Heart failure

- Afflicts > 5 million patients in the United States.
- Is the only cardiovascular disorder increasing in incidence and prevalence.
- Is most common cause of hospitalization in elderly.
- Causes more deaths each year than all cancers combined.

One Out of Three People Will Develop Heart Failure During Their Lifetime

— Framingham Heart Study
Oldest non-infectious non-traumatic disease in human history

Nebri Mummy
3500 years old

Discovered Aug 2015
One of earliest recognized human diseases

Reports recorded on Sumerian and Babylonian tablets

Primary feature was fluid retention (i.e., hydrops or dropsy).
Importance of heart and kidneys first recognized by Ippolito Albertini (17th Century A.D.)

Albertini was the first to describe the syndrome of and postulate a model for heart failure based on scientific observations.
Cardiorenal Hypothesis of Heart Failure

Failing heart

- Decreased blood flow ("forward failure")
  - Renal hypoperfusion
  - Na retention by kidneys
  - Edema

- Increased cardiac filling pressures ("backward failure")
  - Renal congestion

Renal hypoperfusion

Renal congestion

Na retention by kidneys

Edema
Therapies directed at volume depletion

Foxglove: first effective herb inducing a diuresis
• Darwin (1731-1802)
• Withering (1741-1799)

Progress in diuretics
• Mercurials (1920s)
• Sulfa drugs (1940s)
• Oral thiazides (1950s)
• Loop diuretics (1960s)
Conceptual Paradigm for Heart Failure Before 1950

- **Decompensated heart failure**
  - Clinically apparent

- **Compensated heart failure**
Heart Failure Is a Progressive Disease Even When Fluid Retention Is Effectively Treated (c. 1975)
Survival in Class III-IV Heart Failure

% Survival vs Months

1975
Progression of heart failure

Retention of salt and water

Cardiorenal hypothesis

1675-1975

Volume depletion

Progression of heart failure
Hemodynamic Model of Heart Failure

Failing Heart

Decreased blood flow ("forward failure")

Increased cardiac filling pressures ("backward failure")

Na retention by kidneys

Edema
Bedside Catheterization and Imaging Allowed for Evaluation of Cardiac Function

Spiro and Sonnenblick. Prog Cardiovasc Dis 1965;73:295-335
Proposed Frank-Starling Relations in Normal and Failing Hearts

Spiro and Sonnenblick. Prog Cardiovasc Dis 1965;73:295-335
Hemodynamic Model of Heart Failure

Failing Heart

Decreased blood flow ("forward failure")

Na retention by kidneys

Edema

Agents acting to stimulate cardiac contractility (inotropic drugs)

Agents acting to dilate peripheral arteries and veins (vasodilator drugs)

Increased cardiac filling pressures ("backward failure")
Proposed Frank-Starling Relations in Normal and Failing Hearts

Left ventricular output

Normal

Hypoperfusion

Treated heart failure

Untreated heart failure

Congestion

Left ventricular filling pressure

Spiro and Sonnenblick. Prog Cardiovasc Dis 1965;73:295-335
Can Heart Failure Be Treated by Keeping Hemodynamic Variables in Normal Range?

Spiro and Sonnenblick. Prog Cardiovasc Dis 1965;73:295-335
Progression of heart failure

Impairment of cardiac function

Retention of salt and water

Hemodynamic interventions

1675-1975

Cardiorenal hypothesis

1975-

Hemodynamic hypothesis

Progression of heart failure
Intravenous Vasodilator and Inotropic Drugs Markedly Improved Cardiac Performance

Cardiac Output (L/min/m²)

LV Filling Pressure (mm Hg)

Oral Vasodilator and Inotropic Drugs Markedly Improved Cardiac Performance

**Cardiac Output**
(L/min/m²)

- **Prazosin**
  - Cardiac Output: 2.1
- **Amrinone**
  - Cardiac Output: 2.7

**LV Filling Pressure**
(mm Hg)

- **Prazosin**
  - LV Filling Pressure: 24
- **Amrinone**
  - LV Filling Pressure: 30

---

Effect of Prazosin and Amrinone on Exercise Tolerance in Chronic Heart Failure

Weeks Following Initiation of Treatment

Increase in Exercise Duration (s)

Prazosin

Miller et al.

Amrinone

Benotti et al.,
Oral Vasodilator Therapy for Chronic Heart Failure:
A Plea for Caution*

MILTON PACKER, MD
JOSE MELLER, MD, FACC

New York, New York
Response to Dosing with the Oral Vasodilator Prazosin in a Patient With Heart Failure

Packer et al. Circulation 1979;59: 531-9
Response to Repeated Dosing with Prazosin in a Patient With Chronic Heart Failure

Packer et al. Circulation 1979;59: 531-9
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Packer et al. Circulation 1979;59: 531-9
Response to Dosing with the Oral Vasodilator Prazosin in Patients With Heart Failure

Packer et al.
Circulation 1979;59: 531-9
Tachyphylaxis to Repeated Dosing with Prazosin in Chronic Heart Failure

Packer et al.
Circulation 1979;59: 531-9
Tolerance to Repeated Dosing with Prazosin and Nitroglycerin in Chronic Heart Failure

Prazosin

Nitroglycerin

LV filling pressure (mm Hg)

0 hr 2 hr 48 hr Off

n=8

Packer et al.
Circulation 1979;59: 531-9

0 hr 2 hr 48 hr Off

n=35

Packer et al.
What Was Responsible for Attenuation of Hemodynamic Benefit?

