



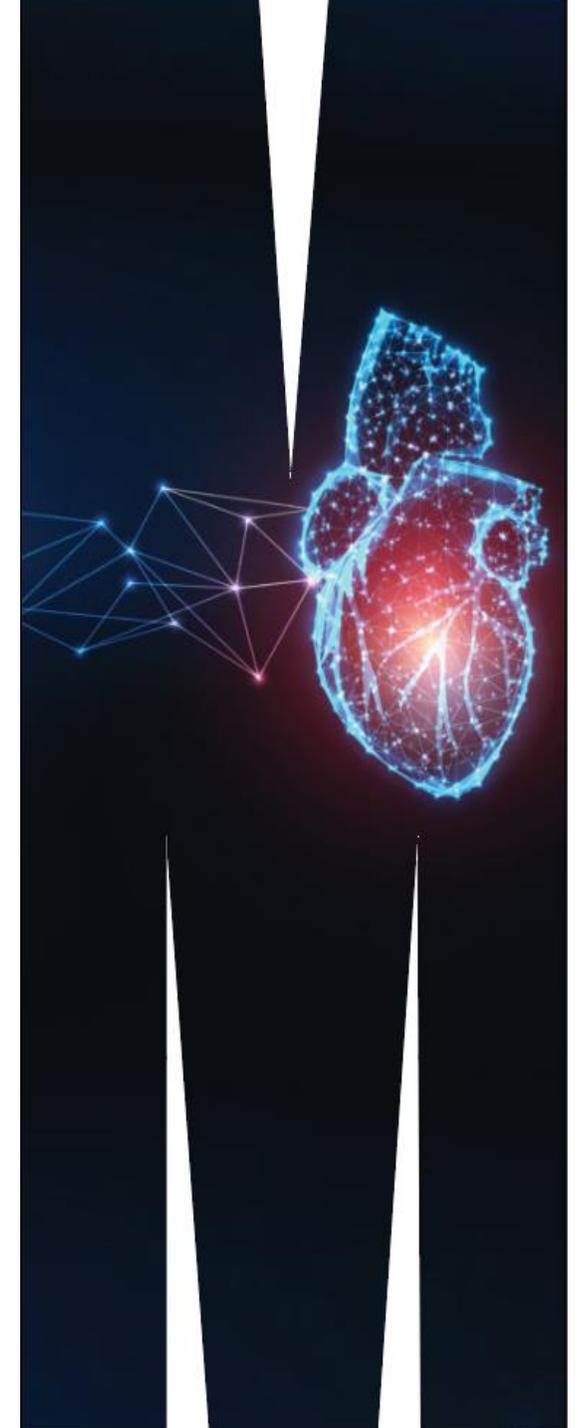
# Current challenges in the treatment of heart failure

**Rebecca Ritchie, Monash University**

Head, Heart Failure Pharmacology Laboratory

Theme Leader, Drug Discovery Biology

Monash Institute of Pharmaceutical Sciences



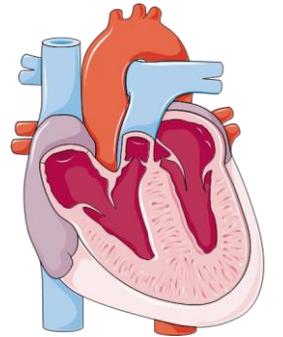
# The Burden of Heart Failure

## 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

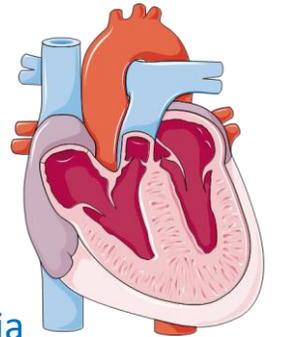
## United Kingdom:

- 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.”

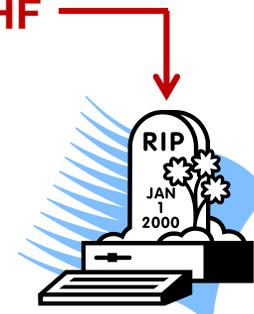
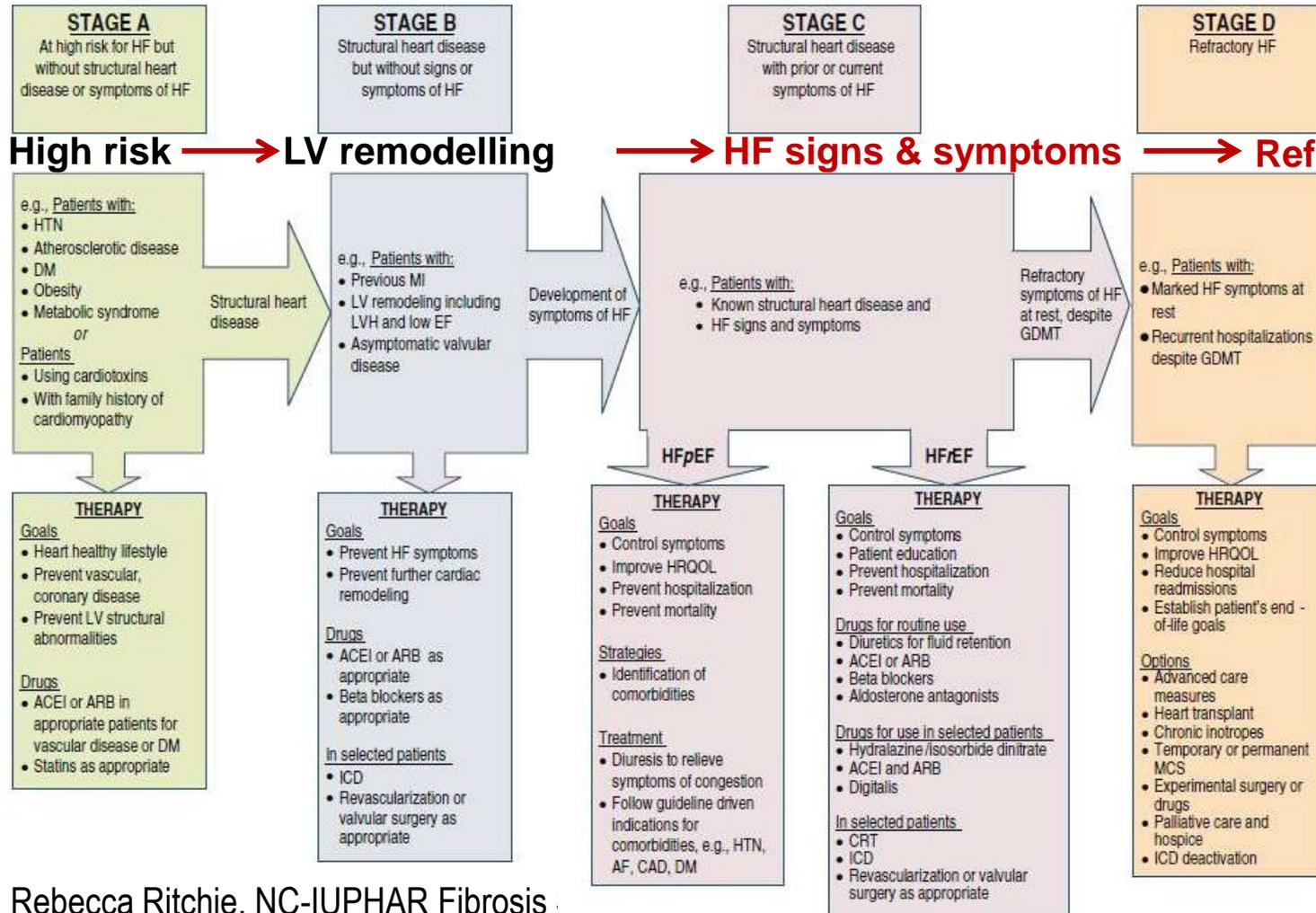
## Australia:

- **~300,000** individuals have HF

Benjamin EJ, et al. *Circulation* 2017; British Heart Foundation tweet 04-09-2019; Newton PJ et al. *Medical Journal of Australia* 2016



