the pathophysiology of angina pectoris. Elevated heart rate is an independent risk factor and one of the most important predictors of morbidity and mortality in healthy subjects at risk for coronary events and in patients with established coronary artery disease. Furthermore, reduction of elevated heart rate has been found to reduce mortality and morbidity in large placebo-controlled clinical trials of patients with coronary artery disease after myocardial infarction and in those with heart failure. Therefore, measurement of heart rate and reduction of elevated heart rate ought to be part of our daily clinical practice of the management of these patients. There is a consensus about this in our national and international guidelines.

What about the methods of measuring heart rate? There is in fact no clear consensus about this.
In most larger clinical trials it is not stated in the methods how heart rate was recorded. In general it is recorded at rest in supine position from ECG, but the conditions are not strictly standardized (e.g. body position, length of rest, whether free of mental or physical stress, intake of coffee or tea or nicotine for a given time prior to the measurement). Definitions of how to measure heart rate ought be given in guidelines, but for that purpose new studies have to be performed in the target population needing heart rate monitoring. One such study is the so-called REALITY in Sweden ( [the current state of Angina treatment in outpatient popuLation and heart rate monitoring survey). Despite the strong evidence of symptomatic and prognostic benefits of heart rate reduction such treatments are widely underutilized in clinical practice. In the European Heart Survey study (1) 3,779 patients with stable angina pectoris were enrolled in 35 countries. The average resting heart rate was 73 beats/min (similar to the BEAUTIFUL trial), 67% of the patients were on betablockers but the dose was only 45% of that used in the large clinical trials. Similar observations were made in the Danish National Registry study (2) of 55,315 patients who survived 30 days after myocardial infarction, 58% received a betablocker at discharge at a dose less than 50% of that in the clinical trials. These facts point to the need to investigate alternative strategies such as new combination therapies including selective sinus node inhibitors.

The BEAUTIFUL trial (3) strongly supports the view that despite the present clinical use of betablockers at low dose (87% in BEAUTIFUL) a high proportion of the patients with stable angina pectoris have resting heart rate >70 beats/min. These patients have a higher morbidity and mortality than those with lower heart rates. Beneficial results on new coronary events were seen when adding ivabradine to further reduce heart rate in these patients.

In conclusion, heart rate should be carefully measured and monitored in patients with coronary artery disease to reduce angina symptoms and improve prognosis. Strong efforts should be made to lower resting heart rate to <70 beats/min in all such patients by using betablockers and ivabradine in combination.

References:

New results with Ivabradine

Jeffrey BORER, New York – USA

Jeffrey S. Borer, M.D., is Professor and Chairman, Department of Medicine and Chief, Division of Cardiovascular Medicine, at the State University of New York Downstate Medical Center and College of Medicine in New York City. He is also Director of The Howard Gilman Institute for Heart Valve Disease and of the Cardiovascular Translational Research Institute at Downstate. Dr. Borer received his BA from Harvard, his M.D. from Cornell and trained at the Massachusetts General Hospital. He spent 7 years in the Cardiology Branch of the NHLBI at the NIH and a year at Guy’s Hospital in London as a Senior Fulbright Hays Scholar, where he completed the first clinical demonstration of the utility of nitroglycerin in acute myocardial infarction, after previously performing the enabling animal studies at the NIH. Upon returning to the NIH, he developed stress radionuclide cineangiography, for the first time allowing non-invasive assessment of cardiac function with exercise. He then returned to Cornell for 30 years, where he developed prognostic standards for regurgitant valve diseases and explored the cellular and molecular biology myocardial dysfunction in valve diseases, while also assessing the role of heart rate modification in treating coronary disease and heart failure. This work now is being continued at SUNY Downstate. He has been an Advisor to the USDa for 32 years, having Chaired the CardioRenal Advisory Committee for 3 terms; most recently, he Chaired the Cardiovascular Devices Advisory Committee. He is President of the Heart Valve Society of America and has served on the Board of Governors/Trustees of multiple local and national professional societies. Dr. Borer has published 400 scientific papers and 4 books, edits the journal, Cardiology, and has received several awards and other recognitions, including the Public Service Medal of the U.S. National Aeronautics and Space Administration.

ABSTRACT

Several descriptors (“risk markers”) can facilitate identification of persons likely to develop coronary artery disease (CAD) or, if already afflicted, to suffer cardiovascular death or other coronary events. Among these is heart rate, for which a large body of epidemiological evidence has demonstrated an association with cardiovascular and total mortality in the general population as well as in patients with CAD. The pathophysiological importance of heart rate in CAD is well known. When CAD is present, heart rate is a critical factor in the generation of ischemia. Experimental data and clinical observations suggest that heart rate also is involved in the pathogenesis of atherosclerosis and plaque rupture. Indeed, a growing body of evidence supports resting heart rate not only as a risk marker but as a risk factor, i.e., a characteristic that, if modulated, is likely to be associated with modulation of the disease manifestations. This may be true for populations with several different types of cardiac disease. However, the evidence is strongest for patients with CAD in that alteration in heart rate now seems to beneficially alter some outcomes in such patients.

The relationship between resting heart rate and cardiovascular mortality in this patient group is strong, graded and independent of other factors such as blood pressure and physical activity.

The results of the recent randomized, controlled BEAUTIFUL (morBidity-mortality EvAhuaLon of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) study underline the importance of heart rate reduction in managing stable coronary disease. Prospective analysis of data from the placebo arm indicate that resting heart rate >70 bpm is a strong independent predictor of adverse clinical outcome, ivabradine, a selective If current blocker and, hence, heart rate slowing agents, significantly improved coronary outcomes in patients with heart rate >70 bpm. Recently presented data in patients with stable CAD enrolled in the TNT trial (Treating to New Targets) have confirmed that heart rate >70 bpm predicts major cardiovascular events. These data, taken together, support consideration of heart rate in defining risk and guiding therapy in patients with CAD.

LIST OF SUGGESTED READINGS


Borer JS, Tardif J-C. Efficacy of ivabradine, a selective If inhibitor, in diabetic patients with chronic stable angina, American Journal of Cardiology, 2009, in press.

Coronary artery disease management: A step further with ivabradine

Philippe G STEG, Paris – FRA

6th Global CardioVascular Clinical Trialists Forum • Paris 2009
MAIN PLENARY SESSION
The future of anti-thrombotic therapy in coronary syndromes at the acute and post-acute phases
Chairpersons: Nicolas Danchin, Dan Atar

Nicolas DANCHIN, Paris – FRA
Nicolas DANCHIN, M.D., F.E.S.C., F.A.C.C., is a Professor of Medicine, Consultant Cardiologist and Head of the Department of coronary artery disease and intensive cardiac care at Hôpital Européen Georges Pompidou in Paris, France. He has a special interest in coronary artery disease, its treatment modalities including interventional cardiology and its prevention, and has written extensively on these and related topics. He is currently President of the French Society of Cardiology, consultant for the French Drug Agency, and a former member of the Scientific Committee of the French National Health Insurance Authority (CNAM). He also co-chairs Task Force 1 of the Cardiovascular Round Table of the European Society of Cardiology. He edits the Annales de Cardiologie et Angéiologie and Consensus Cardio and is on the Editorial board of Heart and ACCEL. To date, he has published more than 300 papers in peer-reviewed journals.

The pharmacology of modern anti-thrombotic drugs: how to maximise the benefit-to-bleed risk ratio?
Tabassome SIMON, Paris – FRA

Resistance to antiplatelet agents: biological fantasy or clinical reality?
Gilles MONTALESCOT, Paris – FRA
Gilles Montalescot is Professor of Cardiology at Pitié-Salpêtrière Hospital in Paris, France where he heads the Cardiac Care Unit. He is a practicing Interventional Cardiologist and has extensive experience in basic and clinical research. He is the director of the INSERM research Unit U856 on Thrombosis.

Dr Montalescot has been an investigator for many of the new drugs developed in the past fifteen years as well as for many of the new interventional technologies. Dr. Montalescot is a senior scientist and has been the national coordinator of many international trials and the chairman of several national or international randomized trials including ADMIRAL, ARMADA, ALBION, STREEPE, ARCHIPELAGO, ABOARD, ACAPULCO and the ongoing AMERICA, ATOLL, ARCTIC and ALBATROSS trials.

Dr Montalescot is an active member of several organizations with a major interest in education and research in thromboembolic diseases. He has been the chairman of the working group on Thrombosis of the French Society of Cardiology and a nucleus member of the Working Group on Thrombosis and Platelets of the European Society of Cardiology. He has served on several task force committees on antithrombotic drugs and acute coronary syndromes. Dr Montalescot has received several awards in his country including the J. Valade Prize from the Fondation de France and the J. Escalle award from the National Academy of Medicine. He is a member of the editorial board of the European Heart Journal and has published over 250 peer-reviewed articles in journals such as The NEJM, JAMA, Lancet, Circulation, ATVB and Circulation Research. He has also numerous international invited lectures to his credit.

How the results of the most recent trials will change the anti-thrombotic strategy in acute coronary syndromes?
Nicolas DANCHIN, Paris – FRA

Post acute coronary syndromes. Risk and management of anti-thrombotic therapy in the ambulatory patient.
Philippe Gabriel STEG, Paris – FRA
Prof. Metra is author of 175 articles in peer-reviewed journals (total impact 14-17, 2008. with Prof. Dickstein of the 2008 meeting of the HFA of ESC, held in Milan in June 

executive board from 2004 to 2006. He has also been a member of the ESC’s 

of Cardiology (ESC) from 2001 to 2008, Prof. Metra served as secretary of the 

and member of the executive committee of the RELAX-HF trial, assessing the 

(10.2, 20, or 30 mg/day) administrated as 4-hour infusions for 3 days in addition to iv loop diuretics. Compared with placebo, rololfylline resulted in trends towards greater proportions of patients with marked or moderately improved dyspnoea and fewer patients with worsening HF and/or renal function.3 This trial is the foundation of the PROTECT trial. The PROTECT trial was aimed at the assessment of the effects of rololfylline, compared to placebo, on symptoms and 60-days outcomes in 2033 patients admitted for acute HF with mild to moderate renal dysfunction and elevated natriuretic peptide plasma levels. Patients were randomised 2:1 to rololfylline or placebo at 0-24 hours from admission. The primary endpoint was a 3 category ordered outcome of treatment success, lack of change, or treatment failure. Treatment success was defined as moderate to marked improvement in dyspnoea of both 24 and 48 hours after randomisation in the absence of treatment failure. Treatment failure included any of the following: death; readmission for HF through Day 7, worsening symptoms and/or signs of HF after Day 2 through 7 or discharge with the need for rescue therapy; persistent renal impairment (SCR increase ≥0.3 mg/dl through Day 7 confirmed at Day 14, or initiation of hemofiltration or dialysis through Day 7). No significant difference was found between rololfylline and placebo with regards of the primary end point. Rolofylline was associated with more successes than placebo, but also more failure (odds ratio versus placebo 0.92, 95%CI 0.78, 1.09, p=0.348). The secondary composite endpoint of death or cardiovascular or renal hospitalization occurred in 30.7% of rololfylline patients (25.7% were hospitalized and 8.9% died) and 31.9% of placebo patients (25.6% were hospitalized and 9.5% died), yielding a time to first event hazard ratio of 0.98, 95% CI 0.83-1.17, p=0.86). Rolofylline did not reduce the incidence of renal impairment compared to placebo (15.0% vs 13.7%, respectively, odds ratio versus placebo 1.11, 95% CI 0.85, 1.46; p = 0.44). More patients on rololfylline experienced nervous system disorders, with 11 patients (0.8%) experiencing seizure and 16 patients (1.2%) experiencing stroke on rololfylline, with no patients experiencing seizure and 3 patients (0.5%) experiencing stroke on placebo.)


