Cardiac Mitotrope:

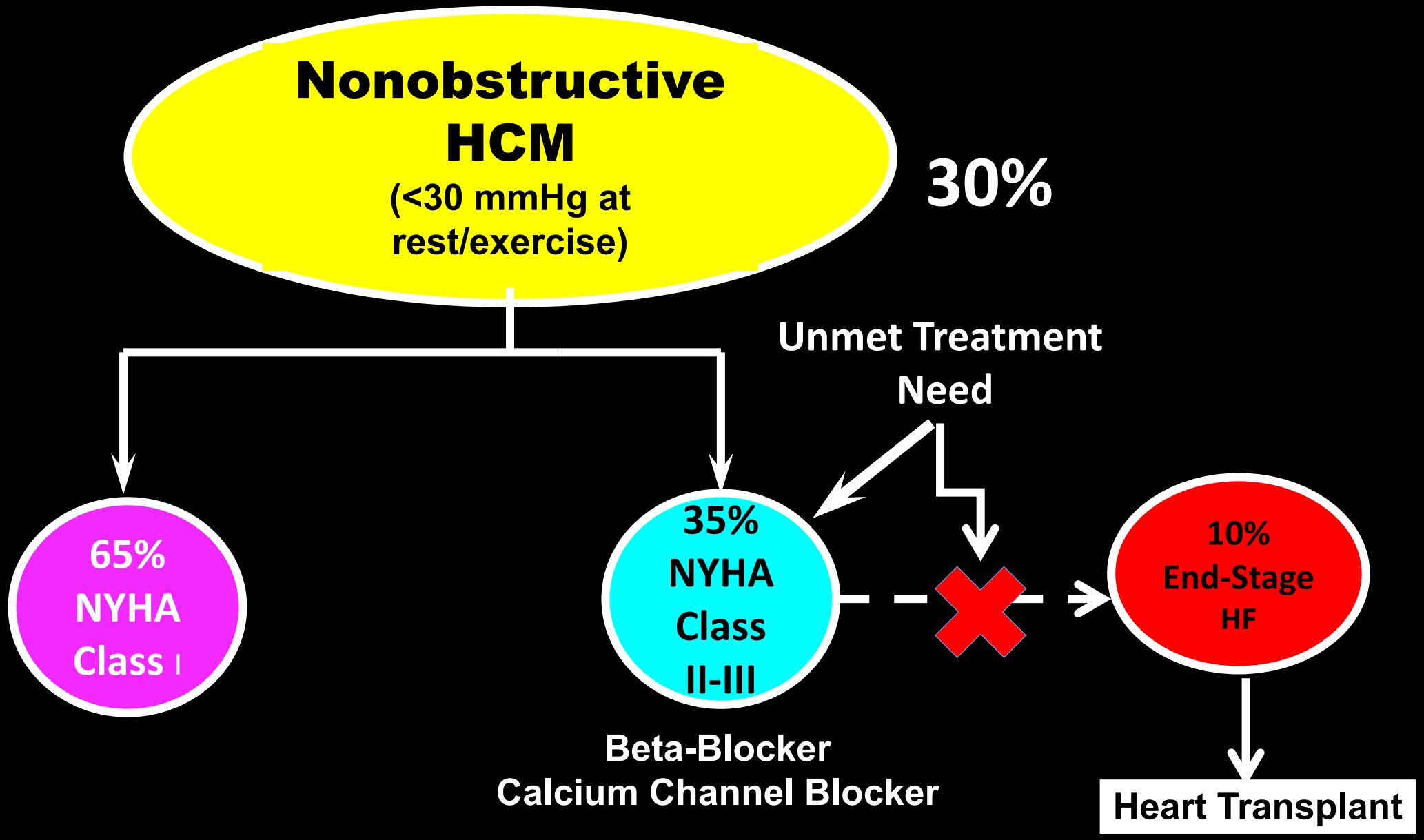
Ninerafaxstat to Provide Optimal Ventricular Energetics in HCM: IMPROVE-HCM

Martin S. Maron, MD

Director, HCM Center

Lahey Medical Center, Burlington, MA

The *Unmet* Treatment Need in *Nonobstructive* HCM



Diastolic Dysfunction in HCM

LV Relaxation:

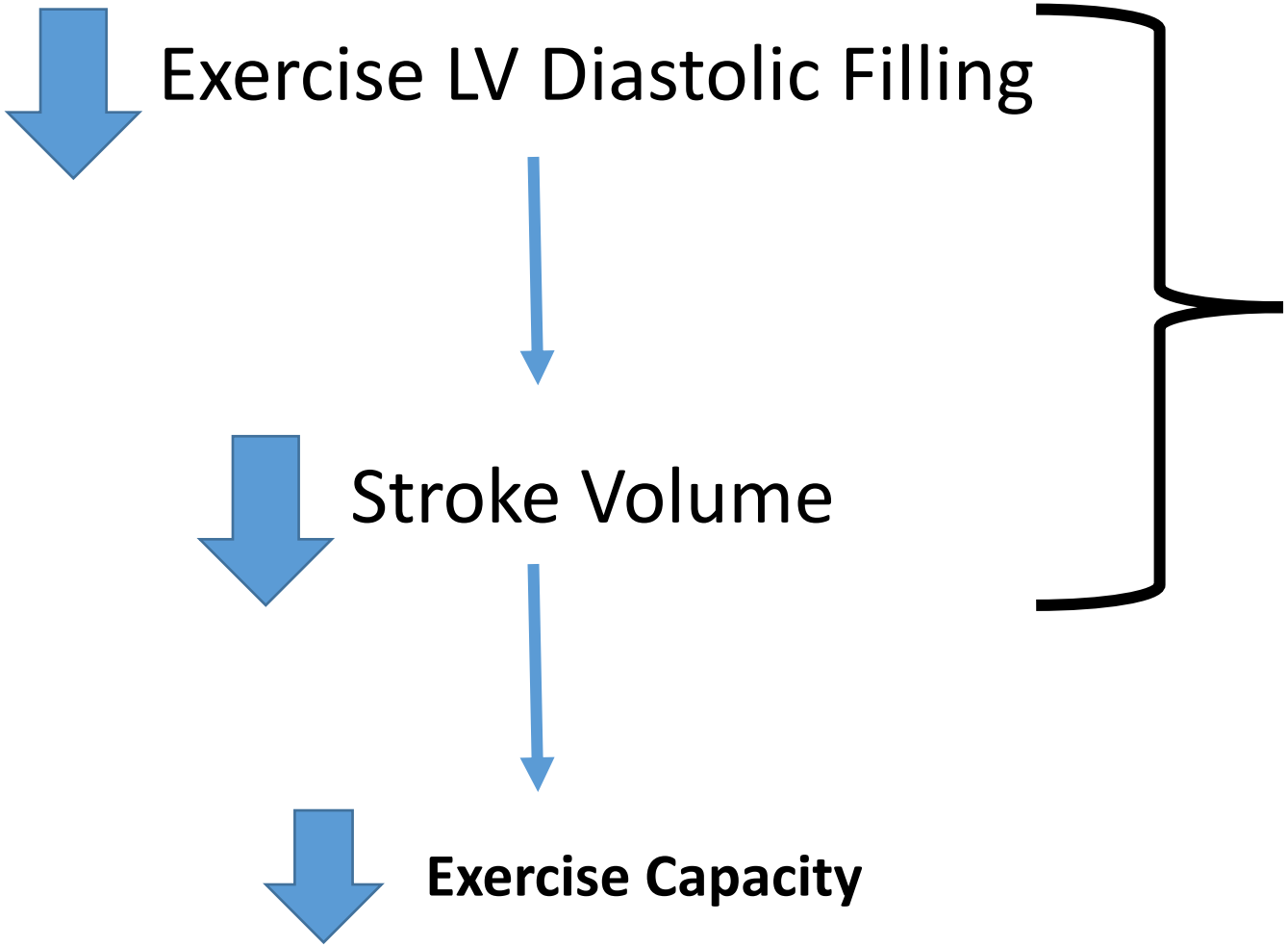
- LV Hypertrophy
- Myocardial Ischemia

LV Distensibility:

- LV Hypertrophy
- Disarray
- Interstitial Fibrosis
- Replacement Scar

Altered LV Diastolic Filling/ Low Stroke Vol

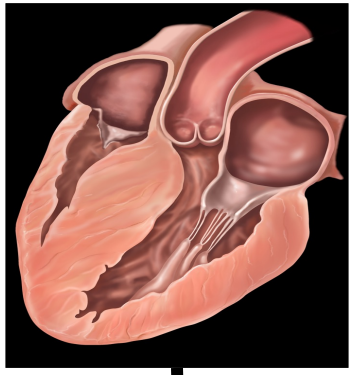
Exercise Capacity in HCM Dependent on Diastolic Filling Characteristics

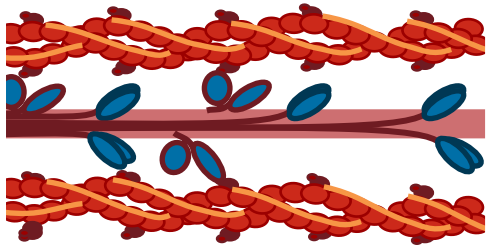


LV diastolic relaxation is high energy-dependent process…

CV disease states like HCM have cardiac energy deficiency translates into impaired ability to increase SV

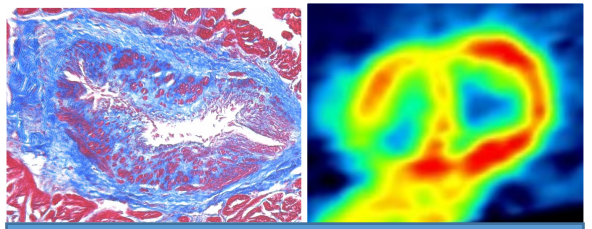
Energy Deficiency is a Primary Consequence of HCM Disease Expression





Energetic Cost of Contraction/Relaxation

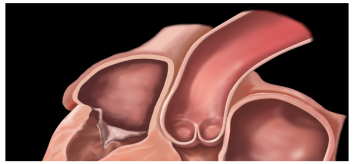
PCr/ATP Ratio



Microvacular Ischemia

Exacerbates Primary Energy Deficiency

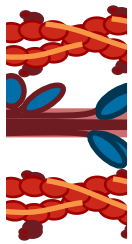
Energy Deficiency is a Primary Consequence of HCM Disease Expression

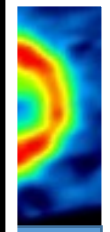


For all these reasons…

Myocardial Energetics Represent an Attractive Therapeutic Target

Mitotropes = Drugs that influence myocardial energetics





Er

Cont

ia

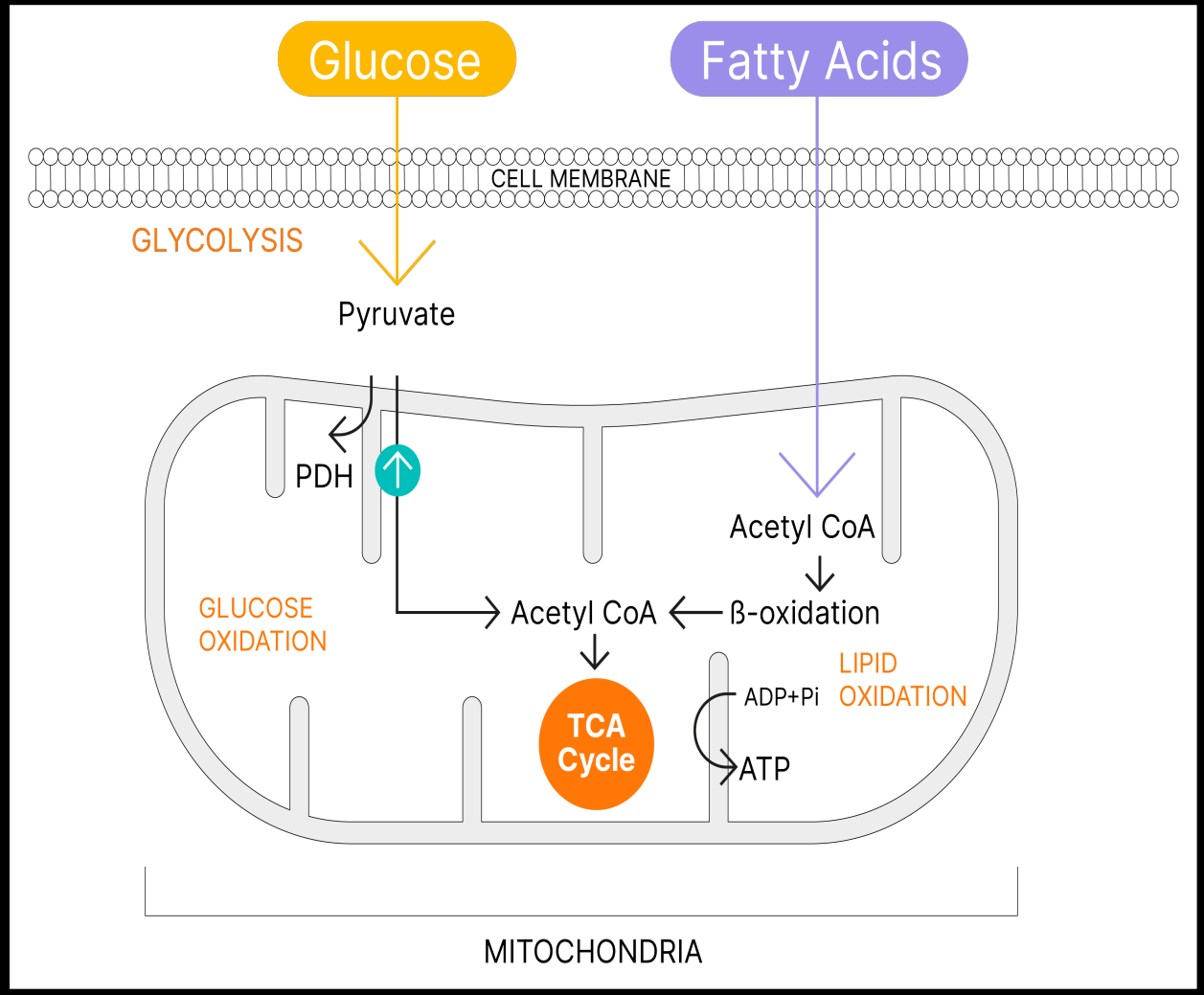
PCr/ATP Ratio

Exacerbates Primary Energy Deficiency

The Normal Heart is a Metabolic Omnivore

Normal Heart:

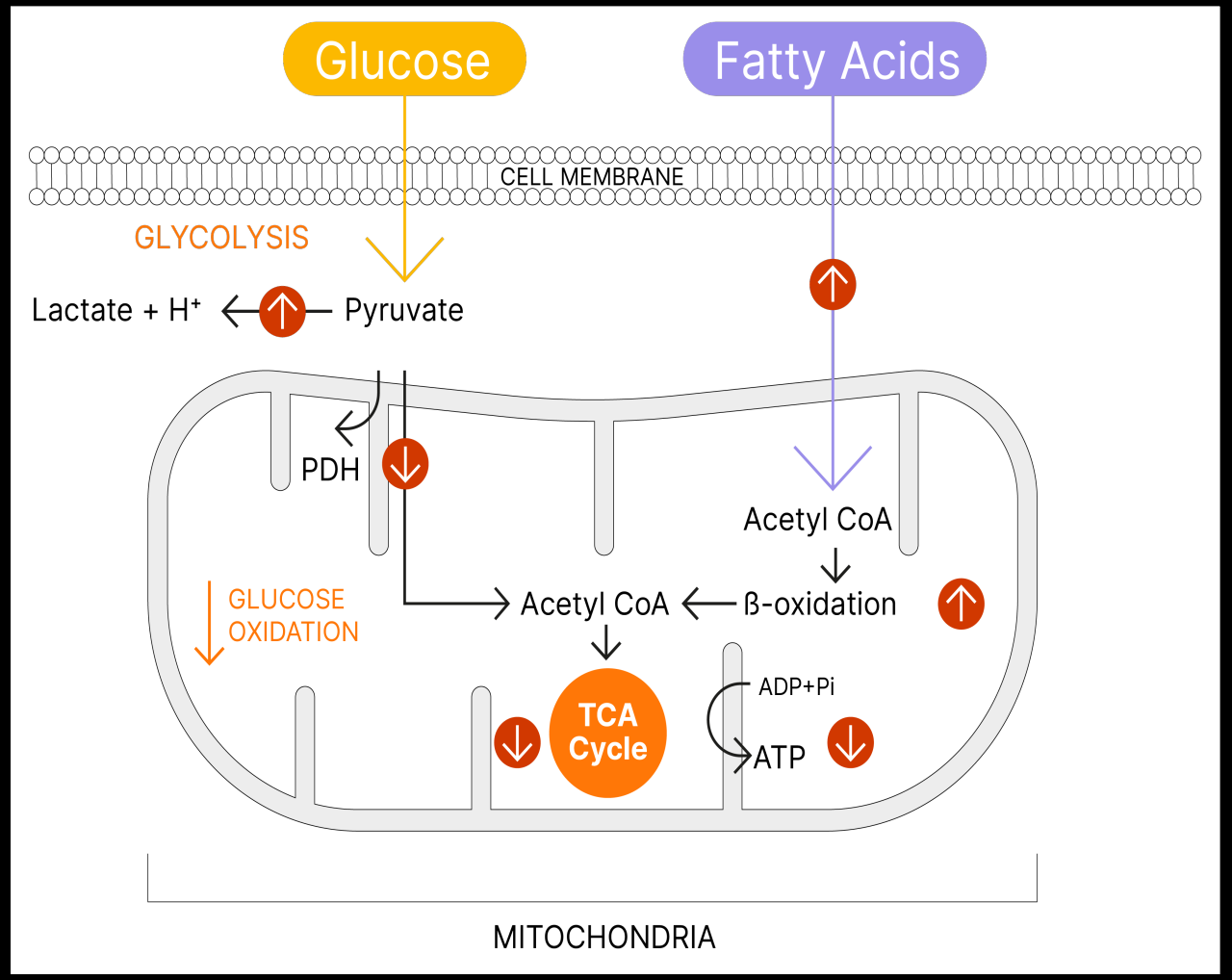
- ~95% of the heart's energetic (ATP) requirements met via oxidative metabolism of fatty acids (FA) and glucose
  - **Fatty Acid Oxidation:** ~40–60% of the total energy produced
  - **Glucose Oxidation**: ~20–40%
- Glucose is the most efficient energy substrate for ATP synthesis (highest number of molecules of ATP produced per molecule of O_2)
- Uncoupling of glycolysis and glucose oxidation impairs the efficiency of ATP generation and can impair cardiac function



Lopaschuk et al., Physiol. Rev 2010

Abnormal Myocardial Energetics in HCM

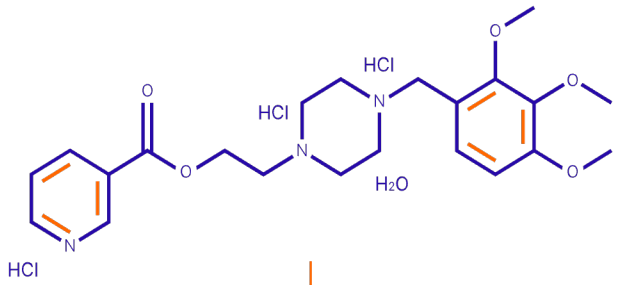
- High rates of FA oxidation inhibit pyruvate oxidation (PDH)
- Glycolysis ↑ but is uncoupled from glucose oxidation
- Drives ↑ lactate, intracellular acidosis
- ↓ Efficiency of ATP production per molecule of O_2

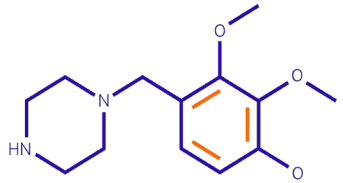


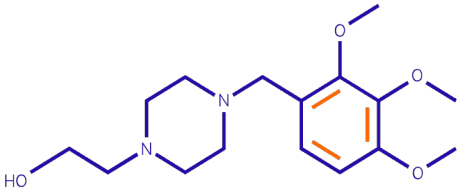
Lopaschuk et al., Physiol. Rev 2010

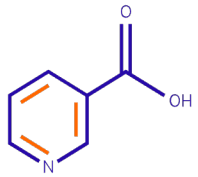
Cardiac Mitotrope: Ninerafaxstat

Ninerafaxstat









Trimetazidine (TMZ)

- Promotes glucose-based metabolism
- Approved in EU for angina since 1970s & ESC recommended 2nd line agent
- 45 million patient-years of experience
- Strong clinical efficacy data in HFrEF (TMZ)

IMB-102

- Novel active structural analog of TMZ
- Improved results over TMZ in animal models of CVD
- Reduced affinity for the dopamine receptor as compared to TMZ