# Stages of Heart Failure



- American Heart Association:
- 2013 HF Guidelines

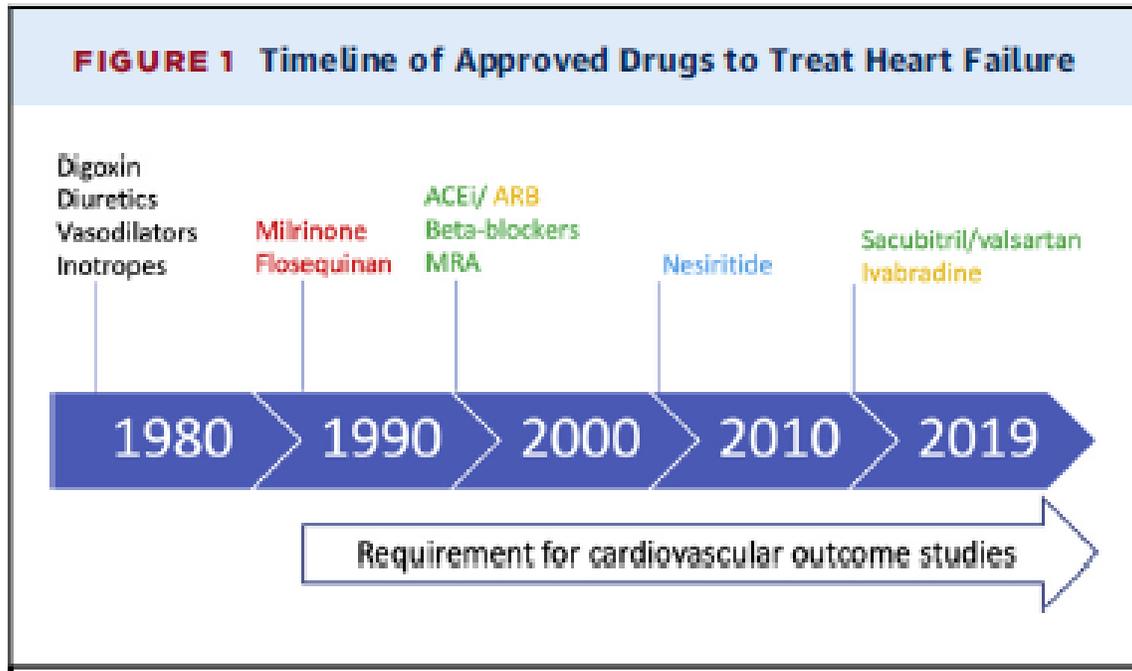
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Houser et al., Circ Res. 2012;111:131-150

# Current Therapy for Heart Failure

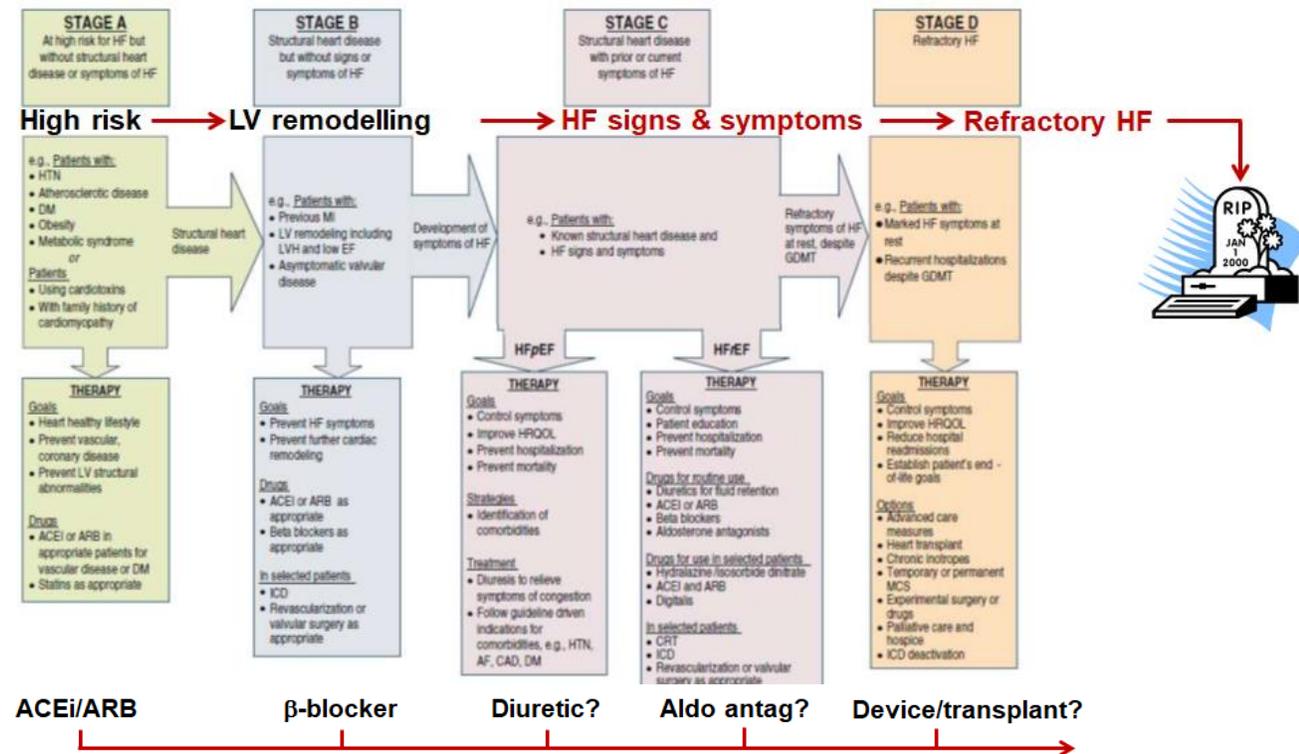
## Current therapies:

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



Fiuzat JACC HF 2020;

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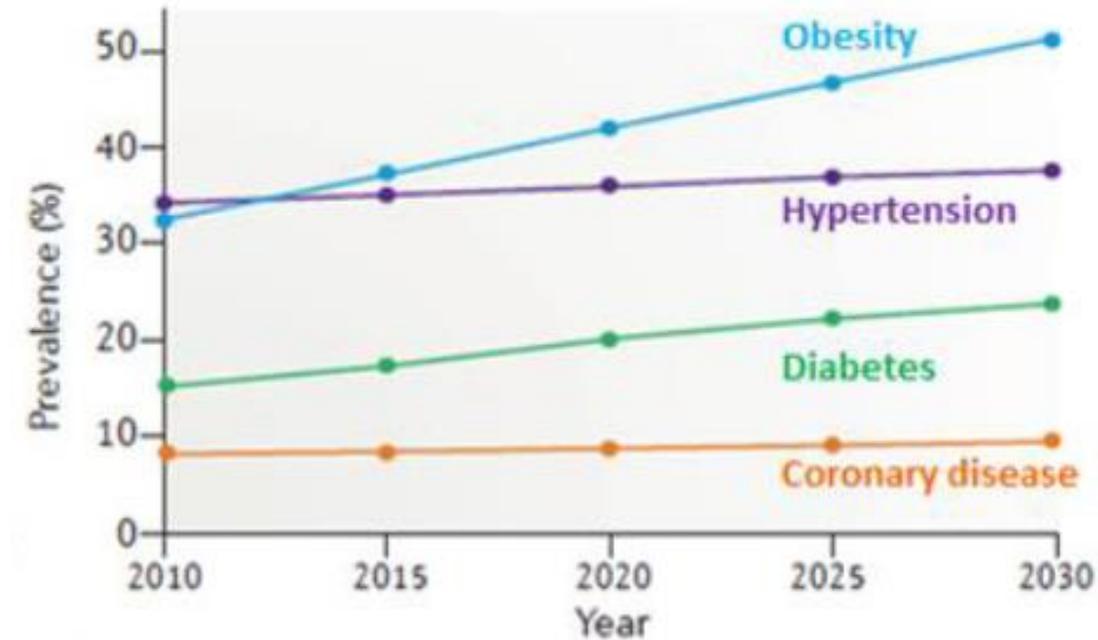