LV filling pressure (mm Hg)

Nitroprusside

n=20

Attenuation of Immediate Hemodynamic Effect of Intravenous Nitroprusside

LV filling pressure (mm Hg)

Nitroprusside

n=20

Rebound Hemodynamic Events After Abrupt Withdrawal of Nitroprusside in Heart Failure

Rebound Hemodynamic Events After Abrupt Withdrawal of Nitroprusside in Heart Failure

LV filling pressure (mm Hg)

Minutes After Withdrawal of Nitroprusside

Rebound Hemodynamic Events After Abrupt Withdrawal of Nitroprusside in Heart Failure

Activation of Endogenous Vasoconstrictors During Vasodilator Therapy in Heart Failure

LV filling pressure (mm Hg)

Nitroprusside

Direct vasodilation

Activation of Endogenous Vasoconstrictors During Vasodilator Therapy in Heart Failure

Nitroprusside

LV filling pressure (mm Hg)

Direct vasodilation

Activation of vasoconstrictor forces

Observed nitroprusside effect

Activation of Endogenous Vasoconstrictors During Vasodilator Therapy in Heart Failure

LV filling pressure (mm Hg)

Nitroprusside

Direct vasodilation

Activation of vasoconstrictor forces

Observed nitroprusside effect

Observed rebound

Activation of Renin-Angiotensin System and Sympathetic Nervous System in Heart Failure

Plasma Renin Activity

Plasma Norepinephrine

Surg Gyn Obstet 1964; 118:767-7
Proc R Soc Med 1965; 58:1063-6
Heart failure

- Increased activation of norepinephrine and angiotensin

Vascular effect
- Constriction of peripheral blood vessels
- Support of blood pressure and renal function

Cardiac effect
- Stimulation of cardiac contractility
- Support of cardiac function
Heart failure

Increased activation of norepinephrine and angiotensin

Vasodilator drug

Constriction of peripheral blood vessels

Negation of hemodynamic benefit
Heart failure

Increased activation of norepinephrine and angiotensin

Vascular
- Constriction of peripheral blood vessels
- Negation of hemodynamic benefit

Cardiac
- Hypertrophy, cell death and fibrosis
- Structural impairment of cardiac function

Vasodilator drug
Effects of Flosequinnan in Heart Failure

LV Ejection Fraction (%)

Exercise Tolerance (s)

Δ Plasma Renin Activity (ng.mg/h)

Δ Plasma Norepinephrine (pg/ml)

Placebo (n=93)
Flosequinnan (n=100)

PROFILE Trial

Baseline

Randomized double-blind

Flosequinan 100 mg/day
(n=1170)

Placebo
(n=1175)

> 20 months
## PROFILE Trial

**Clinical Response at 1 Month**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Flosequinan</th>
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</thead>
<tbody>
<tr>
<td>Improved functional capacity</td>
<td>19%</td>
<td>36%*</td>
</tr>
<tr>
<td>Improved well-being</td>
<td>15%</td>
<td>38%*</td>
</tr>
<tr>
<td>Intravenous therapy for CHF</td>
<td>28%</td>
<td>16%*</td>
</tr>
<tr>
<td>Emergency room visit for CHF</td>
<td>10%</td>
<td>5%*</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>17%</td>
<td>8%*</td>
</tr>
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* = P < 0.05

Packer et al. Circulation 1993; 83:I-301
PROFILE Trial

All-Cause Mortality

Death or HF Hospitalization

Packer et al. Circulation 1993; 83:I-301
PROFILE Trial

All-Cause Mortality

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<tr>
<td>0</td>
<td>100</td>
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</tr>
<tr>
<td>6</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
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Placebo: 41% ↑ in risk
P = 0.0004

Death or HF Hospitalization

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Placebo

Packer et al. Circulation 1993; 83:I-301
Oral Vasodilator Agents That Increase Morbidity or Mortality in Heart Failure

- Flosequinan
- Minoxidil
- Pinacidil
- Epoprostenol
- Calcium channel blockers
Increased activation of norepinephrine and angiotensin

Hypertrophy, cell death and interstitial fibrosis

Increased risk of death
Mimicking actions of norepinephrine and angiotensin

Hypertrophy, cell death and interstitial fibrosis

Increased risk of death

Inotropic drug
β-agonists

Norepinephrine

β-receptor

Cyclic AMP

Phosphodiesterase inhibitors

Phosphodiesterase type III
Effects of Amrinone in Chronic Heart Failure

Cardiac Output

LV Filling Pressure

Exercise Duration

Hemodynamic Effects of Short- and Long-Term Treatment with Amrinone in CHF

Cardiac output (L/min)