Friday December 4th, 2009, 4.30 pm – 7 pm

JOINT SESSION
The CardioRenal Forum – European Society of Cardiology (ESC) Working-Group on Pharmacology and Drug Therapy

Optimising Care at the Cardio-Renal Interface

Chairpersons: Alexandre Mebazza, Bengt Fellstrom

Cardiovascular outcomes in chronic kidney disease, Rationale for future clinical trials.
Faiez ZANNAD, Nancy – FRA

Cardiovascular protection trials in end stage renal disease.
Bengt FELLSTROM (Uppsala – SWE)

Clinical trials targeting renal protection in heart failure and cardiovascular disease:

Marco METRA, Brescia – ITA

Marco Metra, MD, Associate Professor of Cardiology, Section on Cardiovascular Diseases, Department of Experimental and Applied Medicine University of Brescia, Brescia, Italy. Prof. Metra is associate professor of cardiology in the Section of Cardiovascular Diseases of the Department of Experimental and Applied Medicine at the University of Parma and Brescia. He was a research associate at the Committee on Clinical Pharmacology of the University of Chicago, Illinois, (Director, Prof. Leon I. Goldberg) United States, in 1985, returning to the University of Brescia the following year as research associate. His research is focused on heart failure, in particular on the functional evaluation of the patient with heart failure, on the role of sympathetic activity and B-blocker therapy, and on the assessment and treatment of acute heart failure.

Prof. Metra was principal investigator in the Studies of Oral Enoximone Therapy in Advanced Heart Chronic Heart Failure (ESSENIAL) trial and is principal investigator and member of the Executive Committee in the ongoing trials PROTECT and REACH-UP, assessing the effects of the selective adenosine A1 receptor antagonist rololfylline on congestion and renal function in hospitalized patients with acute heart failure, volume overload and reduced renal function (PROTECT) or with worsening renal function (REACH-UP) and he is co-chairman and member of the executive committee of the RELAX-HF trial, assessing the vasodilator relaxin in patients with acute heart failure. He was also a member of the steering committees of the COMET (carvedilol or metoprolol European Trial) and VERITAS (Tezosentan in acute heart failure) trials and is a member of the steering committee of the SHIFT and ASCEND-HF trials concerning medical treatment of chronic and acute heart failure, respectively.

A board member of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) from 2001 to 2008, Prof. Metra served as secretary of the executive board from 2004 to 2006. He has also been a member of the ESC’s Committee for Practice Guidelines (years 2004 to 2006), and has cochaired with Prof. Dickstein of the 2008 meeting of the HFA of ESC, held in Milan in June 14-17, 2008. Prof. Metra is author of 175 articles in peer-reviewed journals (total impact factor, 475) as well as of numerous other publications and book chapters.
Selecting the appropriate design

Positive control, placebo-controlled trials vs. non-inferiority head-to-head comparative trials. Which way to go?

Stuart POCOCK, London – GBR

Yasser KHDER, Boehringer Ingelheim – Paris

Yasser KHDER obtained his medical degree and his specialty in internal medicine from Damascus University, Syria in 1987; subsequently he was graduated as specialist in cardiovascular pathology from Nancy Medical School, France in 1992. Between 1992 and 1996 YK had part time activity as a clinical cardiologist. Meanwhile, he also had a part time academic research assignment in the National Institute of Health and Medical Research (INSERM). During this period YK was successfully graduated as a BSc in clinical pharmacology, a MSc in clinical epidemiology, methods in clinical research and a DSc in human biology from the Nancy University, France.

Currently YK is a Scientific Director Cardiology in Boehringer Ingelheim, leading Dabigatran clinical development program in ACS. Beforehand YK worked 7 years in Novartis Pharma AG, Basel, Switzerland as a Diovan® Global Phase IV Leader, Alikesin European Clinical Team Leader, Protocol Review Committee Cardiovascular Scientific Director and Global Program Leader for a NCE in phase 2B.

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

ABSTRACT

Placebo-controlled, superiority trials are the standard approach to evaluate treatment efficacy. They allow controlling for the placebo effect and require the smallest sample size to detect a treatment effect. Wherever possible and justified, they should be considered as the first choice for medical treatment evaluation as, for instance, when there is no proven reference therapy (ISS 2) and when the tested drug is developed as an add-on to the reference therapy (CURE). However, if a standard treatment exists; placebo-controlled trials are ethically unjustifiable, especially in severe disease conditions such as Acute Coronary Syndromes (ACS) where efficacious treatments exist. Active controlled superiority trials comparing the new medical therapy to the reference therapy are ideal when the tested medical therapy is hypothesised to be superior to reference therapy (TRITON, PLATO). Nevertheless, assay sensitivity is so far required for the validity of these active controlled superiority trials.

In several situations the new medical therapy is hypothesised to be equally efficacious to a proven existing therapy but could eventually offer some advantages in terms of safety, fewer side effects, ease of use or price. In these situations active-controlled trials must be used. An active control arm can therefore be used in the phase 2, dose-ranging studies to help for the dose adaptation during the study course, as well as, the dose selection and the decision-making to move to phase 3 (SEPIA-ACS1). In these situations phase 3 studies are designed as non-inferiority trials. Non-inferiority trials are not easy to design, difficult to conduct and often subject to critics. Good historical placebo-controlled trials documenting the efficacy of the reference therapy must exist; the non-inferiority margin has to be carefully justified by robust data from historical placebo-controlled trials. Moreover non-inferiority margin determination should not be only based on statistical criteria; both feasibility 1979 Clinical relevance should also be taken into consideration. Non-inferiority trials have to ensure that the studied population, the backgrounds therapy, the dosing of the reference therapy and the evaluation criteria are consistent with the historical studies used for the determination of the non-inferiority margin (SYNERGY OASIS 5). Adherence to treatment and data quality are particularly important in non-inferiority trials. It is generally accepted that both the intention-to-treat and the per-protocol populations should be used to conclude of non-inferiority. These trials require larger sample size than placebo or active controlled superiority studies especially if the treatment effect size is neutral, however the sample size could be smaller if the tested drug has some efficacy advantage over reference therapy.

Adaptive design. Strengths and limitation

Sidney GOLDSTEIN, Detroit – USA

Mickael DOMANSKI, Bethesda – USA

Defining the appropriate patient population: ACS, AMI, STEMI/NSTEMI: terminology and definition matters.

David MORROW, Boston – USA

Marleen SIMOONS, Rotterdam – NED

Professor and Chief of Cardiology, Thoraxcenter, Erasmus University Rotterdam, The Netherlands

President European Society of Cardiology 2000-2002

Education

1968 doctoral exam. University of Utrecht

1970 arts examen (qualified physician) M.D.

1976 Doctor of Medicine (Ph.D thesis) University of Utrecht

1978 Registration as cardiologist (after training in internal medicine and cardiology at the University Hospital Rotterdam “Dijkzigt” in Rotterdam.)

Appointments

1989 Assistant Professor, Department Physiology Utrecht

1978 Cardiologist Thoraxcenter, Erasmus University, Rotterdam

1989 Professor of intensive cardiac care Erasmus University and University Hospital Rotterdam “Dijkzigt” in Rotterdam.)

1996 Professor of cardiology, Erasmus University and University Hospital Rotterdam “Dijkzigt” in Rotterdam.)

2003 Chief of Cardiology, Chairman Thoraxcenter and Chairman COEUR (cardiovascular research school Erasmus University Rotterdam)

Field of Scholarship

Intensive care and coronary care: in particular treatment of patients with Acute Coronary Syndromes (myocardial infarction), and management of chronic coronary artery disease.

Exercise physiology, exercise testing, and nuclear cardiology.

Computer analysis of electrocardiograms, and ischemia monitoring.

Since more than 20 years Chairman or member of the Steering Committee of national and international clinical trials, particularly related to acute coronary syndromes.
Study drug and comparator drug related issues:, Clinical and Regulatory challenges.

What is the optimal “reference” comparator?
Gregory Yh LIP, Birmingham – GBR

Timing of randomisation/dosing
Gabriel STEG, Paris – FRA
Nicolas DANCHIN, Paris – FRA

Endpoint definition:
Time to first event vs. cumulative events
Torp PEDERSEN, Copenhagen – DEN
Christian Torp-Pedersen, MD, PhD, FACC, FESC
Professor of Internal Medicine, University of Copenhagen. Senior consultant in cardiology, Gentofte Hospital, Copenhagen. Fellow of the American College of Cardiology and Fellow of the European Society of Cardiology. Research has been mainly biochemistry, cardiovascular epidemiology and controlled clinical trials. Principal investigator of the TRACE study, steering committee member and co-designer of the DIAMOND studies. Steering Committee member of more than 10 international studies, currently most notably ATHENA and SCOUT.

Aldo MAGGIONI, Florence – ITA

Composite events

John WARREN, London – GBR
John Warren is a clinical scientist who works for the UK Medicines Healthcare products Regulatory Agency. He is a member of the European Scientific Advice Working Party since 2003. Previous appointments include Clinical Pharmacology at the Royal Postgraduate Medical School and Senior Lecturer at the National Heart and Lung Institute, with Honorary Consultant status at the Brompton, Charing Cross and Chelsea & Westminster Hospitals. He is the author of over 100 publications in international journals on the physiology and pharmacology of the autonomic system and a book on the Endothelium.

Previously on Editorial Board of Microvascular Research and Clinical Pharmacology & Therapeutics.