# Current challenges in the treatment of heart failure

## Heterogeneity of heart failure patients is considerable

- whether the patient has diabetes and/or other comorbidities

### PROJECTED BURDEN OF HEART FAILURE RISK



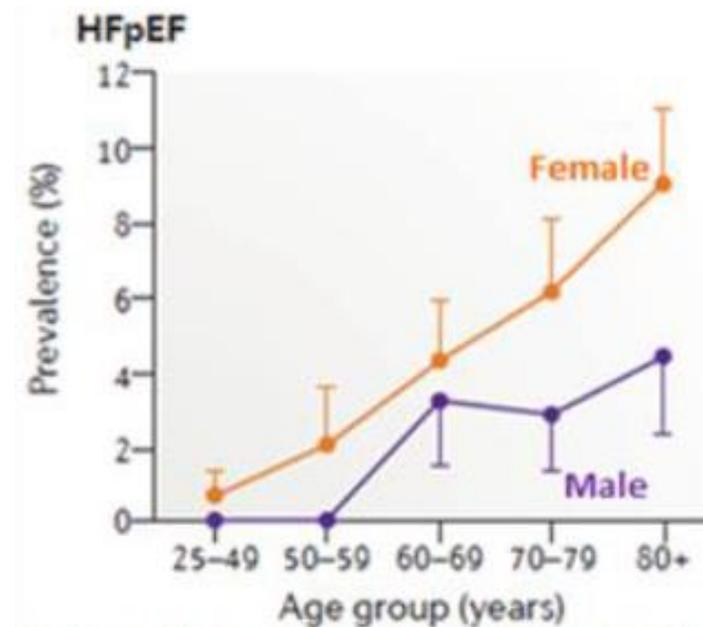
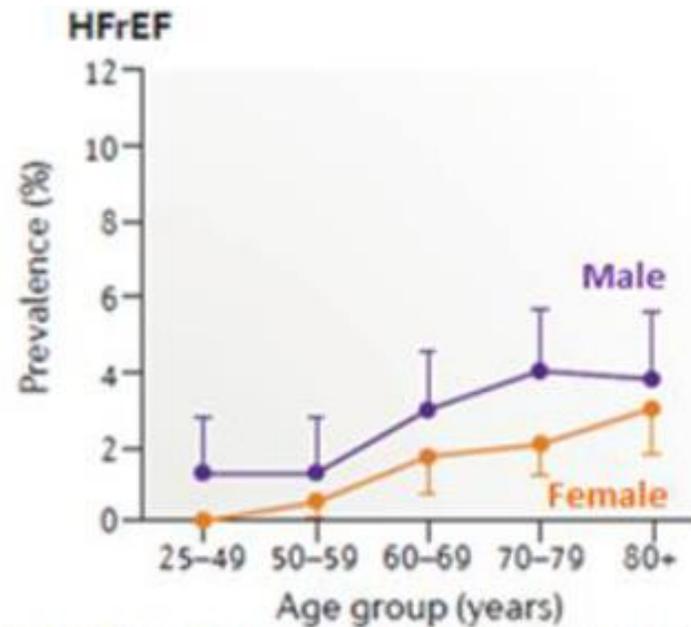
Dunlay SM et al Nat Rev Cardiol 2017

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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

Mohammed et al *Circulation*. 2015; Pieske et al. *Eur Heart J*. 2019; Dunlay et al *Nat Rev Cardiol*. 2017; Redfield *N Engl J Med*. 2016; van Riet et al. *Eur J Heart Fail*. 2016; Shah SJ. *J Cardiovasc Transl Res*. 2017; Seferović et al. *Eur J Heart Fail*. 2018

# 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

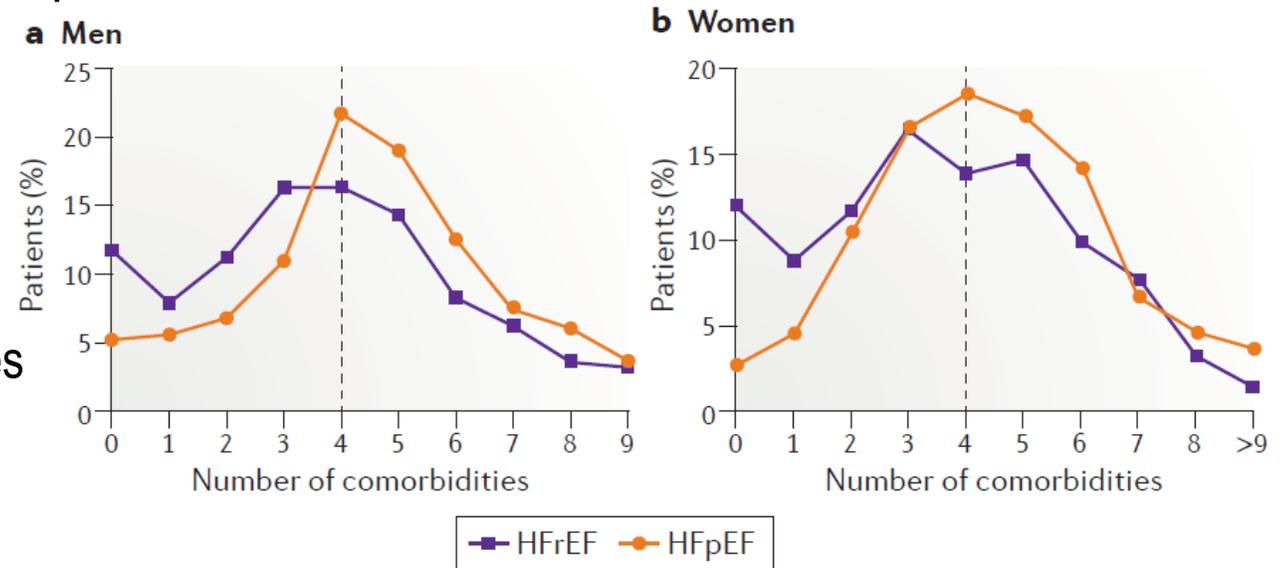


Figure 8 | **Multimorbidity in heart failure in the community.** The frequency distribution of number of comorbid conditions in **a** | men and **b** | women with heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF). Patients with HFpEF more frequently had a higher number of comorbidities<sup>54</sup>.

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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

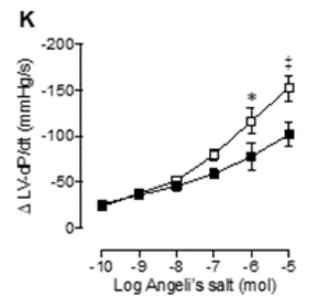
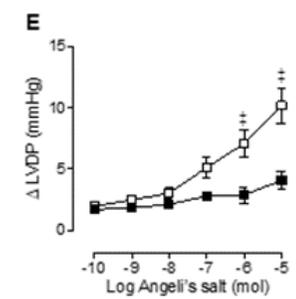
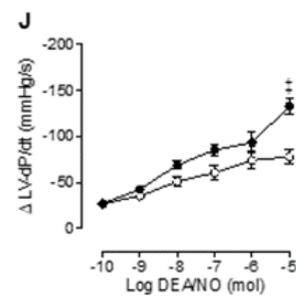
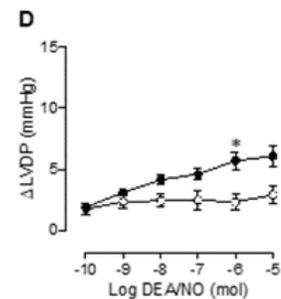
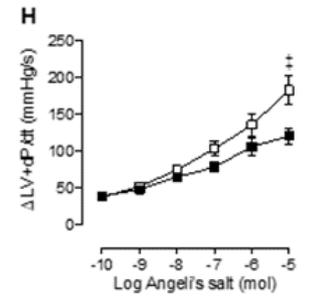
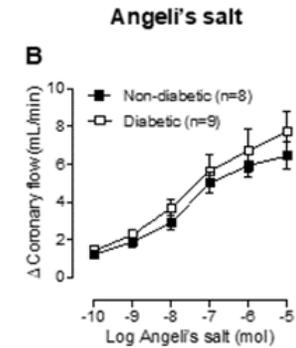
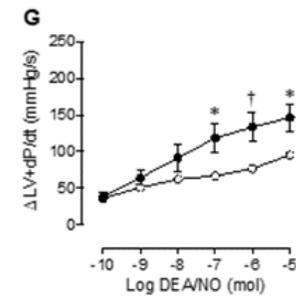
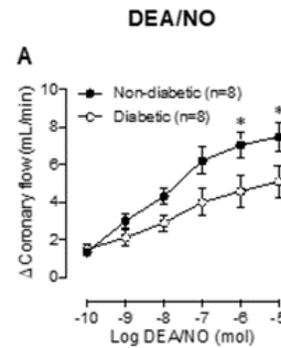
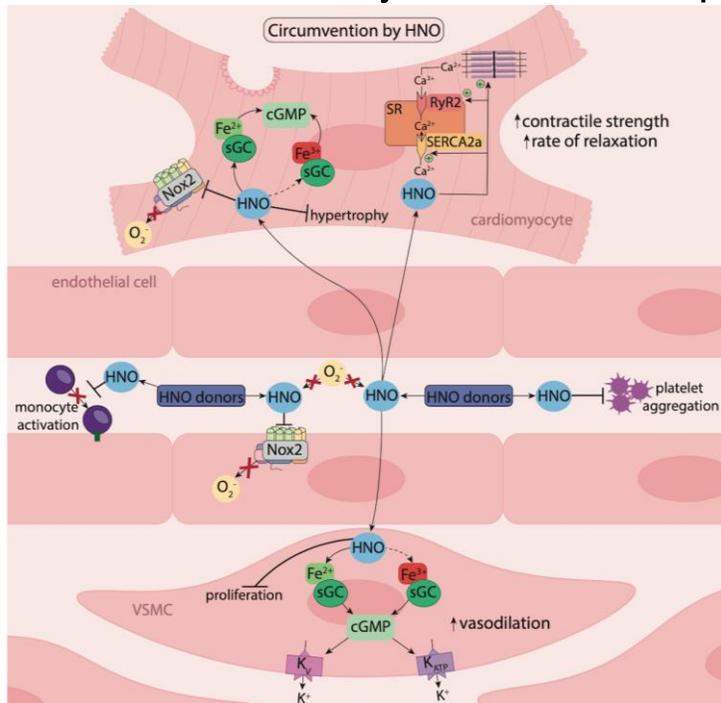
**The mechanisms are different, the comorbidities are different, disease aetiology is different – appropriate management of HFpEF will be different to HFrEF.**