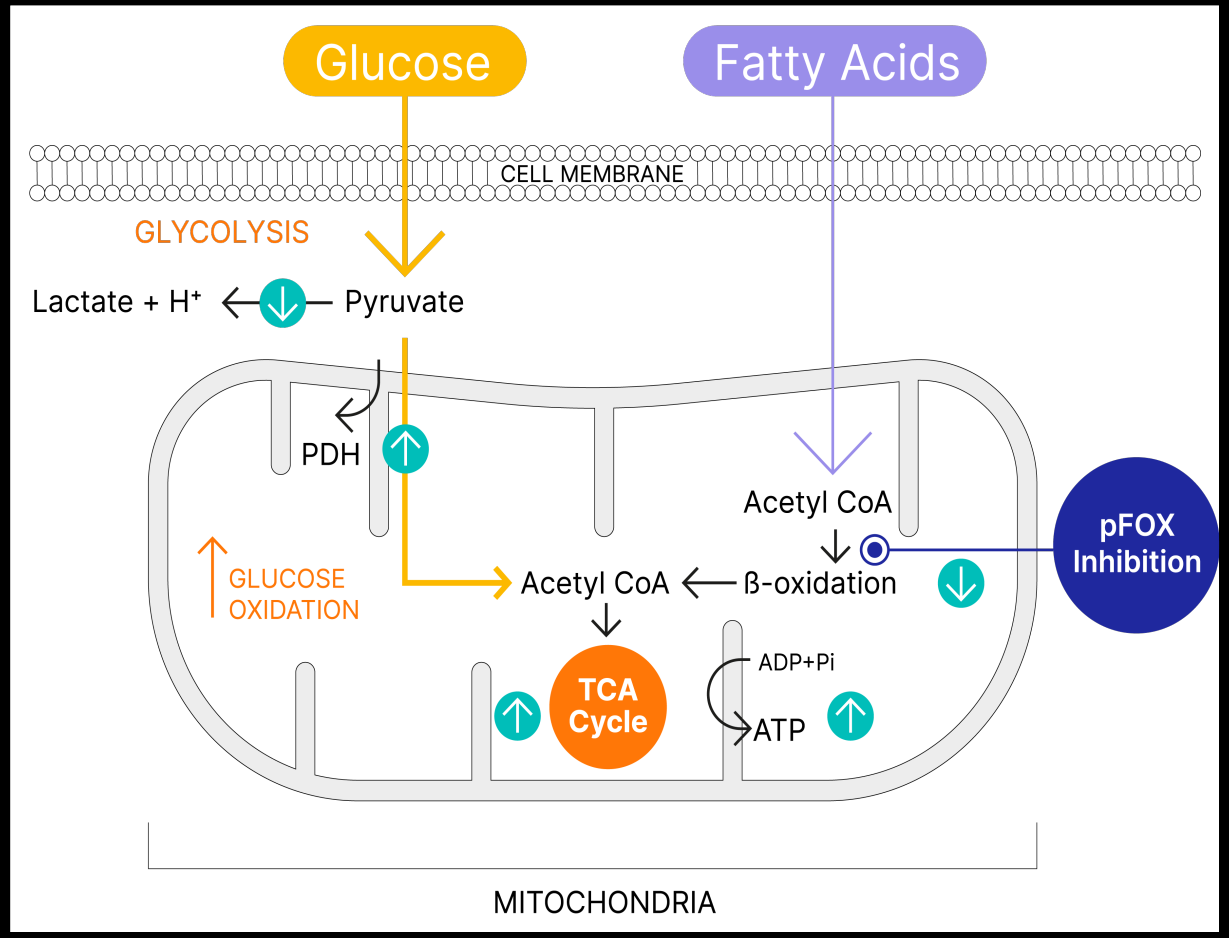
Niacin

- NAD+ precursor -key regulator of cellular metabolism & bioenergetics
- Potentiates efficacy of IMB-102 and TMZ in animal models

Ninerafaxstat:

Switches Metabolism Towards Glucose Use and Optimizes the Efficiency of ATP Generation to Enhance Cardiac Function

- Partial inhibition of mitochondrial fatty acid oxidation
- Shift of cardiac metabolism from using fatty acids towards glucose
- Recoupling glycolysis and glucose oxidation
- ↑ Efficiency of ATP production per molecule of O_2



Modified from Lopaschuk et al., Physiol. Rev 2010 &
Verma et al J Am Coll Cardiol Basic Trans Science 2018; 3:575-587

Metabolic Modulator Perhexiline Corrects Energy Deficiency and Improves Exercise Capacity in Symptomatic Hypertrophic Cardiomyopathy

- **46 Nonobstructive HCM patients with**
- **pVO_2 max <75%**
- **Randomized to Perhexiline vs. Placebo for 3 months**
- **Primary End-Point of increase in exercise capacity (peak VO_2)**

Compared to Placebo:

- ↑ **Peak VO_2**
- ↑ **NYHA Class**
- ↑ **MLHFQ**
- ↑ **Improved Diastolic filling time**
- ↑ **PCr/ATP Ratio**

Abozguia K et al Circulation 2010

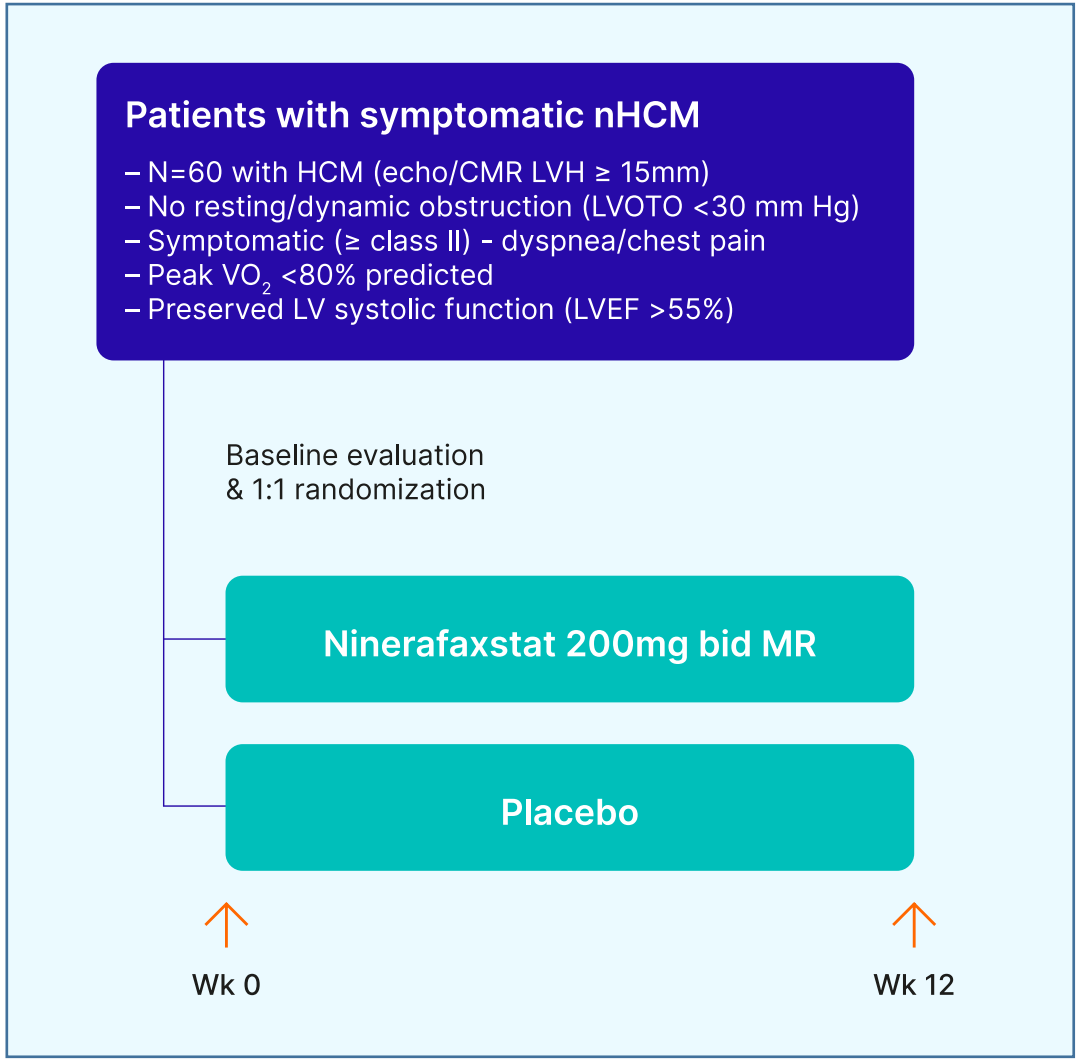
Phase II Study in Nonobstructive HCM
IMPROVE-HCM