ABSTRACT
Separate pieces of evidence that are inadequately convincing on their own may become convincing when combined as a composite. Three questions arise from such an approach:

How should the contribution of each component be weighted?
If the composite is positive, how should the components be interpreted in terms of patient risk benefit?
If such an approach is used to assess efficacy, how can a similar approach be used as a balance for safety?
The holy grail of risk benefit assessment is mortality. This is a composite endpoint of deaths from all causes. There is no difficulty in interpretation as convincing evidence that an intervention prolongs life is persuasive for the patient and the prescriber. Death is accurate; there is no need to convene experts to diagnose borderline cases. It is cheap to collect. With investigator persistence, survival data can be obtained for over 99% of trial participants. It can usually be measured at short time intervals, the time of most deaths being recorded within an accuracy of an hour. The merits of all deaths as an endpoint is that it captures the magnitude of efficacy on the target organ as well as the fatal adverse events from any organ malfunction.

Cardiovascular mortality is useful for identifying benefit from therapy where a signal may be detected that is otherwise not significant in terms of all cause mortality. The definition is not simple. Only a minority of deaths undergo post mortem, even then there is no pathology visible to confirm a fatal arrhythmia.

Common cardiovascular composite endpoints are mostly driven by the rate of non-fatal myocardial infarction. This useful endpoint may be strengthened by the addition of stroke and all cause mortality. Ischaemic or haemorrhagic components of stroke are important to mechanisms of action, but total stroke incidence is what matters to the patient.

Cardiovascular disease is the cause of death in 75% of diabetics and this had led to discussions on the role of MACE (Major Adverse Cardiac Events), or other
composites, to evaluate new signals from diabetes therapy. This is an issue particularly suited to discussion at the present meeting. We are used to explaining the life threatening importance of cardiovascular disease, but usually in the absence of convincing all cause mortality benefit. Perhaps it is time to consider specifying this degree of uncertainty in the label. Should all drug labels include a point estimate and 95% CI to answer the question: “It is likely to affect my life expectancy?”

LIST OF SUGGESTED READINGS
3. FDA opinions on muraglitazar, rosiglitazone and ACCORD.

Balancing benefit vs. risk

Edmond ROLAND, MD, FAHA
Edmond ROLAND MD, FAHA
Dr Roland is graduated from the University of Paris, France and board certified in cardiology. After several years of clinical appointment in academic institutions, he joined the pharmaceutical industry and spent several years in the US. As Head of worldwide cardiovascular clinical research, he gained extensive experience in global drug development and international regulatory processes. Since 2001, he has resumed clinical activities. Currently, Dr Roland is an attending cardiologist at the teaching hospital “Hôpital Européen Georges Pompidou” in Paris. He is also a Clinical Expert for the French Agency for Safety of Health Products (afssaps). In addition, he is a member of the EMEA Efficacy Working Party sub-group on cardiovascular issues. The mission of this therapeutic working group is to develop European guidance documents for the clinical development of cardiovascular products. The cardiovascular working group is also providing technical expertise for the EMEA scientific advices.

ABSTRACT
The benefit/risk assessment is a key step in the drug review and approval process. EMEA has developed a structured list of benefit and risk criteria for reviewers to improve transparency and consistency of regulatory decisions. The presentation will discuss the regulatory approach to benefit/risk assessment of antithrombotic drugs in acute coronary syndromes (ACS). Bleeding is the major adverse outcome of antithrombotic drugs and is closely associated with an increase in fatal and non-fatal adverse events. Assessing causality, is however extremely challenging given the complex relationship that exits between bleeding, antithrombotic therapies, ischaemia and invasive procedures.

The issues of composite end-points and sub-group analysis will be discussed through the results of several recent clinical trials in ACS (ACUTITY, TRITON-TIMI 38 and PLATO studies). Composite end-points are often used as primary end-points in the evaluation of benefit/risk. Although composite end-points may increase the event rate and thus the statistical power of the study, they may mislead if component end-points are of widely differing clinical importance to patients, the number of events in the important components is small and the size of effect differs across components. For example, a claim that a therapeutic intervention reduces a composite of cardiovascular death, myocardial infarction, and revascularisation procedures and treatment had a large effect on revascularisation but not on death or infarction. The use of composite primary end-points for efficacy and safety is frequently complicated by gradients in importance to patients and in magnitude of the effect of treatment across component end-points. Higher event rates and larger treatment effects associated with less important components may result in misleading impression of the impact of treatment. Analyses of sub-groups of study patients to evaluate the heterogeneity of treatment effect may provide useful information to select the patient population which would benefit most of the drug. However, sub-group analyses also introduce analytical challenges and can lead to overstated and misleading results.

References
(EMEA/CHMP/EWP/311890/2007)
Wiviott SD, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes
Wallentin L, et al. Ticagrelor versus Clopidogrel in patients with Acute Coronary Syndromes

Gregory Yh LIP, Birmingham – GBR

Interpretation issues:
Statistically significant vs. clinically meaningful results?
“A Statistical Interpretation of Recent Trials”
Stuart POCOCK, London – GBR
Robert CODY, Merck

Robert J. Cody M.B., M.D. is the Global Director for Scientific Affairs, for the cardiovascular therapeutic area, of Merck Research Laboratories, Merck & Co. Prior to joining MRL, and while on leave of absence from the University of Michigan, he was Vice-President for Medical Affairs and Chief Medical Officer of CereX, Inc., a medical device company in Minneapolis, MN. At the University of Michigan Health System, Dr. Cody was Professor of Internal Medicine and served as Associate Chief in the Division of Cardiology, and Director of the Heart Failure & Transplant Management Program. He was a member of numerous Health System committees, and chaired the Medical School Institutional Review Board for several years.

Dr. Cody received his bachelors degree from St. Joseph’s University in Philadelphia, Pennsylvania, his MD degree from Penn State University, and his MBA from the University of Michigan Business School. Dr. Cody completed a residency in Internal Medicine at the Cleveland Clinic Foundation in Cleveland, Ohio, and his cardiovascular training at Massachusetts General Hospital and Harvard Medical School.

Prior to the University of Michigan, Dr. Cody held faculty positions at the Ohio State University Medical Center and Weill Cornell Medical School, New York-Presbyterian Hospitals. For over twenty-five years, his research focused on neurohormonal control factors in heart failure and hypertension, as well as the pathophysiology of heart failure. This included translational research in the renin-angiotensin-aldosterone system, autonomic control of the circulation, natriuretic peptides, and endothelin. Dr. Cody has led the design and monitoring of numerous international clinical trials in heart failure, and has served as chair of numerous DMC’s for international trials. Dr. Cody has authored or co-authored over 250 original research reports, review articles and book chapters. His honors include an Established Investigator Award of the New York Heart Association, and the James H. and Ruth J. Wilson Professor of Cardiology of Ohio State University. He is currently an editorial board member of the American Journal of Cardiology. He is a Fellow of the American College of Physicians, American College of Cardiology, American Heart Association, and the American College of Physician Executives. He serves as a member of the University of Michigan Health System Advisory Group, and the Board of Trustees of the Hunterdon Health System.

Adjudicating issues

Aldo MAGGIONI, Florence – ITA

Gilles DAGENAIS, Quebec – CAN

ABSTRACT

The Data Safety Monitoring Board (DSMB) monitors progress in patient recruitment, protocol compliance and data quality, and provides advice to the principal investigator about the conduct of the trial and integrity of the data to protect the validity and credibility of the trial. In addition, one of its main responsibilities concerns safety of the participants. Indeed, the DSMB should help to ensure the overall safety of participants in the trial by protecting them from avoidable harm.1, 2

For its meetings, the DSMB receives the data to monitor recruitment, compliance, data quality, adverse events and the outcomes of the study. Some of the outcomes are adjudicated and others are not. Which data should the DSMB see? What are the issues regarding adjudicating cardiovascular outcomes? The presentation will attempt to answer these two questions and will be highlighted with some examples

To fulfill its responsibilities, the DSMB should see the adjudicated and non-adjudicated outcomes. For example, in a trial evaluating warfarin with and without antiplatelet agents, the risk of hemorrhagic and non-hemorrhagic strokes in an old population is high. In such a trial, the DSMB needs most of the strokes adjudicated based on imaging for the safety of the participants and efficacy of the intervention. The DSMB may recommend priority in adjudicating strokes if there is some delay in adjudicating such outcomes.

An example showing some issues in adjudicating is a trial in high-risk patients with hospitalization for congestive heart failure as one of the main outcomes. Adjudication of such an outcome is not always easy.3 First, nowadays more patients are not hospitalized for such an event; they are treated in outpatient clinics or physicians’ offices. Before the trial begins, the DSMB should highlight this point to the principal investigator because it may have an impact on the estimated number of events. During the trial, several aged participants will be...
hospitalized with heart failure and pneumonia or other major infections, or with heart failure and atrial fibrillation with rapid ventricular response. What is the preponderant outcome causing the hospitalization the pneumonia or the heart failure? The adjudicators will make the call. However, the adjudicators may refute one out of four cases considered by the local investigator to be heart failure. The DSMB members should know this information when they are reviewing the adjudicated and the non-adjudicated data of heart failure. Such information is important for assessing the immediate and estimated efficacy of the intervention on heart failure. Adjudication of other outcomes such as a death and myocardial infarction may also have their issues.4-6

References
2 Damocles Study Group A proposed charter for clinical data monitoring committees: helping them to do their job well Lancet 2005; 365: 711-22.

Unblinding issues
Nancy GELLER, Bethesda – USA
Nancy L. Geller has been the Director of the Office of Biostatistics Research at the National Heart, Lung and Blood Institute of the National Institutes of Health since 1990. She directs a group of 12 statisticians who collaborate in the design, implementation, monitoring and analysis of multicenter clinical trials in heart, lung and blood diseases and sleep disorders. She has been involved in a number of cardiovascular trials, including post-CABG, PEACE, AFFIRM, the Women’s Health Initiative, FREEDOM, ACCORD and COAG, a trial testing genetic dosing of Warfarin. She has research interests in clinical trial methodology, especially in issues of clinical trial design, monitoring and multiplicity, i.e., multiple endpoints and multiple treatment comparisons. She is an Associate Editor of Biometrics and a member of the Editorial Board of Clinical Trials. She is a Fellow of the American Statistical Association and recently was elected 2011 President of the American Statistical Association. She is the winner of the 2009 Janet L. Norwood Award for outstanding achievement by a woman in the statistical sciences.

ABSTRACT
We examine some aspects of blinding of outcome data during the course of a clinical trial, considering trial investigators, the steering/executive committees, the data and safety monitoring committee (DSMC), the trial statistician and the trial sponsor. Views on these topics are strong and diverse and we will give opposing views to the following questions.
1. Should the DSMC be blinded to treatment identification or should they be completely unblinded?
2. Might the trial Executive or Steering Committee see data (such as event rates) that all investigators should not see? Should aggregate biomarker data or process data be revealed to some investigators?
3. Should the sponsor ever see outcome data during the course of a trial? With respect to unblinding outcome data, are government sponsors different from industry sponsors? Can the sponsor separate itself from its fiduciary responsibilities?
4. Is the trial statistician bound by the same rules as other investigators? Should the trial statistician be unblinded to treatment assignment? Should the trial statistician work for the sponsor?