Mohammed et al Circulation. 2015; Pieske et al. Eur Heart J. 2019; Dunlay et al Nat Rev Cardiol. 2017; Redfield N Engl J Med. 2016; van Riet et al. Eur J Heart Fail. 2016; Shah SJ. J Cardiovasc Transl Res. 2017; Seferović et al. Eur J Heart Fail. 2018

# Heart Failure with Preserved Ejection Fraction (HFpEF)

## Aberrant NO• signalling as a therapeutic target in HFpEF:

- HNO: redox sibling of NO•
  - Acutely overcomes responses dysregulated cardiac NO• responses in diabetes



# 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

Identifier	Description	Inclusion	Intervention	Status	Data availability
NCT02157506	BMS-986231 dose escalation study (6h i.v. infusion, 3-12µg/kg/min)	LVEF <40%	BMS-986231 vs placebo	Recruited n=70; Completion 31/07/2015	Results published (39)
NCT03016325	BMS-986231 48h i.v. infusion in patients hospitalised for ADHF	LVEF ≤40%	BMS-986231 vs placebo	Recruited n=331; Completion 12/11/2019	No results in HF patients posted
NCT03016325	BMS-986231 8h i.v. infusion on top of diuretic (furosemide)	LVEF <45%	BMS-986231 vs placebo (crossover)	Recruited n=23; Completion 9/01/2020	No results posted; design published (43)
NCT03357731	BMS-986231 5h i.v. infusion	LVEF <40%	BMS-986231 vs GTN vs placebo (crossover)	Recruited n=185; Completion 10/05/2019	No results posted; design published (43)

**Figure 2:** Clinical trial update of HNO donor BMS-986231. Bristol Myers Squibb have several Phase 2 studies in HFpEF patients underway. None include HFpEF patients (despite the urgent clinical need) nor do they include longer-term studies to reduce LV dysfunction and remodelling over the longer-term (despite the drug's oral bioavailability). See text for references.

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 IRE1 $\alpha$
  - 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

Schiattarella GG et al. *Nature*. 2019; Redfield N *Engl J Med*. 2016; Dunlay et al *Nat Rev Cardiol*. 2017

# 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

# The problem of the diabetic heart

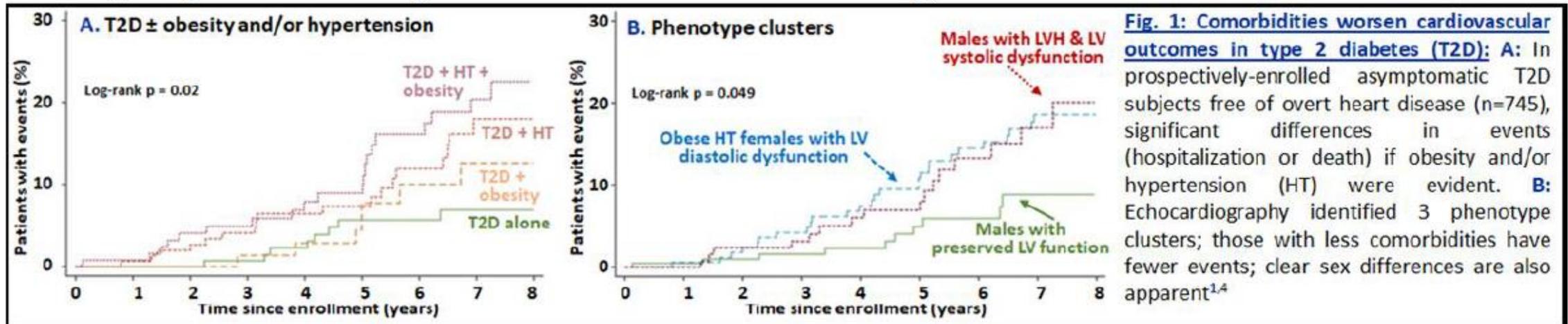
## Diabetes

- 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

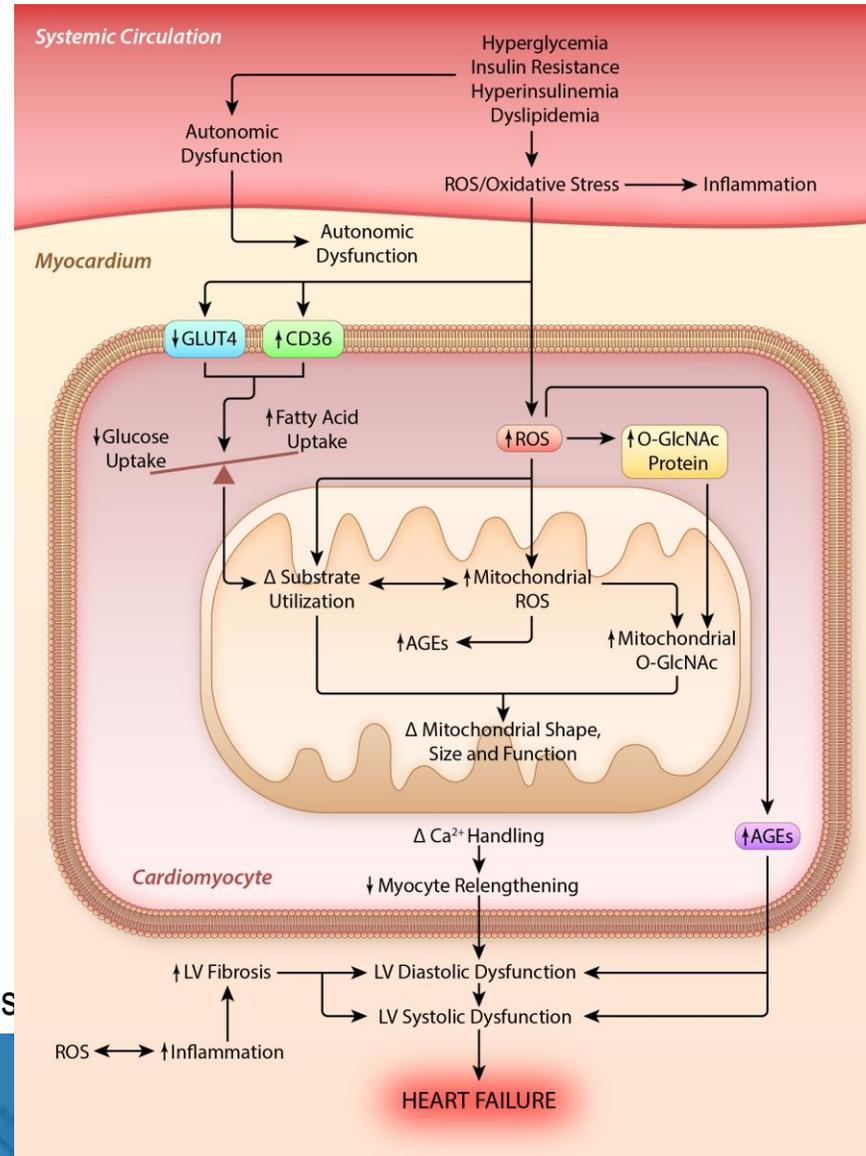
## Diabetes

- 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”



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Ritchie and Abel *Circ Res* 2020

