

Concept loop animation

Let's be direct
about what's **missing in heart failure** treatment

Current treatments do not directly address poor contractility of the heart
HF treatment is heading in the right direction, but opportunities remain

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Malik J Mol Cell Cardiol 2011, 454-B-2; 455-A-1; McMurray NEJM 2010, 236-B-4; Pazos-López Vasc Health Risk Manag 2011, 245-B-Figure 6; Reddi BJA Educ 2017, 159-B-4

Ferrari Eur Heart J Suppl 2016, G6-B-3; Hartupee Nat Rev Cardiol 2017, 36-B-3

Despite treatment advances, the burden of heart failure remains

Ambrosy J Am Coll
Cardiol 2014, 1123-
A-1; 1123-B-1;
Ponikowski Eur Soc
Card 2014, 8-A-
Figure 4 (159,143 +
306,250 + 229,328
+ 73,790 + 626,185
= 1,394,696)

~50% mortality
within 5 years of hospitalization

Ponikowski Eur
Soc Card 2014, 4-
A-2; 5-A-Figure 2

>1,000,000
hospitalizations
every year in Europe and the US

Cowie HFAESC
2014, 7-A-4

~25% readmission
within 30 days of initial hospitalization

TOUCH TO LEARN MORE

Limitations of standard-of-care treatment today



Current standard-of-care treatment options

directly target compensatory/neurohormonal pathways and help to control symptoms

What's missing in standard-of-care heart failure treatment today?

TOUCH TO LEARN MORE

Hartupée Nat Rev
Cardiol 2017, 30-A-1;
31-A-Key points 2; 31-
A-2; 36-B-3; Malik J
Mol Cell Cardiol 2011,
454-B-2; 455-A-1;
Pazos-López Vasc
Health Risk Manag
2011, 245-B-Figure 6

Let's focus on directly improving cardiac contractility and thereby heart function

Hoekstra Eur J Heart Fail 2011, 1013-A-1; Vasani J Am Coll Cardiol 1999, 1948-A-1; 1948-B-1

→ Better **heart muscle function** is associated with survival and better quality of life

Fearnley Cold Spring Harb Perspect Biol 2011, 7-B-3; 10-A-3; 10-B-1; Hartupree Nat Rev Cardiol 2017, 34-B-2; Malik J Mol Cell Cardiol 2011, 455-A-3

→ Heart muscle function is dependent on **key contractile proteins** in the cardiac sarcomere, myosin and actin



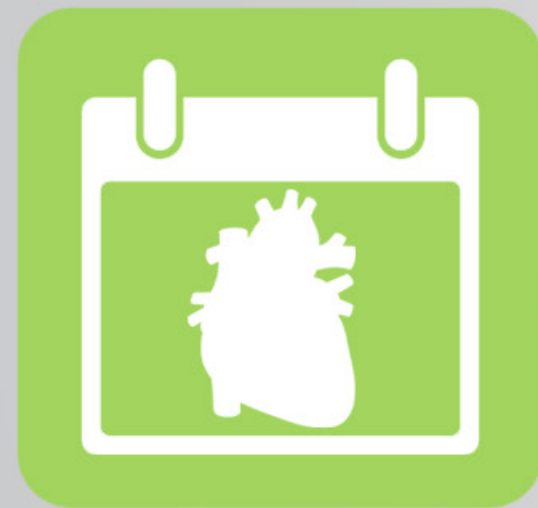
Fearnley Cold Spring Harb Perspect Biol 2011, 7-B-3; 10-A-3; 10-B-1; Hartupree Nat Rev Cardiol 2017, 34-B-2; Malik J Mol Cell Cardiol 2011, 455-A-3

→ **Direct activation** of myosin may boost cardiac contractility

TOUCH TO LEARN MORE

Interactive Menu

Heart failure
today



Heart failure
standard of care



Heart failure
and contractility



Let's be direct about heart failure today



Despite treatment advances, the burden of heart failure remains

~30% mortality within 1 year of hospitalization¹ **~50%** mortality within 5 years of hospitalization¹

>1,000,000 hospitalizations for heart failure occur every year in Europe and the US^{1,2} **~25%** readmission within 30 days of initial hospitalization³ **Up to 70%** of direct heart failure costs are due to hospitalization⁴

Limited quality of life for HF patients; reduced ability to carry out day-to-day activities⁵

Ponikowski Eur Soc Card 2014, 4-A-2; 5-A-Figure 2

Ponikowski Eur Soc Card 2014, 4-A-2; 5-A-Figure 2

Ambrosy J Am Coll Cardiol 2014, 1123-A-1; 1123-B-1; Ponikowski Eur Soc Card 2014, 8-A-Figure 4 (159,143 + 306,250 + 229,328 + 73,790 + 626,185 = 1,394,696)

Cowie HFAESC 2014, 7-A-4

Neumann Dtsch Arztebl Int 2009, 272-B-2

Juenger Heart Jour 2002, 237-B-2

References: 1. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. <http://www.oxfordhealthpolicyforum.org/reports/heart-failure/heart-failure>. Published 2014. Accessed March 15, 2019. 2. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63:1123-1133. 3. Cowie MR, Anker SD, Cleland JGF, et al. Improving care for patients with acute heart failure: before, during and after hospitalization. <http://www.oxfordhealthpolicyforum.org/reports/acute-heart-failure/improving-care-for-patients-with-acute-heart-failure>. Published 2014. Accessed March 15, 2019. 4. Neumann T, Biermann J, Neumann A, et al. Heart failure: the commonest reason for hospital admission in Germany. *Dtsch Arztebl Int*. 2009;106:269-275. 5. Juenger J, Scheilberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart*. 2002;87:235-241.