LIST OF SUGGESTED READINGS
5 Lachenbruch, PA and Wasserstein, R. Guest authorship, mortality reporting and integrity in Rosfexis studies reply. Journal of the American Medical Association 300:904.

Stopping rules in adaptive design trials
Methodological issues
Stuart POCOCK, London – GBR
Mickael DOMANSKI, Bethesda – USA

Ethical issues
Sidney GOLDSTEIN, Detroit – USA
David GORDON, Bethesda – USA
Special Assistant for Clinical Studies, DCVS, NHLBI, NIH
Education: 1971 Ph.D., Department of Chemistry, University of Chicago (Thesis: Optical Activity as a Structural Probe in Biological Membranes and Other Particulate Systems – Information and Artifact.)
1973 M.D., University of Chicago Pritzker Medical School
1981 M.P.H., Department of Epidemiology, University of North Carolina, Chapel Hill (Thesis: Dietary Determinants of Plasma Cholesterol Change in the Recruitment Phase of the Lipid Research Clinics Coronary Primary Prevention Trial.)
Major Projects: Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (CPPT)
Cholesterol Reduction in Seniors Program (CRISP) Pilot Study
NHLBI Conference on Cost and Health Implications of Cholesterol Lowering Workshop on Analysis of Cholesterol-Lowering Trials
Anti-hypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT)
Women’s Angiographic Vitamin and Estrogen (WAVE) Trial
Bypass Angioplasty Revascularization Investigations II Diabetes (BARI 2D) Trial
Cell Therapy Network
Advisor Panels
National Cholesterol Education Program Adult Treatment Panel I-II (sex officio)
National Cholesterol Education Program Adult Treatment Panel III Research Interests/Publications
Dr. Gordon has authored or co-authored more than 70 publications in the field of cardiovascular epidemiology and clinical trials. Topics include: The LRC-CPPT, ALLHAT-LLT, and other cholesterol lowering trials. Lead author of LRC collaborative study design and 2nd results paper.
Role of circulating HDL and triglycerides in coronary artery disease.
Seasonal variation in cholesterol.
Exercise ECG testing as a correlate of cardiovascular risk factors and predictor of cardiovascular events.
Meta-analysis of cholesterol trials.
Impact of diet, exercise, and weight on circulating lipids.
Cholesterol in the elderly.
Handling of interim clinical outcome data by DSMCs.
As a graduate student, Dr. Gordon was the primary author of four peer-reviewed publications on optical activity as a structural probe of particulate systems. As an NHLBI post-doctoral fellow, Dr. Gordon was the primary author of four peer-reviewed publications on the isolation and characterization of cytoplasmic actins.

ABSTRACT

The ethical foundation of any clinical trial rests upon a contract between the sponsor and investigators with the patients who volunteer to participate. Patients agree to accept treatment under a protocol that may be more or less efficacious than what they may receive in conventional medical practice and to be subjected to the burden and risk of undergoing research procedures that may not be of direct benefit to them. In return, they may gain access to a new potentially efficacious treatment that may not be available outside the trial and may receive ancillary medical care that might otherwise be unaffordable. But in addition to these direct tangible benefits, many research volunteers have altruistic motives, such as the desire to contribute to scientific knowledge that may lead to treatments that will improve the lives of future patients who will suffer from the same condition, including perhaps the patient’s children or grandchildren. This contract is embodied by the informed consent process, which among other things, guarantees that the trial asks an important scientific question for which there is equipoise, that the trial will be conducted with integrity and rigor that the patients’ risks will be minimized, and that the trial will be terminated if and when the original state of equipoise no longer exists. Adaptive designs were introduced with the intent of making clinical trials more flexible and more efficient, by allowing certain design changes to be reset during the trial based on the results to that point. For example, one might begin with a small sample size (which could detect only a large effect) and then enlarge the trial if the initial effect estimate falls below that threshold. Or similarly, one might extend the follow-up time or increase recruitment into specific subgroups or even change the treatment allocation ratio of treatments based on interim results at pre-specified times. Statistical methods have been developed to preserve type 1 and type 2 error rates when this is done, usually by enriching or stratumizing the trial and allowing for flexible monitoring of results. However, adaptive designs also pose significant issues that may compromise the contract with research participants:

• Fewer patients are exposed to risk.
• Effective treatments become available to the public sooner.
• Resources saved by earlier elimination of ineffective treatments may be redirected to more promising treatments.

While adaptive designs may be useful in certain situations, conventional designs are preferable at least in settings when the major design parameters are adequately known.

LIST OF SUGGESTED READINGS


Regulatory issue

Amin KADI, MFF – Paris

Professional Experiences
From Oct 2003, President Founder and Managing Director of:
• Monitoring Force France • Monitoring Force Maghreb • BiodataForce
• Monitoring Force Tunisia • Monitoring Force Morocco • Med force Consult Algérie

In charge of regulatory submission files and Medical advisor specifically for the Maghreb’s projects
May 2002 – Sept 2003, EuraXi Pharma – Development Director
• Business Development • Development portfolio
• Development process system • Development Maghreb activities
May 00 – Mars 2002, Pharmacia-Head of therapeutic area Cardiology &
• Management of 4 Project manager
• Development of strategic medico-marketing plan to develop sales for two major products in France (190 & 240 MF)
• Development and follow up of a medical studies plan in the glaucoma
• Pricing fields concerning Xalatan
• Launch of phase IV program concerning Celebrex (3000 GPs & 6000 patients) in arthritis
• Medical manager for EPHEMUS study in France (heart failure and hypertension with epiterenone)
• Registry of d’ALDACTONE on heart failure (RALES)
• Medical manager in France and Tunisia for a morbidity-mortality study on the thrombogenesi prophylaxis with patient hospitalized for a medical reason
August 96 – Mars 99, Roche – Project Manager therapeutic area Cardiology
• Medical Manager – phase IV programs: 9 studies concerning mibefradil and 22000 patients, 4500 GPs et 1000 Cardiologists
• Medical Manager of phase III programs on hypertension and heart failure concerning mibefradil
May 99 – May 00, Roche – Head of therapeutic area Cardiology
• Management of 1 Project manager and 3 ‘medecins régionaux’
• Responsible of medical development
• Registry of a new indication of candevial in heart failure treatment in France
Nov 95 – Dec 95, Lypha Sante – Medical responsible for Bretagne
• Follow of medico-marketing local plan: phase IV concerning fosinopril in hypertension and coronary syndrome
• Formation responsibility of fields force
Dec 95 – July 96, Synthelabo – Medical responsible for Ile de France (Region of Paris)
• Follow of medico-marketing local plan: phase IV concerning inipomp on gastric reflux
• Formation responsibility of fields force
Nov 92 – Nov 94, Cardiologists on Intensive care at le Mars hospital
• Coronarography • Echocardiography • Rhythmic Holter
• ETT

Maghreb Experience, 10 studies:
• Heart failure • Thrombogenesi prophylaxis
• Oncology • Parkinson disease • 2 studies in Hypertension • 2 studies with Cox 2 in surgery • 1 study in dyslipidemia
• 1 study in acute coronary syndrome
• Education and Training 1982 – Baccalauréat D
1988 – Medical Doctor diploma 1992 – Cardiology diploma – Université de médecine d’Angers (49)
1993 – Interventional Cardiology diploma – University Paris V
1994 – Echocardiography diploma – University Paris V
1995 – Paediatric cardiology diploma – University Paris V
2000 – HEC Certificate (management)
2001 – HEC Certificate (hard negotiation)
Laurent BONELLO
Age 32 (born March, the 8th, 1977)
email: laurentbonello@yahoo.fr
CURRENT POSITION :
2008 - Present: Head of the research, head of the catheterization laboratory and of the intensive care unit, Cardiology department, Hopital universitaire nord, Marseille.
Research activity
Late breaking trial presentation
Publication committee members

Young investigator award
- L Bonello et al. Cardiac Troponin Ic: Elevation Following Successful Percutaneous Coronary Intervention: Effects of an Acute Oral Loading Dose of Trimetazidine. Congrès mondial commun de la société européenne de cardiologie et de la fédération internationale de cardiologie (Barcelone 2006): International meeting oral presentation and lectures
1) Individualized anti platelet therapy to optimise outcome. Snowmass Colorado. 2009.
2) Platelet reactivity monitoring to prevent stent thrombosis. ESC Munich 2008.
4) Body Mass Index is the Main Determinant of High On-treatment Platelet Reactivity and of Failed Dose Adjustment According to Platelet Reactivity Monitoring. AHA Orlando 2009.
Selected publications
In press publications (accepted)
Other activities
Reviewer for : the Lancet, Circulation, JACC, international journal of cardiology, American Journal of cardiology, CRM.

Doctor Thibaud DAMY, 27/06/71
Doctor Thibaud Damy qualified in medicine at the University of Paris XI in 1996. After a period of postgraduate cardiology training in several Parisian hospitals and a PhD on the effect of nitric oxide on heart failure at the University Paris VII, he was appointed first as a senior registrar at Paris V University (2004), then at Paris XII (2005-2006) and subsequently in 2007 as a senior lecturer in cardiology and honorary consultant cardiologist at Henri Mondor Hospital, Creteil, France. In August 2008, he obtained a secondment for 16 months as a senior research fellow at the Academic Cardiology Department of Professor John G Cleland at the University of Hull (UK).
Doctor Damy’s main field of interest is heart failure, extending from its epidemiology and physiopathology through to its diagnosis and treatment. Particular current interests include the role of the nitric oxide pathway, neurohumoral systems, sleep apnoea syndrome, right ventricle function, and pulmonary artery pressure in heart failure.
Main publications

Doctor Thibaud DAMY, 27/06/71
Finn Gustafsson

Dr Yasser KHDER
Yasser KHDER obtained his medical degree and his speciality in internal medicine from Damascus University, Syria in 1987; subsequently he was graduated as specialist in cardiovascular pathology from Nancy Medical School, France in 1992. Between 1992 and 1996 YK had part time activity as a clinical cardiologist. Meanwhile, he also had a part time academic research assignment in the National Institute of Health and Medical Research (INSERM). During this period YK was successfully graduated as a BSc in clinical pharmacology, a MSc in clinical epidemiology, methods in clinical research and a DSc in human biology from the Nancy University, France. Currently YK is a Scientific Director Cardiology in Boehringer-Ingelheim, leading Dabigatran clinical development program in ACS. Beforehand YK worked 7 years in Novartis Pharma AG, Basel, Switzerland as a Diovan® Global Phase IV Leader. Altiskerin European Clinical Team Leader, Protocol Review Committee Cardiovascular Scientific Director and Global Program Leader for a NCE in phase 2B. Before Novartis, YK worked 5 years in Merck KGaA, where he led several development programs such as bisoprolol in silent myocardial ischemia, nicorandil in cardiac surgery and PCI as well as Na+/H+ exchanger inhibitor to prevent reperfusion injury at the acute phase of myocardial infarction.
Professor Atul PATHAK
Department of Clinical Pharmacology
Department of Cardiology
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Professor Atul PATHAK, is a Pharmacologist and Cardiologist. He is leading a clinical research team focusing on cardiovascular pathophysiology and clinical pharmacology and is affiliated to INSERM (National Institute of Medical Research). Professor Pathak is consultant in Clinical Cardiology focusing on patient’s care with cardiovascular risk factors (metabolic and cardiovascular) and their consequences such as Heart Failure in the Cardiometabolic department of Toulouse University Hospital. Professor Pathak was resident in Cardiology from 1996 to 2001 and trained in Toulouse (France), Aachen (Germany) and Cleveland (Cleveland Clinic, USA). After that period, he obtained his MD (highest distinction) at the Faculty of Medicine in Toulouse and obtained a tenure position as a research scientist at INSERM up to 2002. He obtained his European Phd (highest distinction) in Clinical and Experimental Pharmacology in 2005. He also worked as a post doctoral research fellow in the Department of Cardiology at Hospital Erasme and Free University of Bruxelles from 2004 to 2005.