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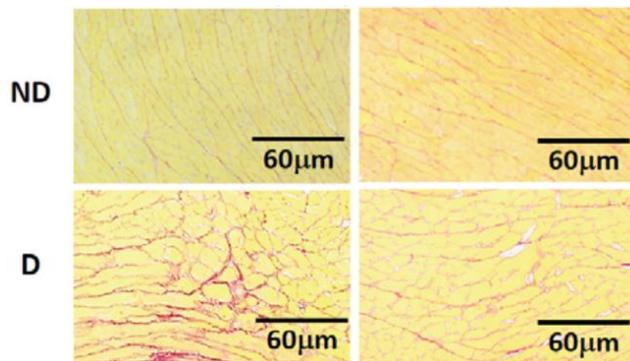
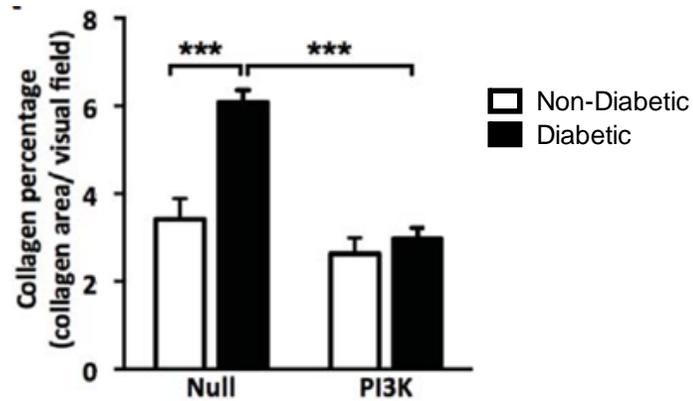
Darnel Prakoso



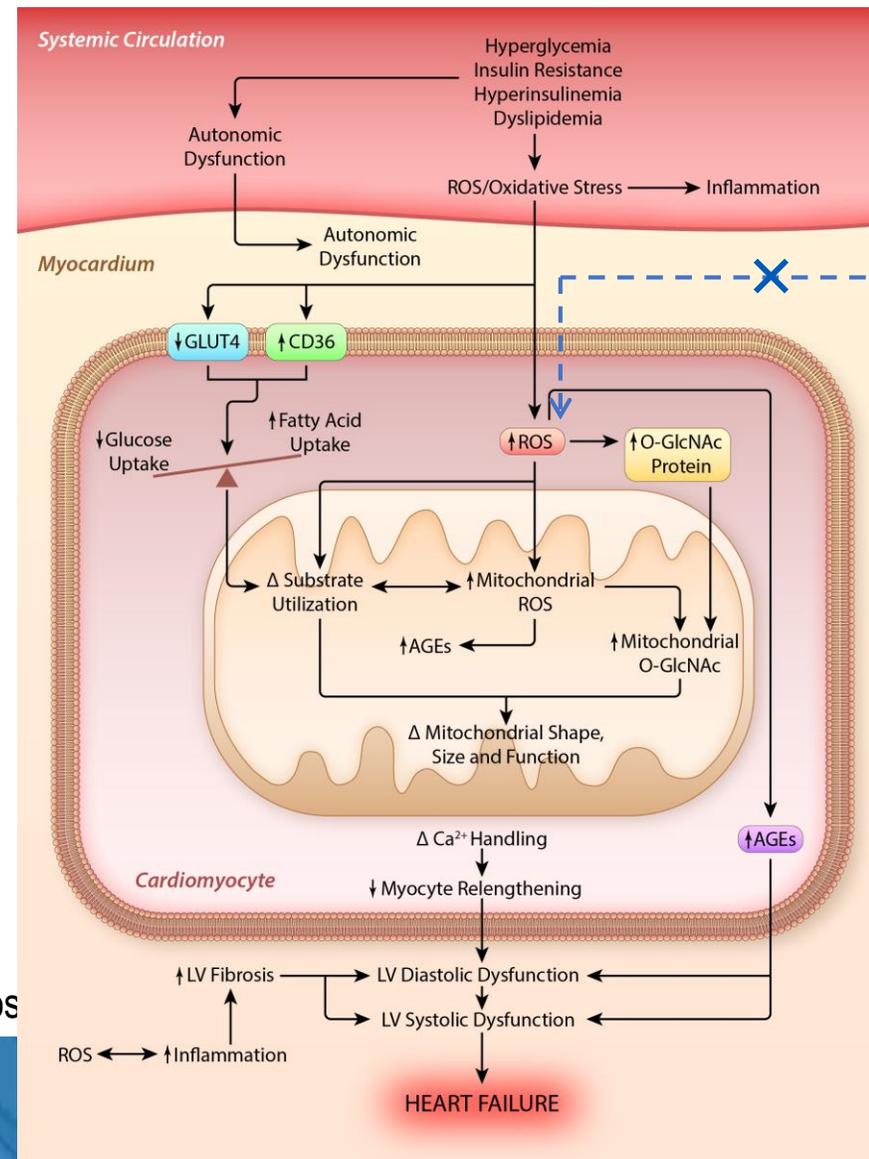
Miles De Blasio



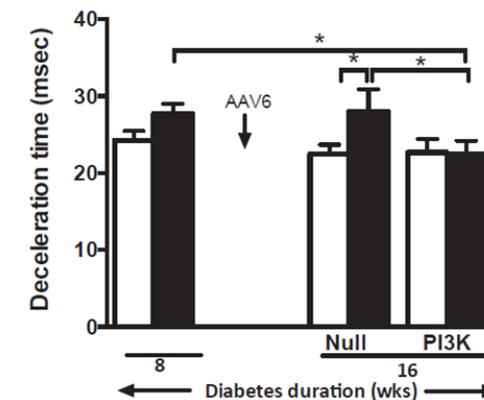
Julie McMullen



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**Antioxidants**  
**caPI3K $\alpha$**   
 Cardiomyocyte-selective Tg mice  
 AAV6 delivery

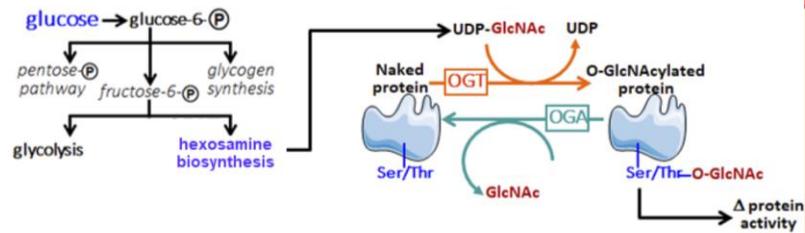


Prakoso *et al*, Clin Sci 2017  
 Ritchie and Abel *Circ Res* 2020

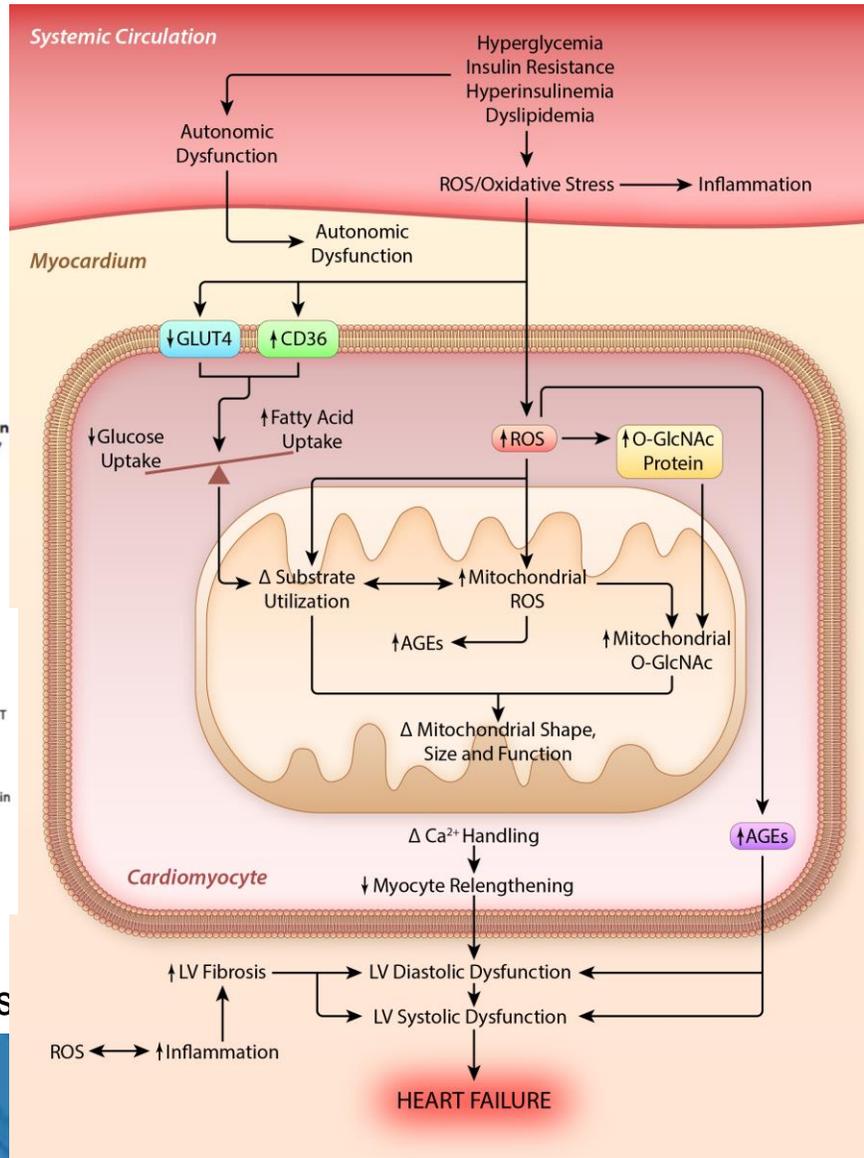
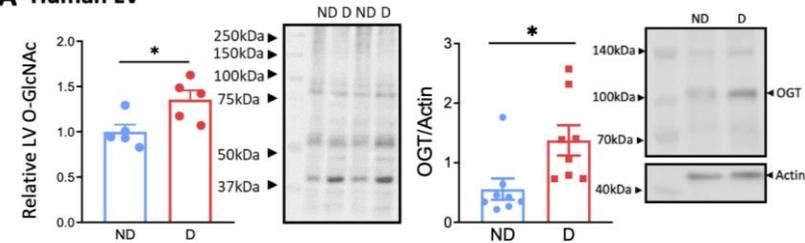
# Targeting contributors to “the diabetic heart”