- 60 nonobstructive HCM patients Class II or II with

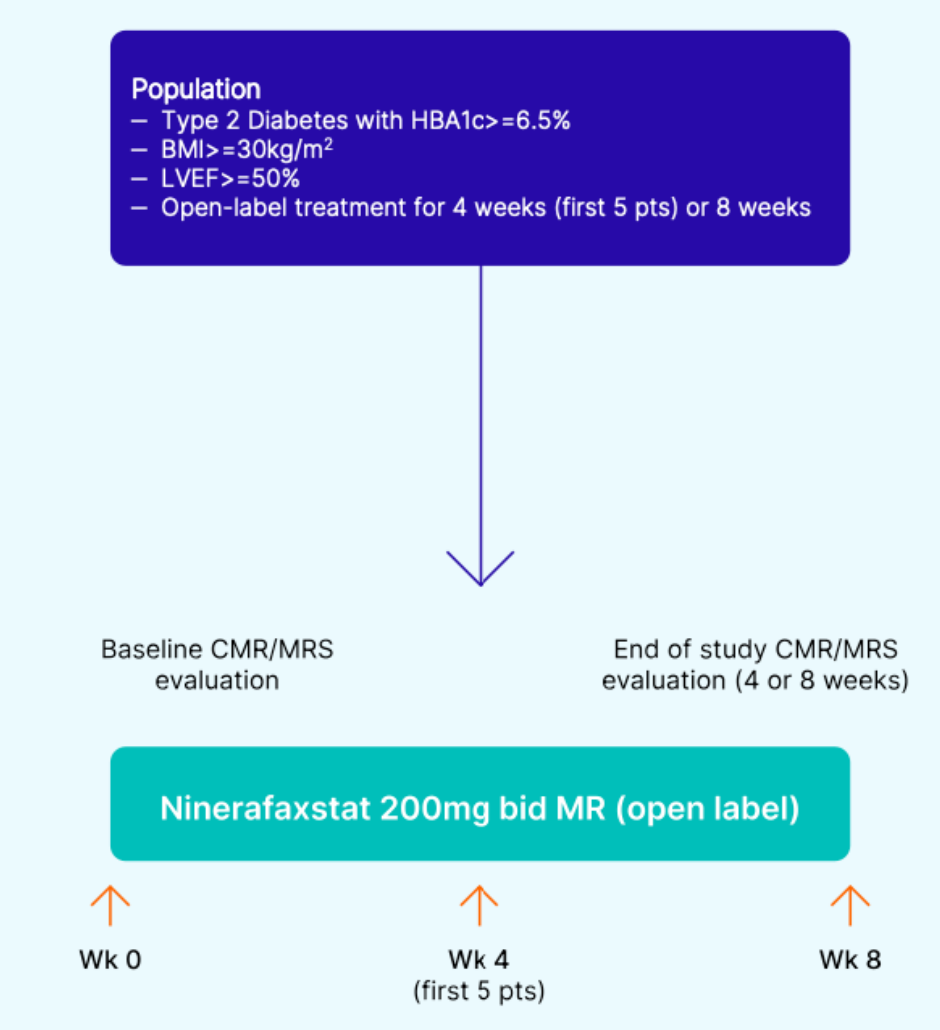
  pVO2 max <80% predicted with EF>55% randomized Ninerafaxstat vs. Placebo for 12 wks

- Key efficacy endpoints
  - Peak VO_2
  - PCr/ATP ratio

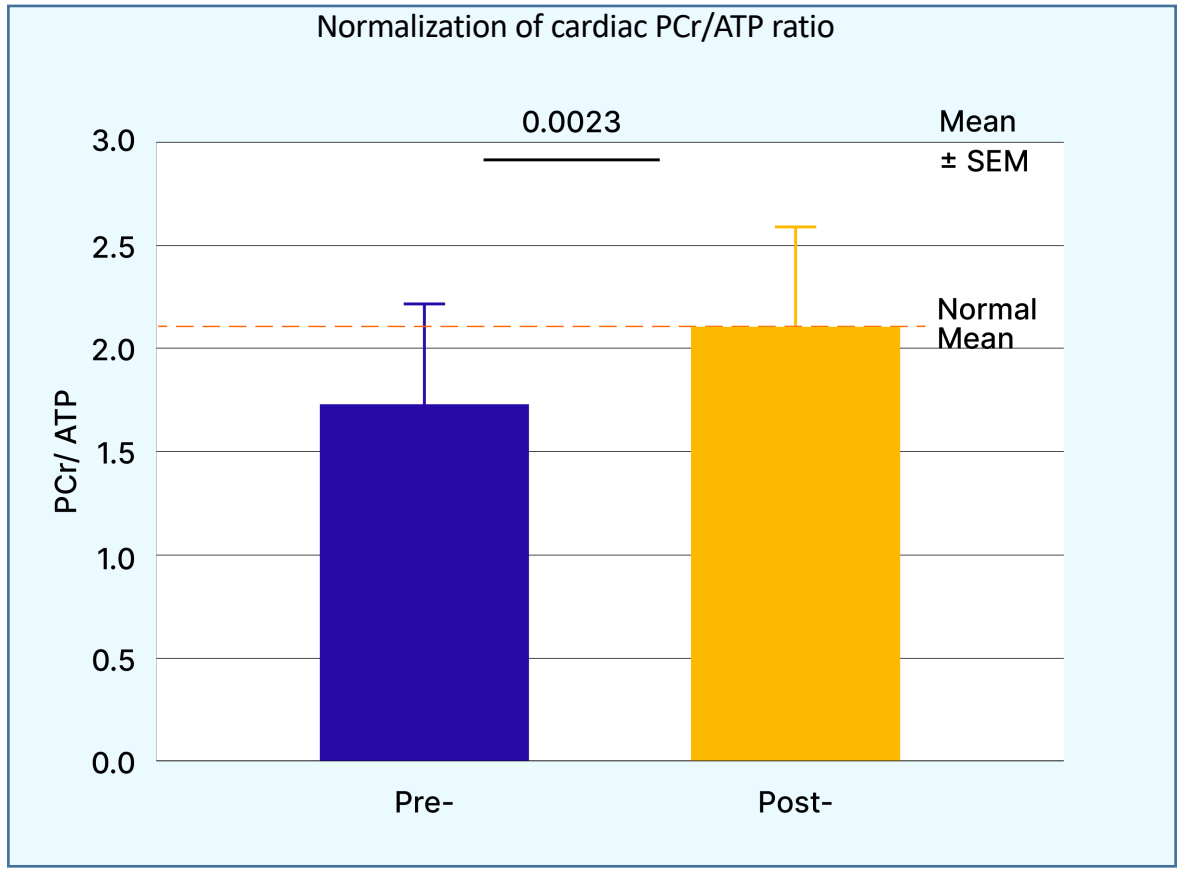
- Other efficacy endpoints
  - LV function, including LV GLS, LV diastolic function and LA strain by echo and CMR
  - Arrhythmia burden
  - Biomarkers incl., cardiac troponin, NT-proBNP
  - Symptoms & health status incl., NYHA functional class and KCCQ



Ninerafaxstat improves cardiac energetics – a hallmark abnormality of the T2D heart and of HFpEF