He joined the Faculty of Medicine at the University Paul Sabatier in Toulouse as an Associate Professor in 2002 and has been Assistant Professor since 2005. He has been nominated full tenure Professor in Clinical Pharmacology in 2009 and is currently leading the Clinical Unit of Cardiovascular Pharmacology in the University Hospital of Toulouse.

Doctor Pathak is the author of more than 80 international publications. His research interests are: (i) new diagnostic tools and treatment of cardiometabolic risk factors and heart failure, (ii) the human sympathetic nervous system, (iii) neurotransmitters of the neuro cardiac synapse and more generally Clinical Pharmacology of Cardiovascular diseases. He is currently leading both a clinical and an experimental team working on the nervous regulation of cardiovascular function and, more particularly, the role of the autonomic nervous system in the control of arterial pressure, cardiac rhythm and contraction, and associated diseases (i.e. obesity, diabetes).

Professor Pathak has been awarded by the ESC (Young Investigator Award), by the British Pharmacological Society and the French Society of Cardiology. He is also member of the French Association of Pharmacologists, the French Society of Hypertension and Cardiology, the American Society for Heart Failure. He is elected President of the Cardiovascular Pharmacology Working Group of the French Society of Cardiology. He has both academic and institutional commitments, among them participation at advisory board at AFSSAPS (French FDA) and HAS for the review of clinical trials protocol, assessment of benefit /risk ratio of drugs (marketed or under development) and medico-economic issues (regarding lipid or blood pressure lowering drugs).

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QIMT BY RADIO FREQUENCY (EXAMINATION OF TRACKING) METHOD OF EVALUATION THICKNESS OF THE INTIMA MEDIA AMONG PATIENTS HAVING CARDIO VASCULAR RISK FACTORS

Clinical implication: about 150 cases: (study realised between October 2007 and March 2009)

Dr. Xavier Castellon 1, Dr. Veron Bogdanova 2
1Department of Cardiology, Private Hospital Athis Mons 38, Jules Valles 91200 Athis Mons - Paris, France

Subjects: Biomarkers and Bio imaging, Outcome research, Prognostication

The main aim of this study is to reveal an early diagnosis of a pre clinical evolution atheroma plaque, in the patients with cardiovascular risk factors. The intima media thickness is an independent cardiovascular risk factor. The measurement of the intima media is increasingly part of clinical evaluation of patients with risk factors. Mass or individual screening of this marker has high cardiovascular risk should be done at present in all patients with Cardio Vascular risk factors. QIMT is a promising method that allows us to calculate the intima media radio in real time on a reliable and reproducible.

Method: QIMT by Radio Frequency, Method of the examination used is in conformity with the IMT protocol of Mannheim standards of normal values according to age, measurements of IMT based on the radio frequency. This study has been done with 150 patients (100 men and 50 women), aged between 45 and 60 years, having cardiovascular risk factors (Dyslipidemia, standard diabetes II no complicated, hypertension and tobacco). All patients having atheroma plaque located in the carotids have been excluded from the study.

Results: 3% of the group of men and 2% women had resulted pathological (≥ 900 micrometers).

Conclusion: The QIMT technics of exploration of an early detection pre clinic evolution of atheroma plaque is easy, specific, chip, and reproducible to use a routine of preventive cardiology. It enables us to calculate in real time the thickness intima media in a few minutes, making the results reliable with a sensitivity of 95% and a specificity of 94%.

Comments: The QIMT can be used as a method of exploration complementary to the Endothelial Function, associates to others high-risk markers (biological: Homocysteine, Willebrand, Micro Albuminuria and Markers of Oxidative Stress: plasmatic rates of the vitamins C, α-Tocopherol, γ-Tocopherol, α-carotene, Lipidic peroxides, oxidized LDL, oxidized Antibodies LDL, OILIGO-ELEMENTS: Selenium, Copper, Zinc, Cu/Zn report/ratio) rate of plasmatic proteins (Proteins thiol) and with VIF (vasodilatation by intermediary of flow) on located in the brachial artery.

EFFECTS OF THREE FISH BASED MEALS/WEEK ON CARDIOVASCULAR RISK FACTORS

Lucio MOs, Valeria Diiati, Giancarla Marcuzzi, Stefano martina, Manoila Bettio, Olga Vitz, Schiaulini Gemma

Aim of this study was to evaluate the effects of three fish meals/week on blood pressure and lipid profile in hypertensive patients. The patients guaranteed to eat fish almost in three meals of the week. To improve the compliance they could buy salmon trout (fresh, smoked or pre cooked) at a 1/3 of market price in affiliated stores in San Daniele del Friuli area. One trout based meal corresponds to 1000 mg omega-3 fatty acids. 78 patients were enrolled in the study, after the first visit 16 were excluded for exclusion criteria The 62 patient underwent to blood pressure measurement, ambulatory blood pressure monitoring and blood samples for lipid profile three times, before the study, after three months and after 6 months of diet. All 76 patients were on stable antihypertensive therapy for almost 4 months and 22 patients were treated with antiarrhythmics (slight male, and 6th decade predominence, respectively), the other treatments with antiarrhythmics in quite similar proportions (A 70% p or P 24% p or S 6% p) + exogenous potassium supplement (K+), the second with the same antiarrhythmics in quite similar proportions (A 70% p or P 24% p or S 6% p) + eplerenone (E).

Results. The occurrence of AF episodes 18 months before the initiation of treatment with E versus 18 months after the initiation of treatment with E. The p treated previously with BB’s (indirect antiarrhen affect), ACEI’s, ARB’s, spironolactone were not included in the study.

Results are structured in the adjacent table:

<table>
<thead>
<tr>
<th>Therapeutic arm</th>
<th>AF Episodes (18 mo. before)</th>
<th>AF Episodes (18 mo. after)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A + K+</td>
<td>8.7+/−1.7</td>
<td>10.6+/−2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P + K+</td>
<td>9.0+/−2.4</td>
<td>10.3+/−1.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>S + K+</td>
<td>8.9+/−0.9</td>
<td>10.2+/−1.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Antiarrhythmic + K+</td>
<td>8.9+/−2.7</td>
<td>10.5+/−2.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>A + E</td>
<td>9.2+/−2.1</td>
<td>3.6+/−2.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P + E</td>
<td>9.0+/−2.5</td>
<td>3.9+/−2.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>S + E</td>
<td>8.9+/−2.4</td>
<td>3.9+/−2.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Antiarrhythmic + E</td>
<td>9.1+/−2.3</td>
<td>3.7+/−1.9</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Conclusions. The specific blocker of mineralocorticoid receptor E is a valuable additional therapeutic option in prevention of AF episodes occurrence. E brings an endogenous potassium, more friendly than K+ exogenic uptake. Beyond, it reduces RAAS activity and could reduce the fibrosis involved in structural remodeling. These beneficial effects were independent of BP lowering and are probably due to the antiinflammation effects of E. This study is going on, in order to improve the statistical significance and clinical relevance.

FROM “HOLIDAY HEART SYNDROME” TO ATRIAL FIBRILLATION. ELECTROPHYSIOLOGICAL CHARACTERISTICS

Polzold Londondoro Sanchez, S. Paccea, Tenazas, M. Pujol

Aim. Atrial fibrillation (AF) and supraventricular tachycardia are common arrhythmias in smoker patients and in those who developed cardiomegaly for several factors, including ethanol consumption for more than ten years. We decide to follow up patients with ethanol problems and controlled by the Emergency Department at the Hospital to determine the possibility to develop AF and alcohol effects in cardiac arrhythmias.

Materials and Methods. We studied a group of 100 patients with history of ethanol consume for many years with atrial fibrillation and without it (Table 1). We performed echocardiography control studies to determine the left auricular sizes, classified the patients for cardiovascular risk factors and including patients with atrial fibrillation history, control thyroidal hormones. We excluded those patients with hormonal alterations.

Results. Alcohol-related atrial arrhythmias might be attributed to intra-myocardial catecholamine release or to toxic direct effect of the metabolite acetaledehyde, affecting the refractory periods and dispersion, as well as conduction velocity and triggering factors. The increased heart rate changes reflected at the ECG were P wave duration significantly prolonged by ethanol – a predisposing factor for atrial fibrillation, because reduces corrected sinus node recovery time. 65% of patients presented first atrial dilatation secondary to alcohol cardiomegaly, but we can not consider that recovering the normal heart size is possible to restablish left atrial size.
CARDIAC AND BRAIN DAMAGE AFTER VERY HIGH TROponin-I LEVEL AFTER CARDIAC SURGERY
O. Londono, S. Pacreau, L. Paredes, M. Pujol

Introduction. Cardiac-specific biomarkers such as troponin-I, troponin-T and CK-MB have been used extensively to predict myocardial injury and ischemia.

High levels of troponines-I leads to an important cerebral hyperperfusion and brain damage associated with cardiac surgery has been extensively studied many times. Cerebral hyperperfusion during cardiopulmonary bypass surgery has long been thought to be a factor in the aetiology of brain damage with evidence of post-operative neurological deficits. Cerebral injury may also occur in the early post-operative period, or alternatively, any intraoperative damage may be exacerbated by hyperperfusion at this stage.

Aim. We have investigated the level of troponin-I release in both off-pump and CPB-technique CABG surgery, as well as postulated a relationship of troponin release and post-operative neurological outcome.

Materials and Results. A total of 50 adult patients undergoing coronary artery bypass graft (CABG) were enrolled into either an off-pump or on-pump groups, with 22 and 28 patients participating in each. Group A (on-pump) underwent myocardial revascularisation with CPB and cardioplegic arrest, while Group B (off pump) underwent beating heart surgery. The measurement of troponin-I is a 1-step enzyme immunoassay method, with specificity and sensitivity set at 0.4 ng/mL.