Maladaptive cardiac glucose metabolism

## C Glucose metabolism to O-GlcNAc



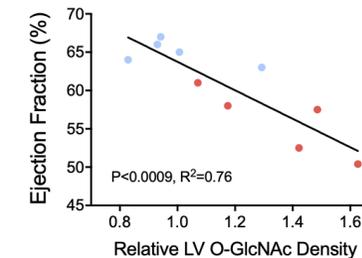
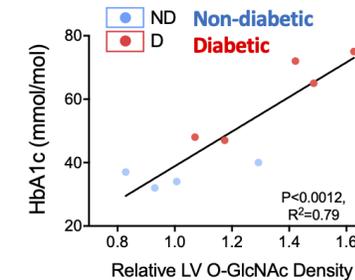
## A Human LV



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Miles De Blasio



Prakoso *et al*, Cardiovasc Res (in revision)  
Ritchie and Abel *Circ Res* 2020

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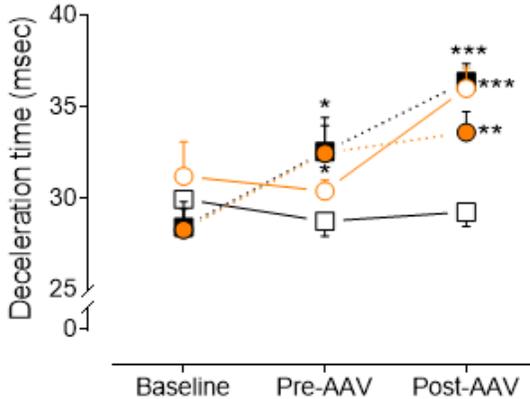
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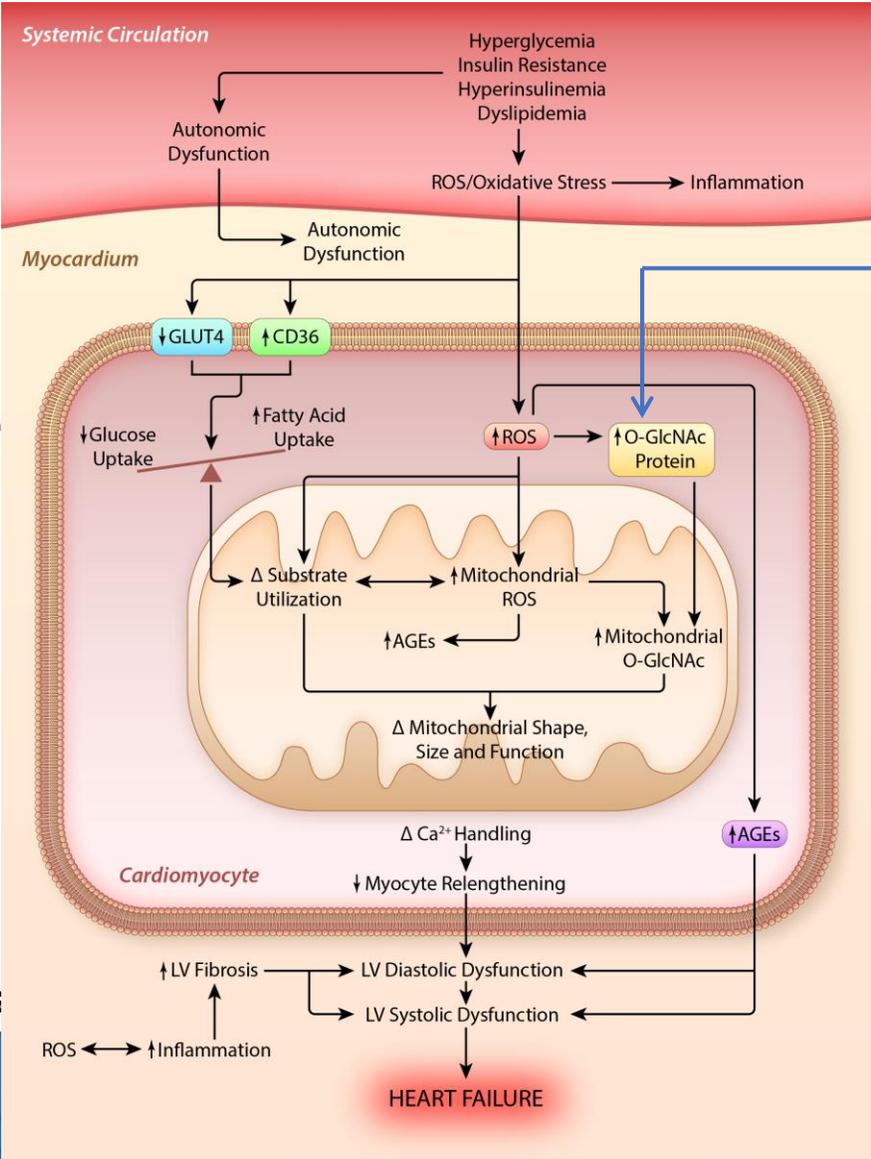
Miles De Blasio

AAV6-hOGT

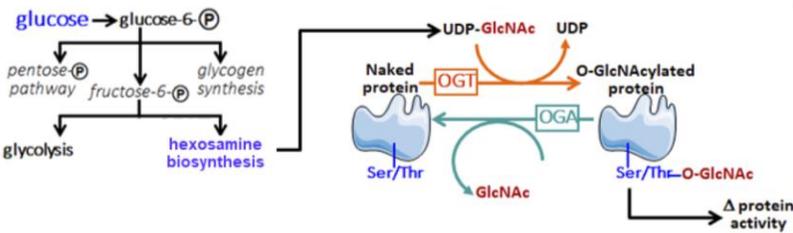
Cardiac-selective AAV6 delivery



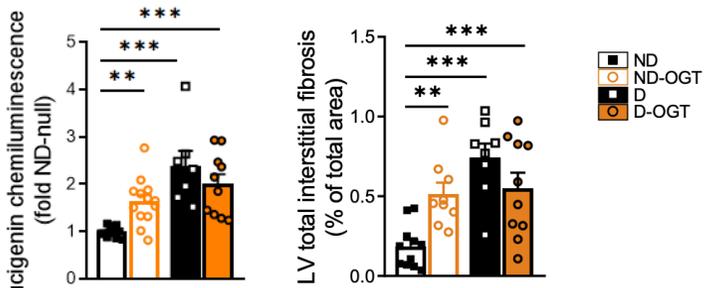
Prakoso *et al*, Cardiovasc Res (in revision)  
Ritchie and Abel *Circ Res* 2020



