NEW AND EMERGING HEART FAILURE THERAPIES: 2018 AND BEYOND

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New and emerging heart failure therapies: 2018 and beyond

Focus on pharmacological therapy

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My employer, Glasgow University, has been paid for my participation in clinical trials (executive/steering committees, endpoint adjudication committees and data monitoring committees), advisory boards and other meetings/lectures by a number of pharmaceutical companies, including: Amgen, AstraZeneca, Bayer, BMS, DalCor, GSK, Novartis and Theracos.
Treatment of HF with reduced ejection fraction (HF-REF)
What’s new?

• Neprilysin inhibition
• Sinus node inhibition
Natriuretic peptides: How the heart protects itself

- The heart is an endocrine organ
- It secretes A and B type natriuretic peptides into the circulation where they act on the blood vessels, kidneys, adrenal glands, brain etc.
- These peptides protect the heart from volume and pressure overload
Neprilysin (neutral endopeptidase EC 3.4.24.11)

- A zinc-dependent membrane metalloprotease first identified in the renal brush-border
- Degrades ANP>CNP>BNP (and also urodilatin?)
- Also bradykinin, substance P, adrenomedullin, enkephalins, apelin, GLP-1
- Angiotensins, endothelins? Amyloid beta-peptides.
- Long history of attempts to develop neprilysin inhibitors alone (1989) and in combination with ACE inhibitors (1997)
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

What is the incremental benefit of neprilysin inhibition? *(designed to augment beneficial vasoactive substances such as natriuretic peptides)*

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**NEP inhibitor**

**Beta-blocker (93%)**

**RAS Inhibitor* (100%)**

**MRA (54%)**

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**versus**

**Beta-blocker (93%)**

**RAS Inhibitor* (100%)**

**MRA (57%)**

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*RAS blocker: valsartan in NEP inhibitor group and enaparil in control group
PARADIGM-HF: Primary outcome
Cardiovascular death or heart failure hospitalization

HR: 0.80 (0.73, 0.87)
p = 0.0000004

What’s in the pipeline?

Focus on on-going large-scale mortality/morbidity outcome studies
What is new in the treatment of heart failure?

**HF-REF:**
- NOAC – rivaroxaban
- Guanylate cyclase stimulator – vericiguat
- Cardiac myosin activator – omecamtiv mecarbil
- Intravenous iron – ferric carboxymaltose and isomaltoside
- SGLT2 inhibitor – dapagliflozin and empagliflozin

**HF-PEF:**
- PARAGON-HF – sacubitril/valsartan
- SGLT2 inhibitor – empagliflozin
Anticoagulation in heart failure

Acute coronary syndrome

Pulmonary embolism

Stroke
Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial

Faiez Zannad¹, Barry Greenberg², John G.F. Cleland³, Mihai Gheorghiade⁴, Dirk J. van Veldhuisen⁵, Mandeep R. Mehra⁶, William M. Byra⁷, Min Fu⁷, and Roger M. Mills⁷*
Hypothesis: Rivaroxaban will reduce morbidity and mortality in pts with HF due to CHD.

Population: 5000 patients; symptomatic HF; CHD; EF ≤40%; BNP ≥200 pg/ml or NT-proBNP ≥ 800 pg/ml; recent exacerbation of HF.

Intervention: Rivaroxaban (2.5mg bid) vs placebo.

Primary endpoint: Death, MI or stroke.

Status: Started 2013.
What is new in the treatment of heart failure?