We used the NIH Stroke Scale, and neuropsychological assessment was assessed on cognitive function using modified Weschler Memory Scale, for which scores were standardized to achieve a comprehensive measure of concentration. A set of statistical analysis was done to correlate troponin-I release with different surgical techniques of CPB and OCPAB. Although each independent technique showed a marked rise of troponin-I from baseline to 6 hours post-operatively, the difference in troponin release was not significant between the 2 groups at specified time intervals (p=0.124). There was however a significant correlation of troponin-I release with the number of grafts used in the surgery, irrespective of the type of grafts or surgical technique. None of the patients in either group showed any neurological or cognitive deficits presenting at day 3 and day 7 post-operatively.

The findings of this study demonstrate that there is no significant short-term cognitive or neurological dysfunctions post-operatively, as indicated by troponin-I release in assessing the severity of myocardial injury, but we need to justify the time spent for surgeons as a important factor for the recovering time and clinical consequences.

NITRIC OXIDE METABOLISM OF THE COMBINED THERAPY OF BISOPROLOLE AND INDAPamide AT OVERWEIGHT HYPERTENSIVE PATIENTS
Svetlana Potabenko, Gerasimchuk Nina

Purpose: Obesity is one of the leading risk factor hypertension. Such pathogenic combination relevant for the development endothelial dysfunction. The aim of the study was to investigate the level of nitric oxide metabolites NO and nitrate/nitrite at overweight patients with arterial hypertension therapy on the dynamics combined bisoprolol and indapamide.

Method: 4Koverweight hypertensive patients (1 – stage, 2-3 degree of arterial hypertension, mean age, mean ± S.D.: 51.3±9.8 years) and 16 practically healthy persons were examined. Blood serum content of nitrite/nitrate anion had been determined by spectrophotometric method with Griess reagent, S-nitrosothiol by fluorometric method. The received data were expressed in mmol/l, mg/l.

Results: Overweight patients with arterial hypertension manifested the increase of S-nitrosotiole blood serum content (0.46±0.51 mmol/l vs 0.22±0.03 mmol/l in controls, p=0.05), the decrease of nitrate anion (NO3¯) blood serum content (13.04±5.86 mmol/l vs 14.19±1.8 mmol/l in controls, p=0.05), the decrease of nitrate anion (NO3¯) blood serum content (18.3±7.83 mmol/l vs 24.06±2.46 mmol/l in controls, p=0.05).

After 14 days of treatment of the bisoprolol in a combination with indapamide we observed the decrease of S-nitrosotiole blood serum content by 21.31% (0.36±0.12 mmol/l), the increase of nitric anion (NO2¯) blood serum content by 34.6% (19.0±7.05 mmol/l), the increase of nitrate anion (NO3¯) blood serum content by 31.2% (27.2±7.6 mmol/l), p<0.05 in comparison with the baseline level.

After 2 month of treatment (n=10) we observed the decrease of S-nitrosotiole blood serum content by 32.2% (0.339±0.13 mmol/l), the increase of nitric anion (NO2¯) blood serum content by 34.6% (19.0±7.05 mmol/l), the increase of nitrate anion (NO3¯) blood serum content by 31.2% (27.2±7.6 mmol/l), p<0.05 in comparison with the baseline level.

Conclusions: 2 months of treatment on the bisoprolol in a combination with indapamide is accompanied decrease of a level S-nitrosotiole and by significant increase of a level stable metabolites NO.

IMPACT OF EDUCATION IN “LIPID – SCHOOL” ON THE QUALITY OF TREATMENT PATIENTS WITH CARDIOVASCULAR RISK FACTORS
Nataliia Pertseva, Tetylun Tamara

Activity: Atherosclerosis is one of the most common cardiovascular disease. The presence of hyperlipidemia results in accumulation of atherosclerotic plates in damaged endothelium of vessels, its narrowing and worsening of heart’s oxygenation.

Acute coronary syndrome, cardiac arrest and stroke (events associated with atherosclerosis) are the most common reasons of death as in Ukraine so in the world. According to results of the long-term project EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) the lipid-lowering therapy directed on the prevention of cardiovascular events and death in patients of high risk is used not so widely. In Ukraine, there are only 1 to 7% of patients receiving statins from of people needing this therapy. It is necessary to organize “Lipid – schools” for patients with lipid disorders in order to increase their level of understanding the health condition and to improve the compliance between patient and medical team.

The aim of the study was to analyze the level of cholesterol and its fractions in patient with cardiovascular risk factors and how statins influence on it.

We made a retrospective analysis of medical case histories of patients with cardiovascular risk factors.

Results: 300 medical case histories were analyzed: 149 (49%) women and a 151 (51%) man patient from age 19 to 98 years (middle BMI 28,16±0,81). Type 1 diabetes mellitus (DM) was found in 49 cases (16%), type 2 DM – in 204 cases (68%). The level of total cholesterol in type 2 DM was determined in 9 (3%) patients (5,26±0.17 mmol/l), in type 2 DM - in 41 (13,6%) patient (4,7±0.1 mmol/l). Statins were assigned in two cases of type 1 DM patients and in 58 (12,6%) cases of type 2 DM patients. Arterial hypertension was found in 205 (68,3%) cases. The level of total cholesterol was measured in 78 (25,9%) patients with arterial hypertension (4,7±0.15 mmol/l). Statins were prescribed for 94 (31,3%) patients with arterial hypertension.

The presence of the carried myocardial infarction was found in 123 (41%) patients, total cholesterol was measured in 51 (17%) cases (4,7±0,12 mmol/l). Statins were prescribed for 80 (30,4%) patients with myocardial infarction.

Conclusions: There are a lot of cardiovascular risk factors in examined patients - BMI is over normal range (28,16±0,81), middle ages – 56,6±0,82 years.

Patients have concomitant diseases, development of cardiovascular diseases is more frequent in men, than in women. However, in spite of presence of cardiovascular risk factors the level of total cholesterol and its fractions is not fully conducted and it hampers the purpose of adequate lipidlowering therapy. Evaluation of the complete level of laboratory tests to determine cholesterol and its fractions, constant clinical monitoring and education in the “Lipid – school” for patients with lipid disorders will increase the patients adherence to lipidlowering therapy, changing their life style, and will significantly reduce the risk of development of cardiovascular events.
A GOOD CONTROL OF CARDIOVASCULAR RISK FACTORS – THE KEY FOR A GOOD PROGNOSIS AND REDUCTION OF MORTALITY.

Dr. O. Londono, Dra. S. Pacreu, Dr. L. Muntaufer, Hospital Universitari Bellvitge, Barcelona, Spain

Aim: We selected a group of 500 patients controlled for us ambulatory during three years with cardiovascular risk factors: hypercholesterolemia, hypertension, lung disease, smoking and diabetes mellitus. Other diseases like hepatic, kidney and oncologic were discharged from the observational study.

Materials and Methods: As a group with a high risk for ischemic events we decide a control every three months with blood analyses for triglycerides, cholesterol and glucose. A treadmill and echo-cardiography doppler were performed twice a year. No diet control was assumed. During a median follow-up duration of 3.6 years, there were 35 discharged patients: 3 sudden death (reasons no studied for us); oncology pathology, 4 vascular cerebral accidents, refused in keeping on control, and others.

Results: Even the rigorous control 6% of patients suffered an ischemic event: infarct of myocardium Killip 1, different localization. The clinical symptomatology was typical for angina instable with positive myocardial enzymes. The coronaryography results showed lesions damage in one coronary artery with small angina instable with positive myocardial enzymes. The very important diagnostic role for our Doppler ultrasound examination was demonstrated.

Conclusions: In patients with cardiovascular risk factors a consciously follow-up and control of these factors can reduce mortality and give good prognosis if an ischemic event occurs. We must understand that cardiovascular events are inevitable even if take the reasonable measures, but the proportion on consequences are lower than in control groups.

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Men</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59 (43-75)</td>
<td>58 (45-70)</td>
<td>58.5 (39-78)</td>
</tr>
<tr>
<td>Diabetes insulin-requireing</td>
<td>25%</td>
<td>18%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Diabetes non-insulin requiring</td>
<td>14%</td>
<td>10%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
<td>37%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Glucose control</td>
<td>37%</td>
<td>42%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Smoking</td>
<td>4%</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>Tread mile</td>
<td>2% (+)</td>
<td>2.6% (+)</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Echo cardiography Doppler 0.3%

Control group: the value indicates patients never required for cardiologic control.

Table 1: Baseline characteristics

RIGHT HEART FAILURE IN A SIMPLE ECHO VASCULAR DOPPLER IMAGE

O. Londono Sanchez¹, S. Pacreú²
1 Hospital Vall d’Hebron, Barcelona, Spain; 2 Hospital del Mar, Barcelona, Spain

The very important diagnostic role for our Doppler ultrasound examination was demonstrated in a very especial case of arterial-venous fistulae. This patient has being operated without later complication.

A 50 years old patient with a history of treated hypertension was referred to our Hospital because of chest pain with elevated for ischemic markers. Was performed percutaneous coronary intervention including implantation of a bare-metal stent. Arterial puncture was realized without any complication, apparently. After the intervention the patient was transferred to the recovery room.

Two hours later the patient called to the nurse because of increasing shortness of breath and appearance of facial, legs and hands edemes. Cardiologist responsible of recovering hall was called and check the patient not finding any special clinical alteration. One hour later the nurse call the interventionist for increasing symptoms. The chest auscultation showed an increasing of pulmonars crepitation, the physical examination note the increased edemes facials and inferior extremities. The puncture femoral right zone was free of hematomes, but auscultation evidenced a systolic murmur. Was performed echo Doppler examination, funding the images showed below.

It was diagnosed an arterio-venous fistula. Was decided to transfer the patient to the surgery room and was operated without later complication. We check once more the film recorded during intervention and found the blood escape at the time when catheters were out.

Three months later control

Conclusions: Our study was conducted to objectively assess baseline rates of vascular complications after any intervention using transfemoral route, and determine the important place that have taken the new perclose system for obtaining arterial hemostasis and the echo-Doppler analyses to provide the maximum information of the arterial status. Three important findings in our study.

<table>
<thead>
<tr>
<th>TABLE I Vascular access site complications identified by blinded physical examination (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perclose suture device</td>
</tr>
<tr>
<td>(n=100)</td>
</tr>
<tr>
<td>Oozing</td>
</tr>
<tr>
<td>Ecchymosis</td>
</tr>
<tr>
<td>Hematoma</td>
</tr>
<tr>
<td>Ecchymosis or hematoma</td>
</tr>
<tr>
<td>Ecchymosis and hematoma</td>
</tr>
<tr>
<td>Pusatile mass</td>
</tr>
<tr>
<td>Distal extremity pain</td>
</tr>
<tr>
<td>Distal extremity discoloration</td>
</tr>
<tr>
<td>New bruut</td>
</tr>
</tbody>
</table>

* Data are presented as number (%) of patients.