## C Glucose metabolism to O-GlcNAc



## Mouse LV

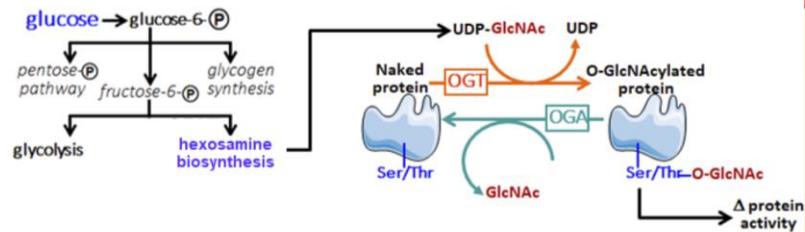


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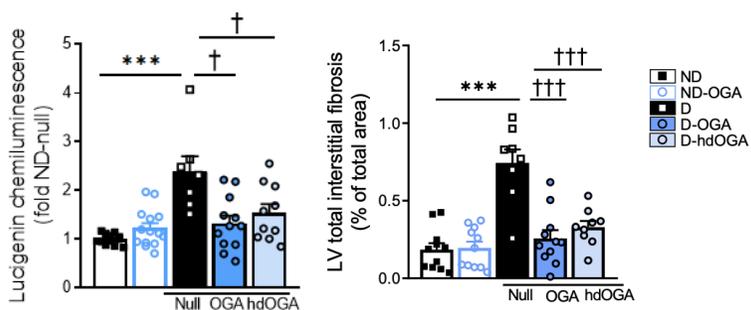
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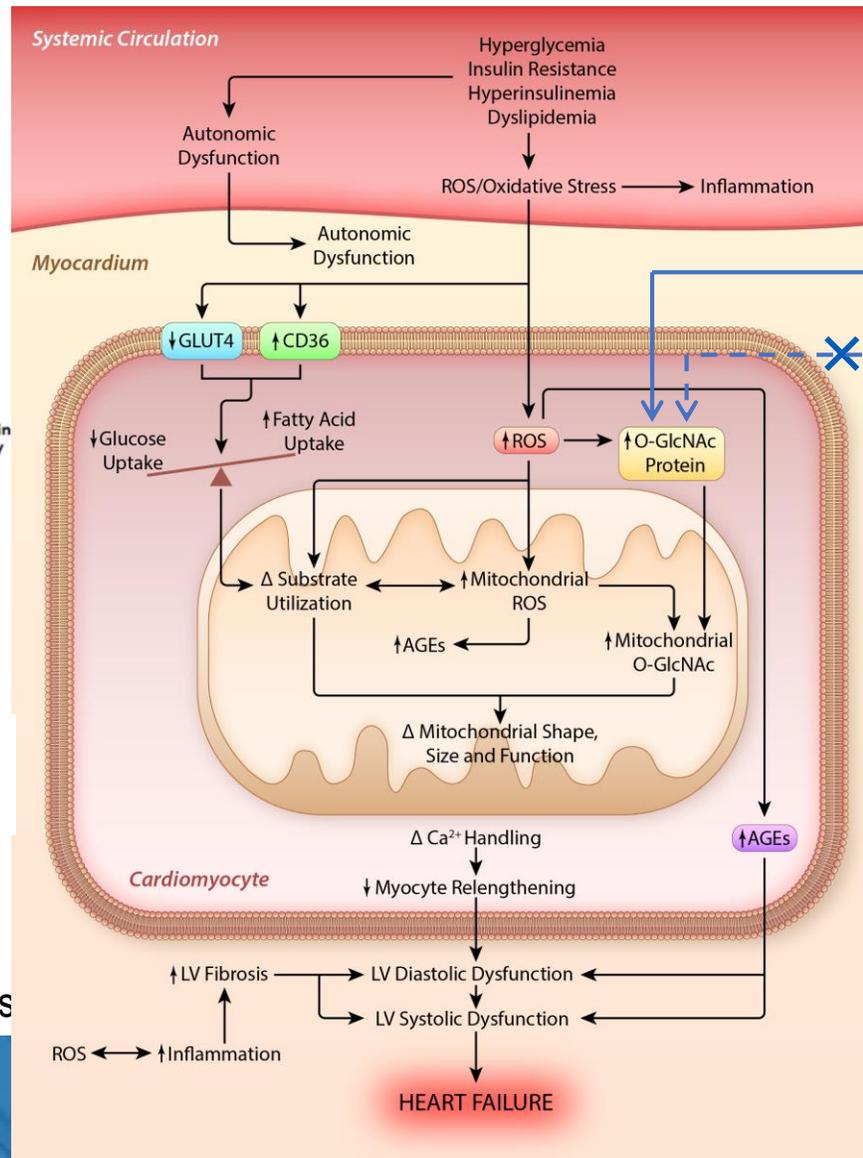
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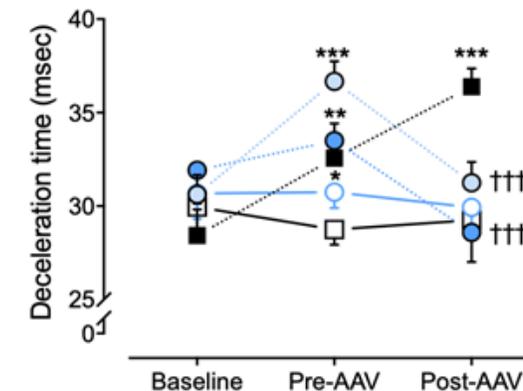


Miles De Blasio

AAV6-hOGT

AAV6hOGA

Cardiac-selective AAV6 delivery



Prakoso *et al*, Cardiovasc Res (in revision)  
Ritchie and Abel *Circ Res* 2020

# Current challenges in the treatment of heart failure

## Big questions and areas of clinical need in heart failure

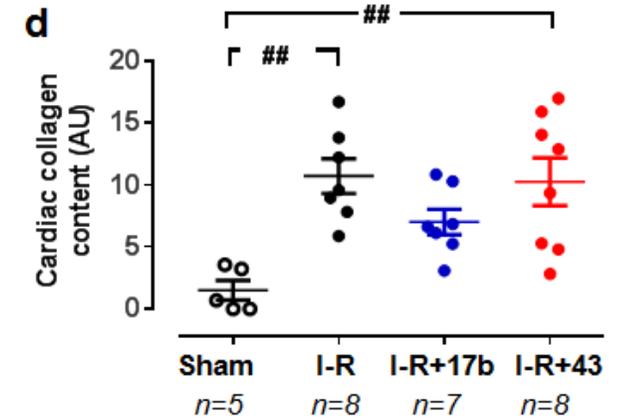
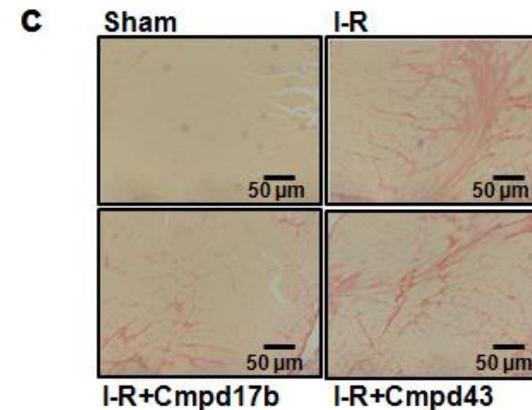
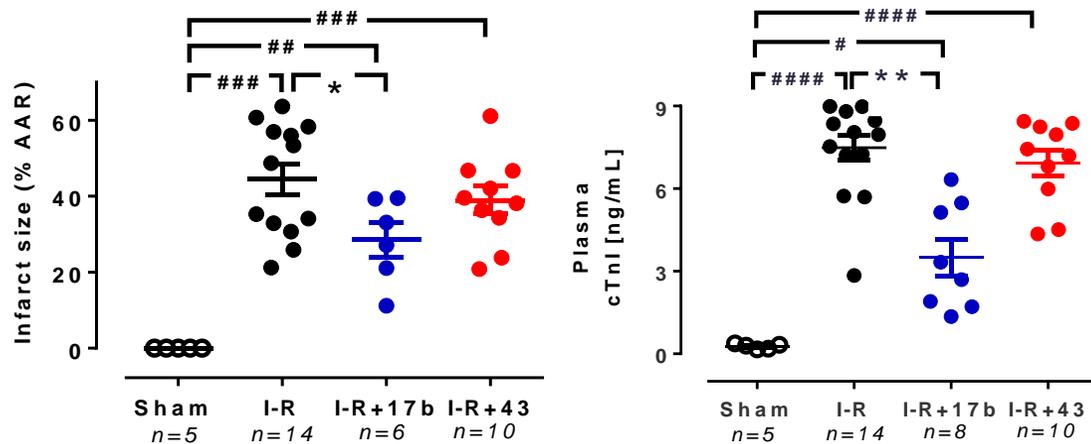
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# New approaches for tackling ischaemic damage