Let's be direct about today's standard of care



To address the heart's failing mechanics, most current treatments (including ACEIs, ARBs, aldosterone antagonists, beta-blockers, and ADH) aim to improve:¹



Heart Rate¹



Volume Status²



Vascular Resistance¹



It is time to explore new opportunities for heart failure therapy

Pazos-López Vasc Health Risk Manag 2011, 245-B-Figure 6

Dalzell ESC Textbook of Intensive and Acute Cardiovascular Care 2018, 5-A-2, Bullets 1-2

Pazos-López Vasc Health Risk Manag 2011, 245-B-Figure 6

Malik J Mol Cell Cardiol 2011, 454-B-2; 455-A-1; McMurray NEJM 2010, 236-B-4; Reddi BJA Educ 2017, 159-B-4

References: 1. Pazos-López P, Petelo-Vázquez J, Carcia-Campos A, García-Buena L, Abugattas de Torres JP, Castro-Beiras A. The causes, consequences, and treatment of left or right heart failure. *Vasc Health Risk Manag*. 2011;7:237-254. 2. Dalzell JR, Jackson CE, Gardner R, McMurray JJV. Acute heart failure: early pharmacological therapy. In: Tubaro M, Vranckx P, Price S, Vrints C, eds. *The ESC Textbook of Intensive and Acute Cardiovascular Care*, 2nd ed. Oxford, UK: Oxford University Press; 2015. 3. Malik FI, Morgan BP. Cardiac myosin activation part 1: from concept to clinic. *J Mol Cell Cardiol*. 2011;51:454-461. 4. McMurray JJ. Systolic heart failure. *N Engl J Med*. 2010;362:228-238. 5. Reddi BAJ, Shanmugam N, Fletcher N. Heart failure—pathophysiology and inpatient management. *BJA Educ*. 2017;17:151-160.

Let's be direct about cardiac contractility



Let's refocus on the science of cardiac myosin and heart contractility

- Better **heart muscle function** is associated with survival and better quality of life^{1,2}
- Heart muscle function is dependent on **key contractile proteins** in the cardiac sarcomere, myosin and actin³⁻⁵

Activation of the cardiac sarcomere can be achieved by different mechanisms, such as increasing intracellular Ca²⁺ concentration or activating cardiac myosin directly^{5,6}



Traditional inotropes

Increase contractility by increasing Ca²⁺ transients, thereby increasing risk of adverse events, such as arrhythmias³⁻⁸

Increased Ca²⁺ concentrations

Risk of arrhythmia

Myosin-actin cross-bridge formation

CONTRACTION

It is time to look at cardiac contractility in a different way

References: 1. Hoekstra T, Lesman-Leegte I, van Veldhuisen DJ, Sanderma R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. *Eur J Heart Fail*. 2011;13:1013-1018. 2. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction. *J Am Coll Cardiol*. 1999;33:1948-1955. 3. Fearnley CJ, Roderick HL, Bootman MD. Calcium signaling in cardiac myocytes. *Cold Spring Harb Perspect Biol*. 2011;3:a004242. 4. Hartupree J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol*. 2017;14:30-38. 5. Malik FI, Morgan BP. Cardiac myosin activation part 1: from concept to clinic. *J Mol Cell Cardiol*. 2011;51:454-461. 6. Reconditi M, Caremani M, Pinzauti F, et al. Myosin filament activation in the heart is tuned to the mechanical task. *Proc Natl Acad Sci U S A*. 2017;114:3240-3245. 7. Petersen J, Felker GM. Inotropes in the management of acute heart failure. *Crit Care Med*. 2008;36:S106-S111. 8. Francis GS, Bartos JA, Adatya S. Inotropes. *J Am Coll Cardiol*. 2014;63:2069-2078.

Hoekstra Eur J Heart Fail 2011, 1013-A-1; Vasan J Am Coll Cardiol 1999, 1948-A-1; 1948-B-1

Fearnley Cold Spring Harb Perspect Biol 2011, 7-B-3; 10-A-3; 10-B-1; Hartupree Nat Rev Cardiol 2017, 34-B-2; Malik J Mol Cell Cardiol 2011, 455-A-3

Malik J Mol Cell Cardiol 2011, 455-A-4; Reconditi PNAS 2017, 3240-A-2; 3240-B-1

Fearnley Cold Spring Harb Perspect Biol 2011, 10-A-3; 10-B-1; Hartupree Nat Rev Cardiol 2017, 34-B-2; Malik J Mol Cell Cardiol 2011, 455-A-2; 456-A-Figure 1-A; Reconditi PNAS 2016, 3244-A-2; Petersen Crit Care Med 2008, S108-C-2; S109-B-2; S109-C-1; Francis J Am Coll Cardiol 2014, 2070-B-2; 2073-A-2; 2076-A-3