<table>
<thead>
<tr>
<th>TABLE II Vascular access site pathology diagnosed by ultrasound (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perclose suture device</td>
</tr>
<tr>
<td>(n=100)</td>
</tr>
<tr>
<td>Hematoma</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
</tr>
<tr>
<td>Femoral artery thrombosis</td>
</tr>
</tbody>
</table>

* Data are presented as number (%) of patients.
ECONOMIC EFFICIENCY OF TREATMENT BY ACENOCOUMAROL IN PATIENTS WITH PERMANENT FORM OF ATRIAL FIBRILLATION, WITH USING PHARMACOGENETICS TESTING
Basil N. Shani1, Dmitry A. Sychev1
1 Institute of Clinical Pharmacology of Science Center of examination of medical applications Rosladravnadar, Moscow, Russia; 2 Moscow State University, Moscow School of Economics, Chair of Financial strategy.

Introduction. Acenocoumarol is the global standard of anticoagulant therapy, but often treatment with acenocoumarol accompanied by adverse drug reactions. Model of personalized medicine, actively developing now, can reduce the number of side effects during therapy of Acenocoumarol, mainly due to individual genetic characteristics (polymorphisms of genes CYP2C9 and VKORC1).

Materials and Methods. In the work we included 84 patients with permanent form of atrial fibrillation, aged 44 to 73 years, of whom 44 men and 40 women, treated at two hospitals in Moscow. These patients were randomized into two equal groups with usual way of selecting dosage of acenocoumarol only, and usual way of selecting dosage with pharmacogenetics testing.

To assess the efficacy and safety of treatment by acenocoumarol, used the results of a retrospective study on the influence of polymorphisms of genes CYP2C9 and VKORC1, the clinical status of the patient, and laboratory findings, the results of research on blood clotting. Also we analyzed the costs of treating both groups by economic standards of the Russian Ministry of Health Care, data and costs of all things for pharmacogenetics testing.

Methods: In the first group, in terms of 100 patients were nearly 25% of light side effects (nasal bleeding) and nearly 5% of serious side effects (bleeding in the digestive tract). In the second group, also in terms of 100 patients, light side effects were observed only in nearly 5% of patients, and serious side effects were not observed at all.

Results. In the first group, in terms of 100 patients were nearly 25% of light side effects (nasal bleeding) and nearly 5% of serious side effects (bleeding in the digestive tract). In the second group, also in terms of 100 patients, light side effects were observed only in nearly 5% of patients, and serious side effects were not observed at all.

Financial expenses in the first group, in terms of 100 patients, were 157785,53 €, and in the second group, in terms of 100 patients, were 146367,52 €.

Conclusions. Selection of the dose of acenocoumarol, with using models of personalized medicine, reduces the risk of side effects in 5 times, and also reduces the costs of treating of 100 patients at 11418,01 €.

LEVELS OF ENDOTHELIN-1 AND RENIN DEPENDING ON THE DAILY STRUCTURE OF ARTERIAL BLOOD PRESSURE IN PATIENTS WITH RHEUMATOID ARTHRITIS
Elena Mikhaylova
Cardiology Department, Yaroslavl Regional Clinical Hospital, Yaroslavl, Russia. e.mikhaylova2@gmail.com

Background: Cardiovascular death is considered the leading cause of mortality in patients with RA. Cardiovascular disease has a tendency to remain silent in the rheumatoid patient. Traditional cardiovascular risk factors do not seem to be responsible for the increased cardiovascular risk.

Objective: To study daily structure of arterial blood pressure in patients with RA, depending on plasma endothelin-1 (ET-1), levels of renin and aldosterone.

Methods: 92 (65%) patients with rheumatoid arthritis (RA), 50 (35%) patients with arterial hypertension (AH) and 30 controls matched on age, sex, and ethnicity. The group of RA was divided into two groups: those who had RA+AH - 55 (59, 7%) and those who didn’t suffer that disease: RA without AH - 37 (40%).

Measurements: Daily monitoring of arterial blood pressure (ABP); the level of endothelin-1 (ET-1) in the blood plasma in all participants; the level of renin and aldosterone in the blood plasma.

Results: Level of ET-1 in patients with RA and AH correlated positively with index of time of Systolic Blood Pressure (SBP) at the day (R=0.69; p<0.005), minimal SBP night (R=0.5; p<0.03) and maximal Dastolic BP (DBP) night (R=0.57; p<0.03, also with the index of time DBP night (R=0.66; p<0.009). There were found out positive correlations between level ET-1 and minimal SBP day (R=0.64, average SBP day r=0.70, index of time DBP day r=0.80, average DBP night r=0.77 at p<0.05). At patients with AH such correlations were not established. At comparison of hormones in plasma, level of renin in patients with RA+AH was 5.6 times less, than in group of patients with AH and in 3 times lower, than in control group (0.16 (0.06; 0.58) ng/ml/hour against 0.47 (0.2; 0.65) ng/ml/hour, p <0.05). In group of patients with RA without AH level of renin was not different then in the control group (0.64 (0.08; 0.4) ng/ml/hour against 0.47 (0.2; 0.65) ng/ml/hour, p <0.05). The level of renin, negatively correlated in patients with RA and AH, with maximal the BP in the day (R =–0.5; p <0.05), unlike this data in patients with AH. The average systolic BP in patients with RA+AH correlated negatively with level of renin (R=-0.41; p<0.01), time index of SBP day (R =–0.37; p=0.03), maximal systolic BP night (R =–0.43; p<0.01).

Conclusion: For patient with RA+AH it is typical the tendency for suppression of renin. The reasons are still not clear. It can be connected with production of serum antibodies to renin (Samorodzjova at al. 1991) and it may be that ET-1 inhibit basic secretion of renin in isolated glomerule and cortical cells of kidneys of rats (Prasad A. et al., 1998.). However the reasons are not clear and the answer may lead to open the new perspectives in treatment of AH at patients with RA.

PROSPECTS OF RESEARCH OF DRUGS WITH METABOLIC ACTION IN THE TREATMENT OF THE PATIENTS WITH HEART'S DISEASES
Sapraty Andriy, Kupnovtsya I.G., Dzivynska O.F., Belegal R.I., Kulyshky I.P.

Drugs with metabolic action are all wider with the traditional facilities of pharmacotherapy of ischemic heart disease. Their advantages are practically complete absence of side effects, tumor necrosis factor (TNF-α) which can involved in the development of obesity and heart disease.

Methods: Clinical inspection of patients with the estimation of psychical and emotional spheres, immunological methods, instrumental methods - electrocardiography, Holter’s monitoring, echocardiography, day’s monitoring of blood pressure, determination of function of endothelia of artery and thickness of layer of its intima-media with the using of test with reactive hyperemia.

Results. The action of corvitine is first represented at the united cardiologic pathology during research on 138 patients and 20 practically healthy people. It is well-proven that in the conditions of acute medicinal test corvitine shows influence on expansion of vessels, changing diameter of humeral artery on 31,7% for patients on ischemic heart disease and on 24,4% - in healthy (p<0.05) and thickness of its layer of intima-media - 4.2% and 8.5% accordingly (p<0.05). Corvitine in the standard chart of pharmacotherapy of patients with the acute myocardium infarction on a background an arterial hypertension and chronic heart failure improves clinical motion of disease regardless of degree of clinical expressed of cardiac insufficiency, normalizes the psychical and emotional states of patients, that in same queue it is possible to consider as displays of increase of index of quality of life, shows an antihypertensive and easy antihypertensive action, carries out a cardioprotective effect, improving structurally functional changes of myocardium. Plugging of corvitine in the complex chart of treatment results in substantial regress of displays of local inflammation, limits the area of necrosis of myocardium, stabilizes interleukine’s status, repressing activity of cytokine’s link of pathogenesis of this pathology.

Conclusions. Corvitine is an effective and safe drugcorrection of chronic heart failure for patients with the acute myocardium infarction, that arose up on a background an arterial hypertension. However for today his subsequent study is perspective with plugging in research as possible of greater amount nosology excellent cardiologic patients different age, sex and races on the basis of construction of charts of international randomized multica clinical tests, that would allow adequately to represent all moments of metabolization of standard principles of pharmacotherapy.

RELATIONSHIPS BETWEEN LEPTIN, TUMOR NECROSIS FACTOR- AND INSULIN LEVELS IN OBESE HYPERTENSIVE PATIENTS
Tetiana Ambrosova, Gaptol Olena Kovalyova Olga

Association of obesity, hypertension and metabolic abnormalities is complex and incompletely understood. It was proposed that adipose tissue can release such adipocytokines as leptin, tumor necrosis factor-α (TNF-α), which is a new factor of a number of important disease processes, such as development of obesity and insulin resistance in the patients with arterial hypertension (AH).

Theaimofourstudywasinvestigate relationships between leptin, TNF-α and insulin blood levels in hypertensive patients with obesity.

Design and methods: 123 patients with AH (53.82±0.91 years old) have been studied. All patients were examined by detailed clinical, anthropometric (height, body mass, body mass index (BMI), waist circumference) and laboratory methods. Blood leptin levels by ‘Leptin (Sandwich) ELISA (DRGInstrumentsGmbH, Germany), TNF-α by ELISA “alpha-TNF (IFA-BEST, Russia), insulin levels by ‘Insulin ELISA (DRG Instruments GmbH, Germany) were measured.

Patients were divided into two groups depend on BMI means: 1 group (n=20) with normal BMI < 25 kg/m2; 2 group (n=103) overweight and obese subjects with BMI ≥ 25 kg/m2. Control group includes 21 healthy persons.

Results: Comparison of average means of leptin, TNF-α and insulin in hypertensives accordingly to BMI showed a significant and statistically higher leptin (11.66±0.74 ng/ml) levels, TNF-α (8.24±0.8 ng/ml) and insulin (17.48±1.57 mg/kU/ml) in 2nd group patients as compared with 1st group patients in which leptin levels was (7.34±0.77 ng/ml), TNF-α levels – (5.70±0.30 ng/ml), and insulin levels (7.78±1.01 mg/kU/ml) (p<0.05 in all cases of comparison) and control group of normotensive persons: leptin levels in which characterized by minimal means (6.21±0.27 ng/ml), TNF-α levels (1.88±0.23 mg/ml), and insulin (5.97±2.71 mg/kU/ml) (p<0.05 in all cases of comparison). In patients with arterial hypertension and obesity it was found positive correlation between leptin and TNF-α levels (R=0.45; p<0.001), between leptin and insulin levels (R=0.37; p<0.001); and between TNF-α and insulin levels (R=0.50; p<0.001).