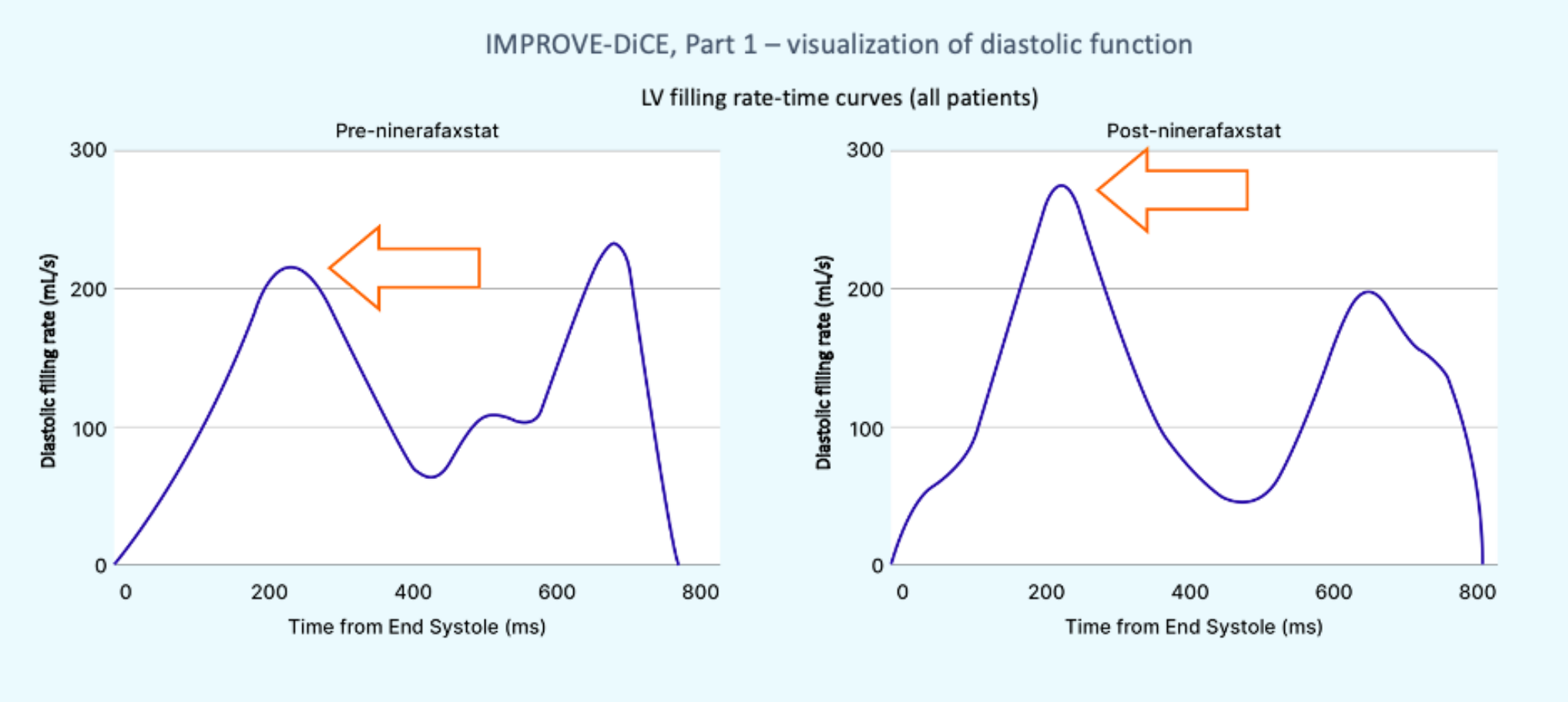


IMPROVE-DiCE, Part 1



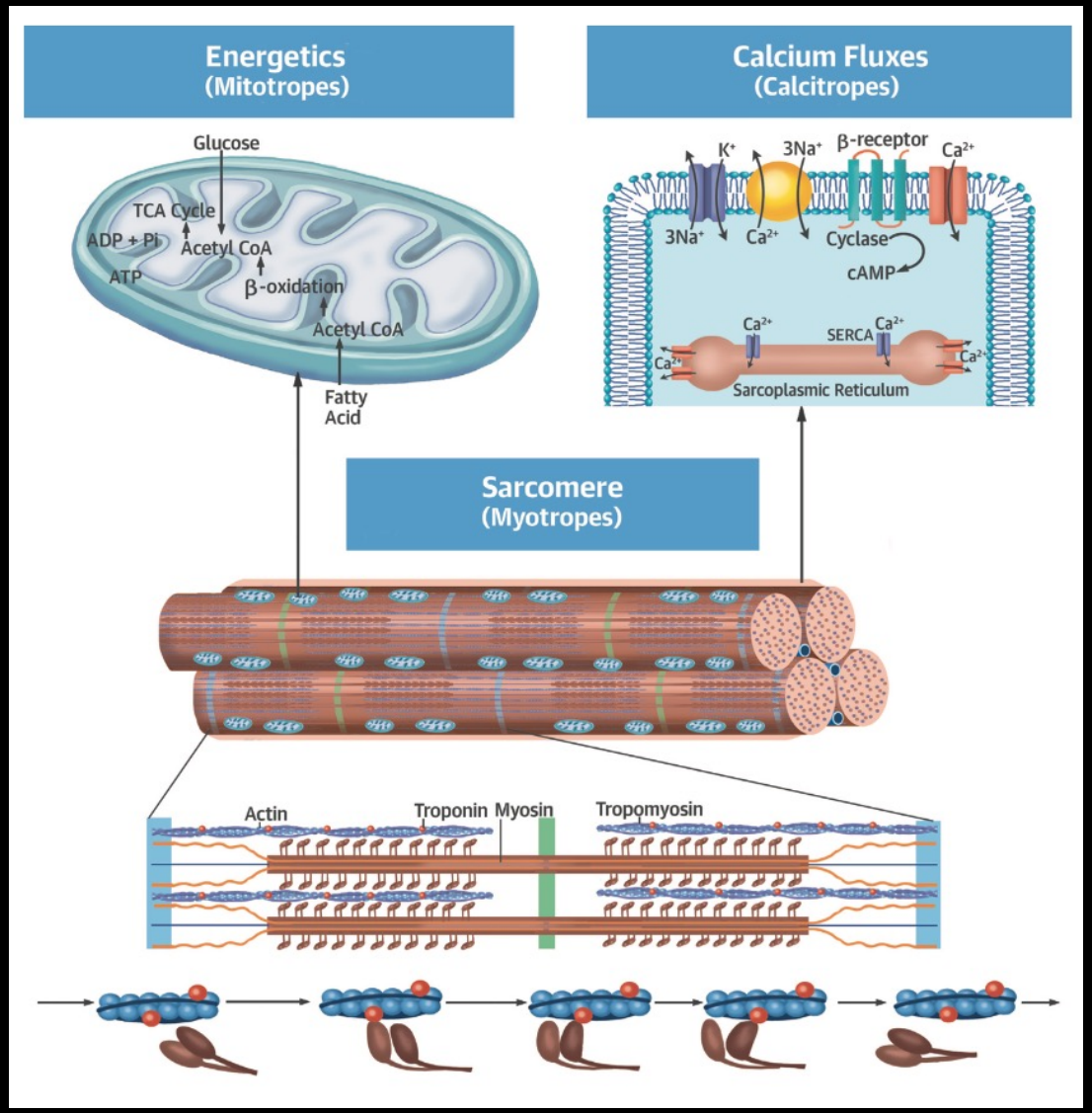
Hundertmark MJ et al., IMPROVE-DiCE, A Ph2 trial investigating ninerafaxstat presented at ESC 2022

Ninerafaxstat improves LV filling by increasing early diastolic relaxation - an active energy dependent process requiring ATP



Hundertmark MJ et al., IMPROVE-DiCE, A Ph2 trial investigating ninerafaxstat presented at ESC 2022

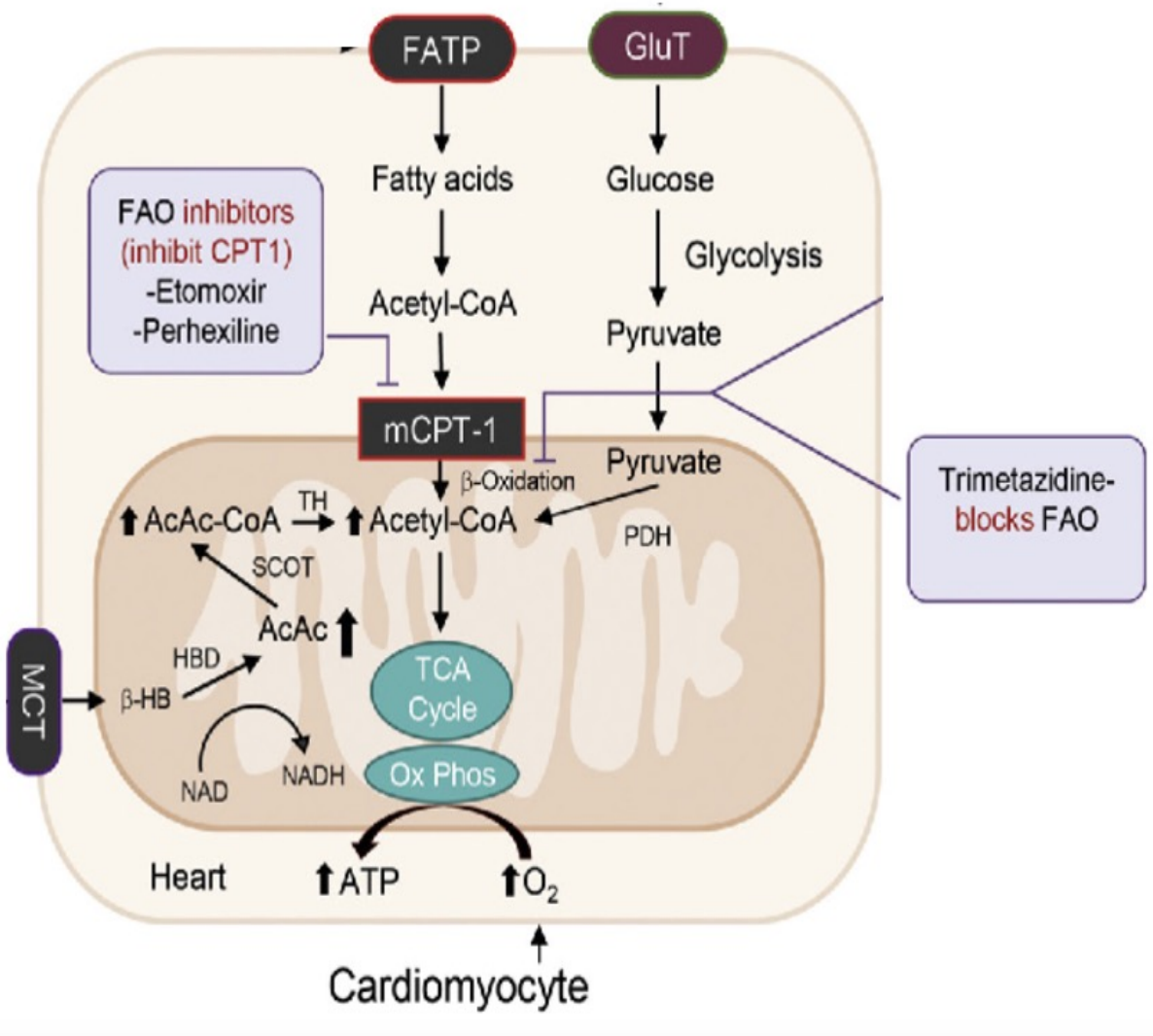
Myocardial Energetics Are An Attractive Therapeutic Target