- **HF-REF:**
  - NOAC – rivaroxaban
  - Guanylate cyclase stimulator – vericiguat
  - Cardiac myosin activator – omecamtiv mecarbil
  - Intravenous iron – ferric carboxymaltose and isomaltoside
  - SGLT2 inhibitor – dapagliflozin and empagliflozin

- **HF-PEF:**
  - PARAGON-HF – sacubitril/valsartan
  - SGLT2 inhibitor – empagliflozin
Approaches to increasing cGMP: Soluble guanylyl cyclase (sGC) stimulation
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator

The VICTORIA Trial

Paul W. Armstrong, MD, Lothar Roessig, MD, Mahesh J. Patel, MD, Kevin J. Anstrom, PhD, Javed Butler, MD, MPH, MBA, Adriaan A. Voors, MD, PhD, Carolyn S.P. Lam, MBBS, PhD, Piotr Ponikowski, MD, Tracy Temple, BScN, Burkert Pieske, MD, Justin Ezekowitz, MBChB, MSc, Adrian F. Hernandez, MD, Joerg Koglin, MD, PhD, Christopher M. O’Connor, MD
What else is in the pipeline? (Phase 3 mortality/morbidity trials)

**COMMANDER-HF**

- **Hypothesis:** Rivaroxaban will reduce morbidity and mortality in pts with HF due to CHD
- **Population:** 5000 patients; symptomatic HF; CHD; EF ≤40%; BNP ≥200 pg/ml or NT-proBNP ≥ 800 pg/ml; recent exacerbation of HF.
- **Intervention:** Rivaroxaban (2.5mg bid) vs placebo.
- **Primary endpoint:** Death, MI or stroke

**VICTORIA**

- **Hypothesis:** Vericiguat will be superior to placebo, added to SOC, in patients with symptomatic chronic HF-REF (LVEF <45%)
- **Population:** 4872 patients; iv therapy for exacerbation of HF in past 3 months/hospitalization within 6 months and elevated NPs
- **Primary endpoint:** CV death or HF hospitalization: target 1561 events (powered for CV death).

1NCT01877915 2NCT02861534
What is new in the treatment of heart failure?

• **HF-REF:**
  • NOAC – rivaroxaban
  • Guanylate cyclase stimulator – vericiguat
  • Cardiac myosin activator – omecamtiv mecarbil
  • Intravenous iron – ferric carboxymaltose and isomaltoside
  • SGLT2 inhibitor – dapagliflozin and empagliflozin

• **HF-PEF:**
  • PARAGON-HF – sacubitril/valsartan
  • SGLT2 inhibitor – empagliflozin
Omecamtiv mecarbil —
a cardiac-specific myosin activator

Mechano-chemical cycle

OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

“More hands pulling on the rope”

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO$_2$

Omecamtiv mecarbil

ATOMIC-AHF
Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure

COSMIC-HF
Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure

Intravenous  Oral
COSMIC: Effects of omecamtiv mecarbil

Heart rate

NT-pro BNP

LVESV

Stroke volume

LVEF

Lancet 2016; 388: 2895–903
Hypothesis: Omecamtiv mecarbil will reduce morbidity and mortality in patients with HF-REF

Population: ~8000 patients; symptomatic HF; EF ≤35%; Current HF hospitalization or prior HF hospitalization/ED visit in past year; elevated BNP or NT-proBNP.

Intervention: Omecamtiv mecarbil vs. placebo.

Primary endpoint: Cardiovascular death or first heart failure event.

Status: Enrolling.

https://clinicaltrials.gov/ct2/show/NCT02929329
The human face of heart failure

- Atrial fibrillation
- Diabetes
- Anaemia
- Iron deficiency
- CHD/angina
- Hypertension
- Asthma/COPD
- Prostatic disease
- Psychiatric illness

- Hyperkalaemia
- Arthritis
- Glaucoma
- Cachexia
- Hyperuricaemia/gout
- Renal impairment
- Sleep apnoea
- Parkinson’s disease
- Cognitive impairment
What is new in the treatment of heart failure?

