Current challenges in the treatment of heart failure

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The Burden of Heart Failure

Heart failure: a major cause of death worldwide

- Predicted to develop in 1 in 5 people in their lifetime, is a major cause of death.
- There is no effective “cure” for heart failure.
- Treatment of heart failure remains the same, regardless of the type of heart failure present in the patient, their gender, or whether the patient has diabetes and/or other comorbidities.

United States:

- >6.5 million individuals have HF;
- 1 million new cases are diagnosed annually
- Despite advances in diagnosis and treatment, 1-year mortality after HF hospitalization > 30%

Cresci S, *Circ Genom Precis Med* 2019 A Scientific Statement From the American Heart Association

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The Burden of Heart Failure

**United Kingdom:**

- **BHF:** heart failure (HF) hospital admissions have risen by a third in 5 years
- ~920,000 people have HF → greater burden on health services than 4 common cancers combined
- HF patients stay in hospital for ~10 days (2x the average of all diagnoses)
  - Prof Nilesh Samani (BHF Medical Director): “HF poses a growing and increasingly complex challenge…. how we diagnose, treat and care for these patients could be far better.”

**Australia:**

- ~300,000 individuals have HF

### Stages of Heart Failure

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF
- **High risk**
  - LV remodelling

**STAGE B**
Structural heart disease but without signs or symptoms of HF
- **HF signs & symptoms**

**STAGE C**
Structural heart disease with prior or current symptoms of HF
- **Refractory HF**
  - Refractory symptoms of HF at rest, despite DCM

**STAGE D**
Refractory HF
- **Refractory HF**
  - Refractory HF symptoms at rest
  - Recurrent hospitalizations despite DCM

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- American Heart Association:
- **2013 HF Guidelines**

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**THERAPY**
- **Goals**:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities

**Causes**
- **ACEI or ARB as appropriate**
- Beta blockers as appropriate
- In selected patients
- **ICD**
- Revascularization or valvular surgery as appropriate

**Therapy**
- **Goals**:
  - Prevent HF symptoms
  - Prevent further cardiac remodeling

**Drugs**
- ACEI or ARBs as appropriate
- Beta blockers as appropriate
- In selected patients
- **ICD**
- Revascularization or valvular surgery as appropriate

**Hypertension**
- **Goals**:
  - Control symptoms
  - Improve QOL
  - Prevent hospitalization
  - Prevent mortality

**Diastolic**
- **Goals**:
  - Control symptoms
  - Improve QOL

**Hypertrophic Cardiomyopathy**
- **Goals**:
  - Control symptoms
  - Improve QOL

**Hypertension**
- **Goals**:
  - Control symptoms
  - Improve QOL

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Houser et al., Circ Res. 2012;111:131-150
Current Therapy for Heart Failure

Current therapies:

- largely based on clinical trials in patients where left ventricular ejection fraction is reduced, HFrEF

Fiuzat JACC HF 2020;
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Current challenges in the treatment of heart failure

Heterogeneity of heart failure patients is considerable

- whether the patient has diabetes and/or other comorbidities

PROJECTED BURDEN OF HEART FAILURE RISK

Dunlay SM et al Nat Rev Cardiol 2017

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Current challenges in the treatment of heart failure

Heterogeneity of heart failure patients is considerable

• whether the patient has diabetes and/or other comorbidities
• the type of heart failure present
• patient gender

Dunlay SM et al Nat Rev Cardiol 2017
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Current challenges in the treatment of heart failure

Big questions and areas of clinical need in heart failure

• Heart Failure with Preserved Ejection Fraction (HFpEF)
• The diabetic heart (“diabetic cardiomyopathy”)
• Myocardial Infarction (and subsequent cardiomyopathy)

Cardiac fibrosis one of the common underlying factors
Heart Failure with Preserved Ejection Fraction (HFpEF)

HFpEF: an ever-expanding clinical burden:

- HFpEF describes a diagnosis of heart failure in symptomatic patients whose LV EF is >50%
- in whom noncardiac causes of symptoms have been excluded
- phenotype is now more common than HFrEF in hospital admissions for HF
- Risk of HFpEF increases sharply with age
- additional risk factors for development of HFpEF include obesity and hypertension in particular

Heart Failure with Preserved Ejection Fraction (HFpEF)

HFpEF likely represents a spectrum of several aetiologies

- depending on which comorbidities are also present
- Females (esp elderly) overrepresented
- HFpEF is particularly heterogeneous
- Multimorbidity is common in HF
  - more pronounced in HFpEF
  - ~50% of patients have >5 major comorbidities

Dunlay et al Nat Rev Cardiol. 2017

Figure 8 | Multimorbidity in heart failure in the community. The frequency distribution of number of comorbid conditions in a men and b women with heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF). Patients with HFpEF more frequently had a higher number of comorbidities. 

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Heart Failure with Preserved Ejection Fraction (HFpEF)

Characteristics of HFpEF

- increased cardiac mass, fibrosis and stiffness in human HFpEF, with ↓ microvascular density
- exercise intolerance, elevated left atrial pressure (LAP, particularly on exercise), pulmonary congestion and arterial stiffness are fundamental features
- systemic inflammation is also considered a key characteristic

The mechanisms are different, the comorbidities are different, disease aetiology is different – appropriate management of HFpEF will be different to HFrEF.