- **The 3 components of cardiac function:**
  1. **Contractile elements that consist of the myosin, actin filaments and regulatory proteins**
  2. **Cycling elements responsible for the storage and flux of myocardial Ca^{2+}**
  3. **Energetic elements that include ATP produced by the mitochondria required for myosin activity**
- **Myocardial energetics are attractive therapeutic target because of energy dependence of myocardial contraction and metabolic derangements in myocardium of patients with a variety of CV disorders, including HCM**

Psotka, M.A. et al. J Am Coll Cardiol. 2019;73(18):2345–53.

Mitotropes Target Metabolic Modulation in Mitochondria



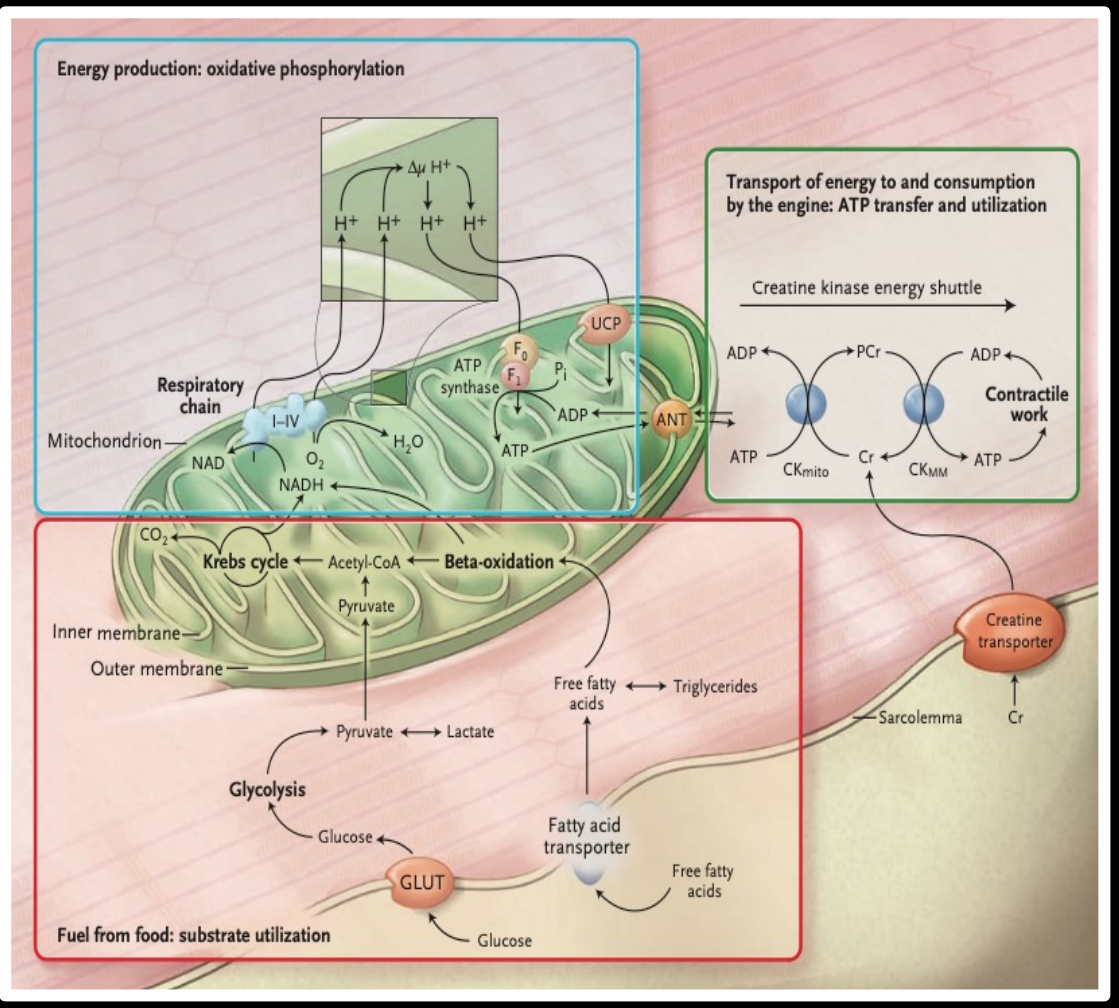
- Myocardial energetics are centered around mitochondrial energy production, and drugs acting at the mitochondria are called **Mitotropes**.

- Cardiac function is inextricably linked to metabolism, with dysregulation of cardiac metabolism pathways implicated in a range of cardiac complications

- Potential therapeutic target: modulation of fatty acid oxidation (FAO):
  - Perhexiline inhibits CPT1, the protein that translocates fatty acids into the mitochondria
  - Trimetazidine (TMZ) partially blocks the mitochondrial oxidation of fatty acids by inhibition of long-chain 3-ketoacyl-CoA thiolase (3-KAT), which enhances glucose oxidation.

Birkenfeld, Andreas L. et al. *Pharmacology & Therapeutics* 194 (2019): 132–144.