Conclusion: Results of our clinical study indicate statistically significant elevation of leptin, TNF-α and insulin levels in patients with arterial hypertension related to overweight and obesity presence and positive statistically significant correlations between these parameters.
LONG-TERM EFFICACY OF NEBIVOLOL MONOTHERAPY IN PATIENTS WITH MASKED HYPERTENSION

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Background: Elevated blood pressure is a major risk factor for cardiovascular disease morbidity and mortality in specific occupational group - train's operators and locomotive crews.

Objective: The purpose of this study was to investigate the antihypertensive activity of nebivolol monotherapy over a twelve-month period in patients with profession related stress factors and masked hypertension (MH).

Methods: This was an open labeled, prospective, controlled, twelve-month study of the efficacy of nebivolol (Nebilet®, Berlin-Chemie, Germany) in 30 males with MH. Nebivolol was administered at the initial dose of 2.5–5 mg once a day. If the target blood pressure (BP) level was not reached, the dose was titrated up every two weeks by 2.5 mg/day. “Office” systolic and diastolic blood pressure (SBP and DBP), BP before the beginning of work and 24-hour monitoring of BP (DMPB) were performed.

Results: Treatment with nebivolol resulted in statistically significant reduction in DBP and SBP from baseline within first week of study period. During the long-term treatment, the effects increased; the maximal reduction of BP by 19.3% (p<0.001) was observed after 12 weeks of therapy and stayed at the same level after 12 months. 88.9% of patients had a good response to monotherapy, in 12% of cases the combined therapy was required.

The positive influence of nebivolol on the main DMPB parameters was confirmed. Based on the DMPB data, the average SBP level during the nebivolol treatment decreased: daytime SBP by 10.0% (p<0.001), nighttime SBP by 7.0% (p<0.001) and daily SBP by 6.8% (p<0.001).

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SUCCESSFULNESS OF TWO PHARMACOLOGICAL STRATEGIES FOR CONVERSIONS OF RECENT-ONSET ATRIAL FIBRILLATION AND PERSPECTIVES OF LOCAL DRUGS DELIVERY

Goran MIUCEVIC, Strinic D., Gavranovic Z, Udakic N, Bakula M

Introduction. Pharmacological conversion of recent-onset atrial fibrillation is important practical issue. RELATED TO QUESTION OF THE ESC WG ON CARDIOVASCULAR PHARMACOLOGY AND DRUG THERAPY “How to best achieve cardioversion”, we analyzed successfullness of a single drug and sequential drug administration strategies. Furthermore, we tried to enhance the review with an idea on increasing the efficacy of conversion by local delivery of drugs.

Methods. A systematic review of controlled trials, published in indexed journals, with antiarrhythmic drugs (of a class III, IC and IA, and atrial-selective) was performed. Eligible studies had to be randomized, controlled, parallel-designed, human trials that prove efficacy of pharmacological cardioversion of recent-onset atrial fibrillation.

Results. High diversity in conversion rate of a single antiarrhythmic drug administration is shown, depending on drug dosage and time of its application. Sequential drug administration showed high success rate, but higher time consumption (Table 1).

Table 1. Pharmacological conversion of recent-onset atrial fibrillation

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SUCCESS rate</th>
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<tbody>
<tr>
<td>Single antiarrhythmic agent strategy</td>
<td></td>
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<td>Class</td>
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Conclusion. Atrial-selective drugs have rapid onset of action, but sequential administration of older antiarrhythmic drugs shows excellent success rate. To enhance short-term success rate, local delivery of atrial-selective drugs may be needed. Possible models are proposed.

MOXONIDIN AND LUNG FUNCTION IN PATIENTS WITH ARTERIAL HYPERTENSION AND MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Natalya Stepchenko, Sidorov A.A., Mostovoy Y.Y.

This work is devoted whether moxonidin has an influence on lung function in patients with arterial hypertension (AH) and concomitant moderate chronic obstructive pulmonary disease (COPD).

Methods. The 34 patients with arterial hypertension (AH) and concomitant moderate chronic obstructive pulmonary disease (COPD) were included to study. Blood pressure was measured and the spirometry was performed before and after 3 month of therapy. After two weeks without antihypertensive medications (washout period) moxonidin was prescribed to all these patients. 10 patients take moxonidin in total daily dose of 0.2 mg, another patients were treated with moxonidin 0.4 mg. The therapy of COPD was stable during this period and it consists of long-acting β2-agonist salmeterol in total daily dose 100 mcg and short-acting β2-agonist salbutamol pro rena.

Results. Before treatment BP was 154,5±2,7/96,8±1,3 mm Hg and it was 128,3±3,7/79,3±2,5 mm Hg after taking moxonidin. The data of spirometry before taking moxonidin are FVC 81,4±3,3%, FEV1 69,3±3,4%, PEF=72,3±3,1%. These data are changed after treatment. FVC = 92,2±4,2%*, FEV1= 83,2±2,3%*, PEF=86,3±3,6%(* p<0.05 with the data on before treatment).

Conclusion. Moxonidin is effective antiarrhythmic drug. Treatment with moxonidin also improves lung function in patients with concomitant COPD. It has no direct influence on data of spirometry. Perhaps, these positive effects connected with diminished pressure in pulmonary artery and with improvement of mechanics of breath.

FIBRINOGEN AS A RISK FACTOR OF THE DEVELOPMENT OF CARDIOVASCULAR DISEASES IN PATIENTS INFECTED BY HELICOBACTER PYLORI M. Sechenov, M

Vladimir Popov, Grechushnikov V.B., Nelyubin V.N., Popov V.V.

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Background: As is well known, Helicobacter pylori (H.P.) infection is the main reason of the development of chronic gastritis, gastric or duodenal ulcer disease and stomach cancer. However, recent numerous studies prove the wide enough range of extragastral manifestations of the H.P. Infection. In a number of articles the role of the infectious process caused by H.P. as a risk factor of the development of cardiovascular diseases is discussed. However, a number of studies have reported conflicting results.

Objective: The aim of the study was to examine a possible relationship between H.P. infection and cardiovascular disease in patients with gastrointestinal tract disorders.

Methods: One hundred twenty-six (126) patients with gastrointestinal tract disorders were investigated. 54 (42.8%) males and 72 (57.1%) females aged 19 to 81 were involved. Esophagogastroduodenoscopy (EGD), abdominal ultrasonography (USG), blood biochemistry (cholesterol, HDL, LDL, VLDL, fibrinogen), C-reactive protein were performed. Diagnostics of the infection H. pylori was performed by histological and cytological methods (by the quick urease test and PCR method).

Results. The EGD revealed 65 (51.5%) cases of gastritis, 32 (25.3%) cases of acute and chronic gastric and duodenal erosion, 2 (1.58%) cases of duodenal ulcer, 14 (11.1%) cases of cicatricial and ulcerous gastrointestinal alterations, 13 (10.3%) cases of esophagitis. The following concomitant diseases were revealed:

- 38 (30.1%) patients had coronary heart disease, 31 patients had H.P. (+) (81.5%);
- 77 (61.1%) patients had essential hypertension, 66 patients had H.P. (+) (85.7%);
- 11 (8.7%) patients had different types of heart rhythm disturbance.

Conclusion. Apparently, the H.P. infection in patients with chronic gastrointestinal tract disorders can influence on the development of concomitant cardiovascular diseases by means of the increase of blood fibrinogen. H.P. infection and plasma fibrinogen concentration are important risk factor for cardiovascular disease.

Approach focusing on the efficacy of eradication of H.P. infection on the prevention and treatment of cardiovascular diseases should be a potential target for new cardiovascular clinical trials.
STATINS AND SERIOUS MUSCULOSKELETAL ADVERSE REACTIONS: OVERVIEW OF POST-MARKETING SURVEILLANCES AND RANDOMIZED CLINICAL TRIALS

Katerina Zakharchenko, Popov V.
Moscow Medical Academy named after I.M. Sechenov, Moscow, Russia.

Objectives: The aim of the study was to analyze safety data from key randomized clinical trials (CT), post-marketing surveillances and other medical databases about a possible relationship between musculoskeletal Serious Adverse Reactions (SAR) of statin therapy.

Methods and Results: Major reports of statin therapy safety from the following database: WHO (Pharmaceuticals newsletter), FDA safety alerts, Canadian Adverse Reaction Newsletters (CARN), Australian Adverse Drug Reaction Advisory Committee (ADRAC) Bulletins, MEDLINE, PubMED, Medscape and available reports from randomized clinical trial were identified for analysis.

We reviewed alerts and reports that contain information about frequency of serious and uncommon musculoskeletal reactions rhabdomyolysis during statin therapy (Cerivastatin wasn’t included).

Key randomized CTs demonstrated the following rates of rhabdomyolysis during statin therapy: 1.6 incidences above placebo per 100 000. According to the data from ASCOT, GREACE, AVERT, MIRACL, PROVE-IT for Atorvastatin - cases of rhabdomyolysis is 0.03%, Simvastatin (4S, HPS, A to Z Studies) – total cases 0.06%, Rosuvastatin (JUPITER, AURORA, CORONA) -0.007% cases, Pravastatin and Fluvastatin - 0 %.

We also analyzed post marketing databases. In US in 2006: the following numbers of spontaneous SARs of rhabdomyolysis were registered: for Atorvastatin – 348 cases, Simvastatin – 760 cases, Rosuvastatin – 103 cases, Pravastatin – 75 cases, Fluvastatin - 56 cases.

However, the FDA has continued to receive reports of statin-associated dose-related rhabdomyolysis in 2008 related to combinations of Simvastatin/Amodarone.

There are 35 cases of all rhabdomyolysis reports received from marketing authorisation of statins in Canada according to CARN in 2001; and there are 8 new cases of rhabdomyolysis associated with statins registered in 2004. CARN in 2007 reported that 46 deaths were statin-associated, 24 from them related to atorvastatin, the percentage of rhabdomyolysis was not provided.

In ADRAC total numbers rhabdomyolysis reports up 2004 for Simvastatin - 91; Atorvastatin - 26, Pravastatin - 5, Fluvastatin - 2, by late 2007 in Australia received 5846 adverse reactions reports, that implicated a statin, almost 1/3 were of muscle disorders, the percentage of rhabdomyolysis was not indicated.

Conclusions: The study demonstrated on the basis of data, available from published reports of CTs and post-marketing reports of musculoskeletal SAR, such as rhabdomyolysis, that it is necessary to take into account the possible risk while using dangerous combinations and doses of statins during the statin-therapy. Thus cardiologists and GP appear to become a very important informative source for registrations of such SARs during the post registration phase of the pharmacovigilance.

And also the findings must be a motive for the development of the new statins’ generation and tracking and prevention of the possible SAR.
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