• **HF-REF:**
  • NOAC – rivaroxaban
  • Guanylate cyclase stimulator – vericiguat
  • Cardiac myosin activator – omecamtiv mecarbil
  • Intravenous iron – ferric carboxymaltose and isomaltoside
  • SGLT2 inhibitor – dapagliflozin and empagliflozin

• **HF-PEF:**
  • PARAGON-HF – sacubitril/valsartan
  • SGLT2 inhibitor – empagliflozin
Iron distribution and turnover

Dietary iron

Muscle (myoglobin) (300 mg)

Liver parenchyma (1000 mg)

Duodenum (average, 1–2 mg per day)

Plasma transferrin (3 mg)

Storage iron

Circulating erythrocytes (Hb) (1800 mg)

Reticuloendothelial macrophages (600 mg)

Utilisation

Other iron-containing enzymes (100 mg)

Bone marrow (300 mg)

Utilisation

Bone marrow (300 mg)

Utilisation

Other iron-containing enzymes (100 mg)

Sloughed mucosal cells, desquamation, menstruation, other blood loss

Iron loss * 1–2 mg/day

* no physiological pathway for iron excretion

What we know about iron deficiency and iron therapy in heart failure

- Iron deficiency (with or without anaemia) is common in heart failure.
- In HFrEF, treatment of iron deficiency with intravenous iron improves symptoms, quality-of-life and functional capacity (oral iron does NOT).
- Intravenous iron replacement seems to be safe (but relatively small numbers of patients in short-term studies).
- We do not know whether intravenous iron reduces hospital admissions or death.
New mortality/morbidity trials with intravenous iron: Hospitalized patients

**IRON-MAN**

- **Population:** 1300 patients. LVEF <45%, NYHA class II – IV. Iron deficient – TSAT <20% and/or ferritin <100 ug/L. Evidence of higher risk: current or recent HF hospitalisation OR out-patients with NT-proBNP >250 ng/L in (>1,000 ng/L in AF) (or BNP of > 75 pg/mL/300 pg/mL)
- **Intervention:** Intravenous iron (III) isomaltoside vs placebo.
- **Primary endpoint:** CV death or HF hospitalisation.

**Affirm-AHF**

- **Population:** 1100 patients; hospitalized for acute HF; EF <50%; serum ferritin <100 ng/mL or ≤299 ng/mL if transferrin saturation (TSAT) <20%. Hb must be >8g/dL.
- **Intervention:** Intravenous ferric carboxymaltose vs placebo.
- **Primary endpoint:** CV death and HF hospitalization: at 52 weeks (recurrent events).

ClinicalTrials.gov ¹NCT02642562 ²NCT02937454
FAIR-HF 2¹

- **Population:** 1200 patients with HF. Iron deficient – TSAT <20% and/or ferritin <100 ug/L. Haemoglobin of 9.5 to 14.0 g/dL
- **Intervention:** Intravenous ferric carboxymaltose vs placebo.
- **Primary endpoint:** CV death and HF hospitalization (recurrent events).

HEART-FID²

- **Population:** 3014 patients; NYHA class II-IV. EF ≤35%; serum ferritin <100 ng/mL or ≤299 ng/mL if transferrin saturation (TSAT) <20%. Hb must be >9 and <13.5 g/dL. Recent HF hospitalization or elevated NPs.
- **Intervention:** Intravenous ferric carboxymaltose vs placebo.
- **Primary endpoint:** Death and HF hospitalization: at 52 weeks and change in 6MWT at 24 weeks.

ClinicalTrials.gov ¹NCT03036462 ²NCT03037931
What is new in the treatment of heart failure?

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  - Cardiac myosin activator – omecamtiv mecarbil
  - Intravenous iron – ferric carboxymaltose and isomaltoside
  - SGLT2 inhibitor – dapagliflozin and empagliflozin

• **HF-PEF:**
  - PARAGON-HF – sacubitril/valsartan
  - SGLT2 inhibitor – empagliflozin
SGLT-2 inhibitors

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight. Also renoprotective (in diabetes)?
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

The key findings in EMPA-REG OUTCOME

Cardiovascular mortality

Heart failure Hospitalization

Hazard ratio, 0.62 (95% CI, 0.49–0.77)  
P<0.001

Hazard ratio, 0.65 (95% CI, 0.50–0.85)  
P=0.002
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group

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SGLT2 inhibitors: How do they work?