Heart Failure with Preserved Ejection Fraction (HFpEF)

Aberrant NO\(^{\bullet}\) signalling as a therapeutic target in HFpEF:

- HNO: redox sibling of NO\(^{\bullet}\)
  - Acutely overcomes responses dysregulated cardiac NO\(^{\bullet}\) responses in diabetes

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Velagic et al Frontiers Pharmacol 2020, manuscript in preparation 2020
Heart Failure with Preserved Ejection Fraction (HFpEF)

Aberrant NO• signalling as a therapeutic target in HFpEF:

- HNO donors limit diabetic cardiomyopathy in mice; Next-gen HNO-donor pharmacotherapies in development for HF

Cao et al Circ HF 2015; Hartman et al JACC. Bas Transl Sci 2018; Maack Eur Heart J 2019

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Heart Failure with Preserved Ejection Fraction (HFpEF)

Aberrant NO• signalling as a therapeutic target in HFpEF:

• observations of nitrosative stress in human HFpEF formed the basis of a new model of HFpEF
  − associated with increased activity of iNOS and enhanced S-nitrosylation of IRE1α
  − triggers defective XBP1 splicing (a detrimental, rather than a protective, consequence of S-nitrosylation)
• did not include females & was only undertaken in young mice (roughly ~20yrs-old in humans)
• lack of age- and gender appropriate models with common concomitant co-morbidities represents a roadblock in preclinical studies searching for new drug targets in HFpEF

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The problem of the diabetic heart

Diabetes

• increases heart failure risk >2.5-fold, independent of concomitant comorbidities; more-so in females.
• significant heterogeneity across patients with LV dysfunction and diabetes
• comorbidities commonly incorporating obesity, dyslipidaemia and hypertension
The problem of the diabetic heart

Diabetes

- heterogeneity also encompasses the nature of the impairments in LV function,
  - at the level of cardiac relaxation and compliance (‘diastolic dysfunction’) or
  - impaired cardiac contractility (‘systolic dysfunction’).
- This has important implications for therapy, with multiple, distinct phenotypic patient clusters described, each exhibiting different degrees of LV systolic and diastolic dysfunction.

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Targeting contributors to “the diabetic heart”

Rebecca Ritchie, NC-IUPHAR Fibrosis Symposium 2020

Ritchie and Abel Circ Res 2020
Targeting contributors to “the diabetic heart”

Rebecca Ritchie, NC-IUPHAR Fibrosis Symposium November 2020

Ritchie and Abel
Circ Res 2020

- Antioxidants
- caPI3Kα
- Cardiomyocyte-selective Tg mice
- AAV6 delivery

Prakoso et al, Clin Sci 2017
Ritchie and Abel Circ Res 2020
Targeting contributors to “the diabetic heart”

Maladaptive cardiac glucose metabolism

Glucose metabolism to O-GlcNAc

C. Glucose metabolism to O-GlcNAc

- Glucose to glucose-6-P
- Pentose pathway
- Glutamine synthesis
- Hexitol pathway
- Fatty acid utilization
- Mitochondrial O-GlcNAc
- Fatty acid uptake
- Mitochondrial ROS
- Mitochondrial O-GlcNAc

Systemic Circulation
- Autonomic Dysfunction
- ROS/Oxidative Stress
- Inflammation

Myocardium
- Autonomic Dysfunction
- ROS/Oxidative Stress
- Inflammation

Cardiomyocyte
- Delta Ca^2+ Handling
- Myocyte Relengthening
- LV Fibrosis
- LV Diastolic Dysfunction
- LV Systolic Dysfunction

HEART FAILURE

Prakoso et al, Cardiovasc Res (in revision)
Ritchie and Abel Circ Res 2020
Targeting contributors to “the diabetic heart”

Maladaptive cardiac glucose metabolism

C. Glucose metabolism to O-GlcNAc

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Glucose → glucose-6-P → pentose pathway → fructose-6-P → glycogen synthesis

Hexitol pathway: fructose-6-P → hexosamine biosynthesis

Naked protein → O-GlcNAc → UDP-GlcNAc → UDP

AAV6-hOGT

Cardiac-selective AAV6 delivery

Prakoso et al, Cardiovasc Res (in revision)
Ritchie and Abel Circ Res 2020
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Maladaptive cardiac glucose metabolism

C Glucose metabolism to O-GlcNAc

Mouse LV

AAV6-hOGA
AAV6hOGA
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New approaches for tackling ischaemic damage

➢ Exploiting receptor mechanisms that promote resolution of inflammation: annexin-A1/formyl peptide receptors
  o FPR agonism as cardioprotection – but it’s the type of agonism that’s important
  o FPR small-molecule agonists with biased signalling profile may represent an innovative approach for the development of pharmacotherapy for MI (both early necrosis as well as protecting cardiac function)

Qin CX*, May LT* et al., Nature Commun. 2017, 2018

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Take home message

- Clearly, one size does not fit all; gender, heart failure phenotype and concomitant comorbidities likely impact the efficacy of pharmacotherapies for tackling cardiomyopathy.
Acknowledgments

Heart Failure Pharmacology
Darnel Prakoso, Miles de Blasio, Mitchel Tate, Owen Woodman, Liz Vecchio, Minh Deo, Charlie Cohen, Anida Velagic, Selena Peng, Ting Fu, Alex Parker, Abhi Sharma, Natasha Alexander; Jerome Lall

Cardiovascular Pharmacology
Dr. Chengxue Helena Qin

Cardiovascular & Pulmonary Pharmacology
A/Prof. Barbara Kemp-Harper

Preclinical Cardiology Microsurgery and Imaging Platform
Prof Xia-Jun Du, Dr Xiao-Ming Gao, Dr. Helen Kiriazis, Dr. Daniel Donner
A/Prof Julie McMullen