Heart is a High Energy Demand Organ



- **The heart consumes more energy than any other organ**
- **To meet high energy demand, cardiomyocytes demonstrate "metabolic flexibility" regarding the selection of energy substrates such as fatty acids and glucose:**
  - **Fatty Acid Oxidation: ~40–60% of the total energy produced**
  - **Glucose Oxidation: ~20–40%**
- **Cardiac energetics is quantified by the PCr/ATP ratio using magnetic resonance spectroscopy.**

Neubauer S, N Engl J Med. 2007 Mar 15;356(11):1140-51

A major component of both rare and common cardiac disease is insufficient access to ATP causing energy deficiency

Hypertrophic cardiomyopathy	Sarcomeric mutations lead to energy wasting and energetic impairment driving hypertrophy	Excessive ATP consumption
Heart failure	Profound myocardial metabolic remodeling with reduced mitochondrial oxidative capacity	Reduced ATP generation & energy wastage "The failing heart is an energy-starved engine out of fuel"
Ischemic heart disease	Ischemia disrupts cardiac energy metabolism due to inadequate perfusion and oxygen availability	Reduced ATP generation

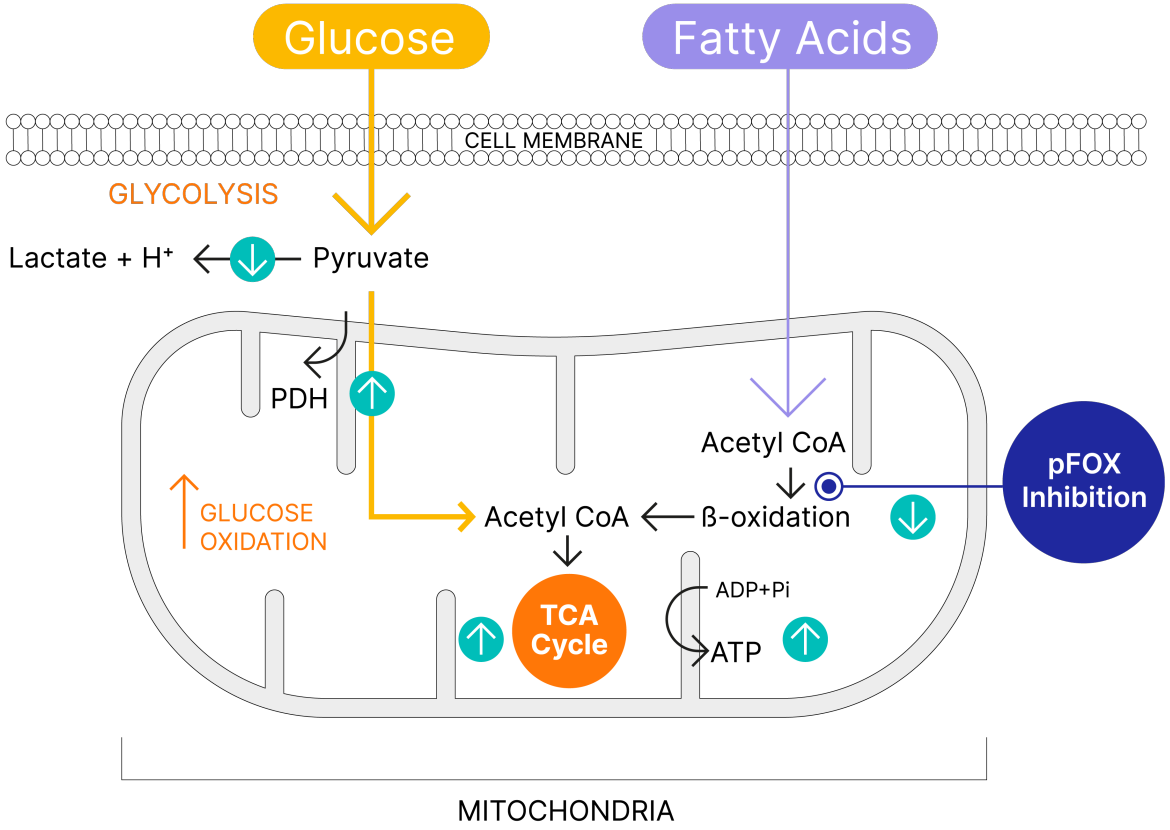
Cardiac energy deficiency leads to a multitude of symptoms and functional changes:

- **Breathlessness**
- **Fatigue**
- **Reduced exercise capacity**
- **Arrhythmia**
- **Angina**

Neubauer, N Engl J Med 2007

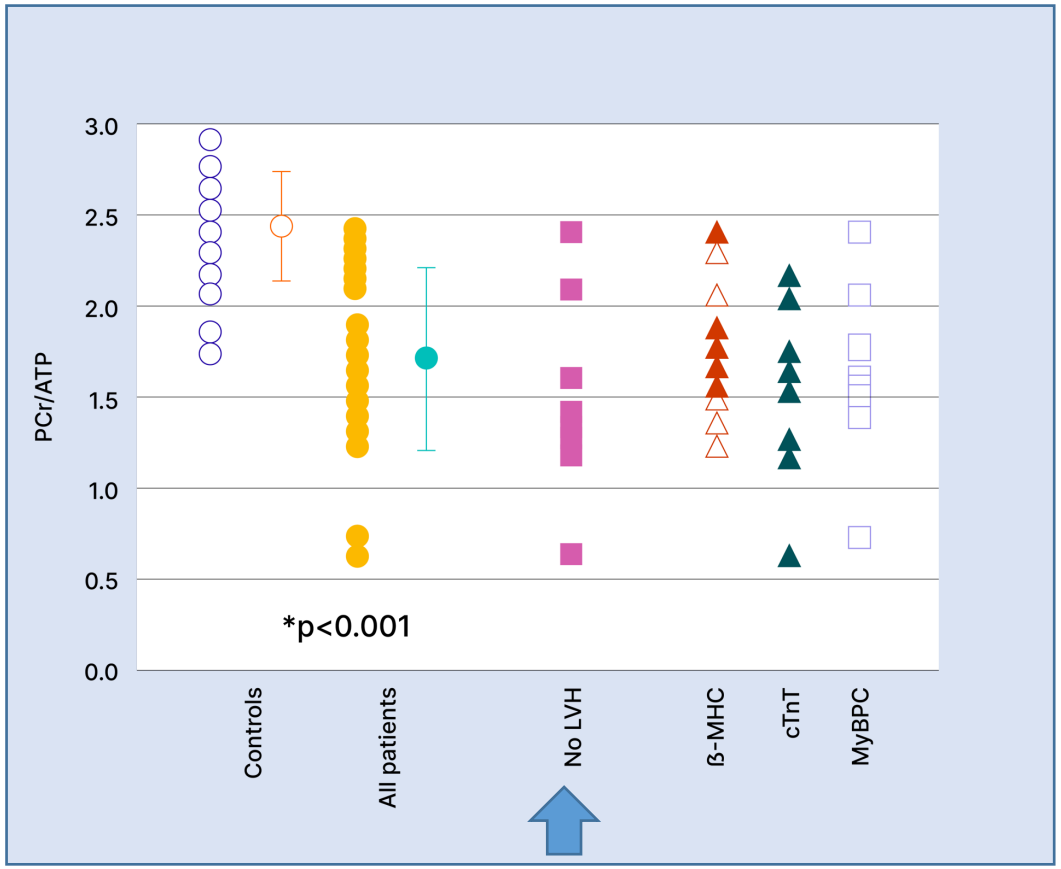
Ninerafaxstat is a novel mitotrope designed to optimize the efficiency of ATP generation and enhance cardiac function

- Uncoupling of glycolysis and glucose oxidation has an important role in the development of cardiac inefficiency and functional impairment in cardiac disease
- Ninerafaxstat acts through partial inhibition of mitochondrial fatty acid oxidation (pFOX)
  - This reciprocally stimulates mitochondrial glucose oxidation
  - Net effect of shifting cardiac substrate metabolism towards glucose is increased efficiency of ATP generation
  - This results in improved cardiac mechanical efficiency



Modified from Lopaschuk et al., Physiol. Rev 2010 &
Verma et al J Am Coll Cardiol Basic Trans Science 2018; 3:575-587

Cardiac energy deficit is evident before hypertrophy develops in patients with HCM



- Energy deficiency is an early feature of HCM and present in disease carriers before development of left ventricular hypertrophy (LVH)
- Non-invasive measurement of cardiac energy reserves using ^{31}P-MR spectroscopy shows a ~30% reduction in cardiac PCr/ATP in HCM relative to healthy controls
- Abnormal cardiac energetics is an early and fundamental feature of HCM pathogenesis resulting in an increase in the energetic cost of force production
- "energy compromise" has been proposed as a possible stimulus for the development of cardiac hypertrophy in HCM,

Crilley JG et al J Am Coll Cardiol. 2003:1776-82.