"The metabolodiuretic promise of SGLT2 inhibition: The search for the sweet spot in heart failure"

Verma, McMurray & Cherney
JAMA Cardiol. Published online June 21, 2017.
SGLT-2 inhibitors

• How do they work?
  – Diuretic/natriuretic effect?
  – Improved myocardial metabolism?
  – Na\(^+\)/H\(^+\) exchanger?
  – Improved renal function?

• Can they be used to treat established HF?
  – Existing trials largely about prevention of incident HF
  – Just HF patients with diabetes or all HF patients?
What else is in the pipeline? (Phase 3 mortality/morbidity trials)

**EMPEROR-Reduced**¹

- **Hypothesis:** Empagliflozin will be superior to placebo, added to SOC, in patients with symptomatic chronic HF-REF
- **Population:** 2850 patients; symptomatic HF; EF ≤40%; EF 36-40%/NT-proBNP ≥2500 pg/ml; 31-35%/≥1000 pg/ml; ≤30% ≥600 pg/ml; eGFR ≥20 ml/min/1.73 m²; SBP ≥100 mmHg
- **Primary endpoint:** CV death or HF hospitalization

**Dapa-HF**²

- **Hypothesis:** Dapagliflozin will be superior to placebo, added to SOC, in patients with symptomatic chronic HF-REF
- **Population:** 4500 patients; symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml; eGFR ≥30 ml/min/1.73 m²; SBP ≥95 mmHg
- **Primary endpoint:** CV death or worsening HF event

¹NCT03057977 ²NCT03036124
HF with preserved EF (HF-PEF)

We still do not have evidence-based treatment
Key large RCTs in HF-PEF

**PEP-CHF**
- **Placebo**
- **Perindopril**
- HR (CI) 0.92: (0.70–1.21)
- P=0.55

**CHARM-Preserved**
- **Placebo**
- **Candesartan**
- HR (CI) 0.89: (0.77–1.03)
- P=0.12

**I-Preserve**
- **Placebo**
- **Irbesartan**
- HR (CI) 0.95: (0.86–1.05)
- P=0.35

**TOPCAT**
- **Placebo**
- **Spironolactone**
- HR (CI) 0.89: (0.77–1.04)
- P=0.14
What is new in the treatment of heart failure?

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- Intravenous iron – ferric carboxymaltose and isomaltoside
- SGLT2 inhibitor – dapagliflozin and empagliflozin

**HF-PEF:**
- PARAGON-HF – sacubitril/valsartan
- SGLT2 inhibitor – empagliflozin
PARAGON-HF
Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejection fraction

Target patient population: ~4,800 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

Active run-in period

Screening

Valsartan 80 mg BID*

Sacubitril/valsartan 200 mg BID

Randomization 1:1

valsartan 100 mg BID

Double-blind treatment period

Valsartan 160 mg BID

On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

~240 weeks

Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1. ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BID=twice daily; CV=cardiovascular; HF=heart failure; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association

https://clinicaltrials.gov/ct2/show/NCT01920711
What is new in the treatment of heart failure?

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- Intravenous iron – ferric carboxymaltose and isomaltoside
- SGLT2 inhibitor – dapagliflozin and empagliflozin

**HF-PEF:**
- PARAGON-HF – sacubitril/valsartan
- SGLT2 inhibitor – empagliflozin
Hypothesis: Empagliflozin will reduce morbidity and mortality in patients with HF-PEF.

Population: 4126 patients; symptomatic HF; EF >40%; NT pro BNP >300 pg/ml (> 900 pg/ml for patients with AF); structural heart disease or HF hospitalisation in prior 12 months.

Intervention: Empagliflozin 10 mg once daily vs. placebo.

Primary endpoint: CV death or HF hospitalization (Secondary – first and recurrent HF hospitalization)

Status: Enrolling?
Summary and conclusions

• Exciting times in heart failure!
• We continue to make progress in HFREF — new treatment reducing mortality (sacubitril/valsartan).
• New mechanisms and new trials — more than at any time ever before!
• Large trial in HFPEF just completed enrollment and a new one started.