## ➤ Exploiting receptor mechanisms that promote resolution of inflammation: annexin-A1/formyl peptide receptors

- FPR agonism as cardioprotection – but it's the type of agonism that's important
- 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)



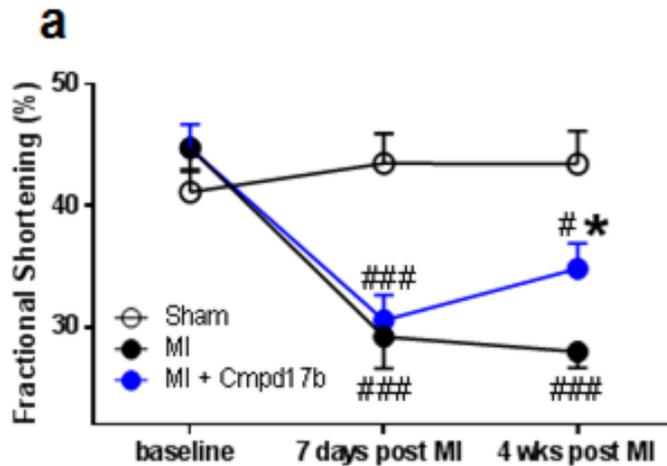
● Cmpd17b  
● Cmpd43

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

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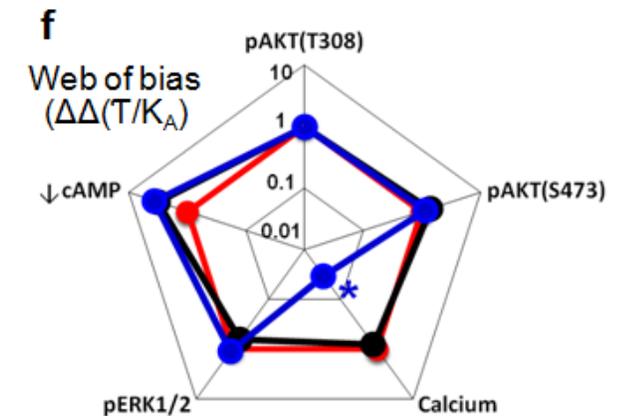
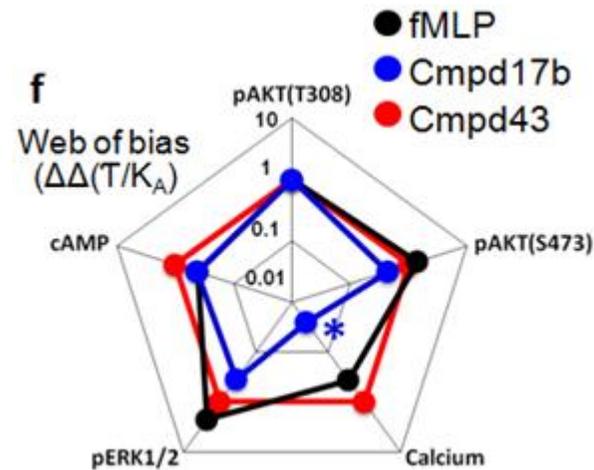
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Signaling fingerprint in hFPR1-CHO cells

hFPR2-CHO cells



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

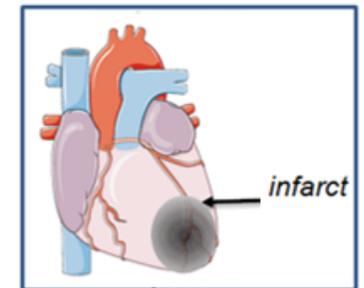
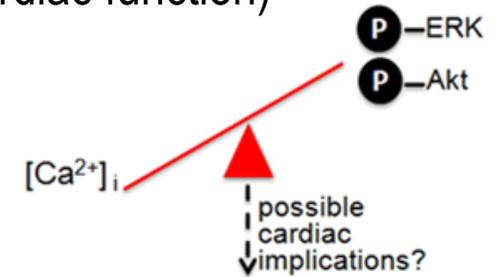
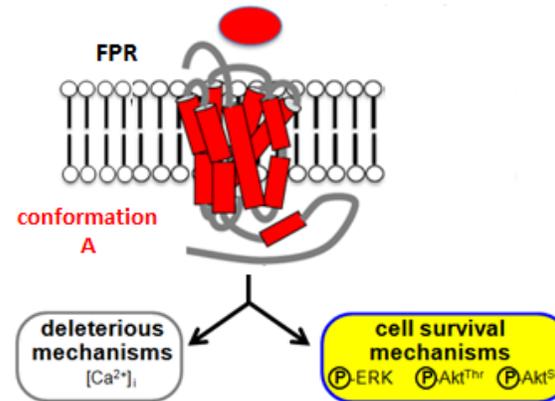
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# New approaches for tackling ischaemic damage

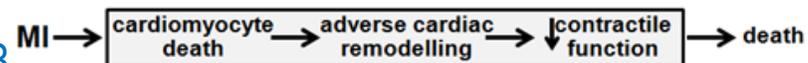
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conventional FPR agonist (e.g Cmpd43)



No net cardioprotection



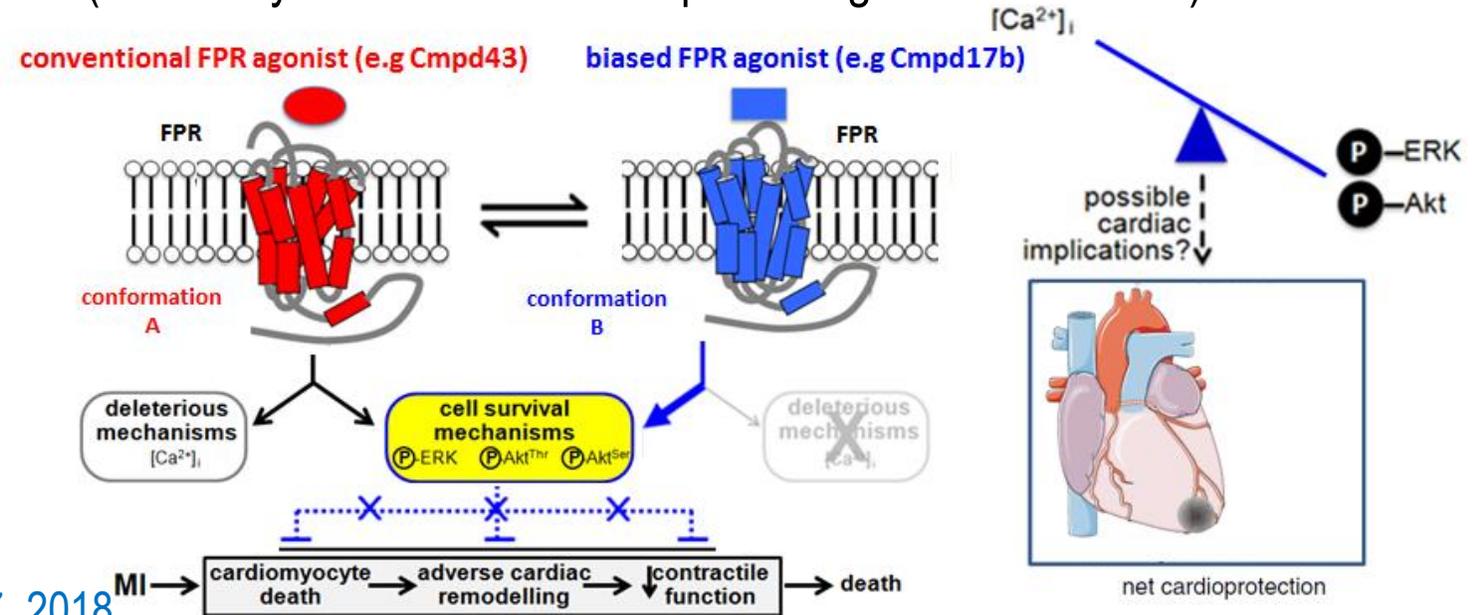
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## Take home message

- 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

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## Cardiovascular Pharmacology

Dr. Chengxue Helena Qin



## Cardiovascular & Pulmonary Pharmacology

A/Prof. Barbara Kemp-Harper



## Preclinical Cardiology Microsurgery and Imaging Platform

Prof Xiao-Jun Du, Dr Xiao-Ming Gao, Dr. Helen Kiriazis, Dr. Daniel Donner  
A/Prof Julie McMullen