Baseline Day 1 Day 3 2-3 Months Withdrawal

Amrinone (600 mg/day, n=31)

Packer et al. Circulation 1984;70;1038-47
PROMISE Trial

Randomized double-blind

Baseline

Milrinone 40 mg/day
(n=561)

Placebo
(n=527)

21 months

PROMISE Trial

All-Cause Mortality

Months

% Survival

Placebo

Milrinone

28% ↑ in risk
P = 0.038

PROMISE Trial

Mortality in Class IV Patients


% Survival

53% ↑ in risk
P = 0.006

Placebo
Milrinone

Months

Oral Positive Inotropic Agents That Increase Mortality in Chronic Heart Failure

\[ \beta \text{-adrenergic agonists (stimulate synthesis of cyclic AMP)} \]

- Xamoterol
- Ibopamine

Phosphodiesterase inhibitors (inhibit breakdown of cyclic AMP)

- Milrinone
- Enoximone
- Vesnarinone
A Byzantine View of Heart Failure

(In hydrops the trouble lies in) the humours, having abandoned the extremities, might move in some other direction and so endanger the patient's life.

If we do not get rid of the humours, they will move . . . to some vital organ and even to the heart itself. If that happens, the damage will be irremediable.

— Nicholas Callicles (c. 1118)
Physician to Alexios I Komnenos
Cardiac Dysfunction Produced by Excessive Activation of Sympathetic Nervous System and Renin-Angiotensin System

Sympathetic nervous system

- *Pheochromocytoma* predictably led to myocardial necrosis
- Treated by surgical removal of the adrenal

Renin-angiotensin system

- *Renovascular hypertension* predictably led to myocardial hypertrophy and fibrosis
- Treated by surgical removal of the kidney
Angiotensin II and Norepinephrine Can Exert Cardiotoxic Effects in Susceptible Hearts

Angiotensin II and Norepinephrine Can Exert Cardiotoxic Effects in Susceptible Hearts

Angiotensin II Toxicity

% Area of necrosis

8

12

16

20

Angiotensin II Concentration

% Myocyte viability

60

70

80

90

100

Norepinephrine Exposure

Norepinephrine Toxicity

Stretched

Unstretched

Treatments

Activation of or sensitization to effects of norepinephrine and angiotensin

Peripheral vasoconstriction

Hypertrophy, cell death and fibrosis

Initial cardiac injury

Functional impairment of cardiac function

Structural impairment of cardiac function

Treatments
Progression of heart failure

Cardiorenal hypothesis
  Retention of salt and water

Hemodynamic hypothesis
  Impairment of cardiac function

Neurohormonal hypothesis
  Endogenous factors with biological effects

Blockade of hormonal systems
EDITORIAL REVIEW

The Neurohormonal Hypothesis: A Theory to Explain the Mechanism of Disease Progression in Heart Failure

MILTON PACKER, MD, FACC
New York, New York

Because physicians have traditionally considered heart failure to be a hemodynamic disorder, they have described the syndrome of heart failure using hemodynamic concepts and have designed treatment strategies to correct the hemodynamic derangements of the disease. However, although hemodynamic abnormalities may explain the symptoms of heart failure, they are not sufficient to explain the progression of heart failure and, ultimately, the death of the patient. Therapeutic interventions may improve the hemodynamic status of patients but adversely affect their long-term outcome. These findings have raised questions about the validity of the hemodynamic hypothesis and suggest that alternative mechanisms must play a primary role in advancing the disease process.

Several lines of evidence suggest that neurohormonal mechanisms play a central role in the progression of heart failure.

Activation of the sympathetic nervous system and renin-angiotensin system exerts a direct deleterious effect on the heart that is independent of the hemodynamic actions of these endogenous mechanisms. Therapeutic interventions that block the effects of these neurohormonal systems favorably alter the natural history of heart failure, and such benefits cannot be explained by the effect of these treatments on cardiac contractility and ejection fraction. Conversely, pharmacologic agents that adversely influence neurohormonal systems in heart failure may increase cardiovascular morbidity and mortality, even though they exert favorable hemodynamic effects. These observations support the formulation of a neurohormonal hypothesis of heart failure and provide the basis for the development of novel therapeutic strategies in the next decade.

(J Am Coll Cardiol 1992;20:248-54)
Angiotensin II

ACE inhibitors

β-blockers

Norepinephrine

Cardiac injury and remodeling
Comparison of Short- and Long-Term Effects of Prazosin and Captopril in Heart Failure

Packer et al., Am J Cardiol 1986;57:1323-7
Comparison of Short- and Long-Term Effects of Prazosin and Captopril in Heart Failure

Packer et al., Am J Cardiol 1986;57:1323-7
Comparison of Short- and Long-Term Effects of Amrinone and Carvedilol in Heart Failure

Comparison of Short- and Long-Term Effects of Amrinone and Carvedilol in Heart Failure

Krum et al., Circulation 1995; 92:1499-1506
Packer et al. Circulation 1984;70;1038-47
Early Advocates for the Neurohormonal Hypothesis for Chronic Heart Failure
Effect of ACE Inhibitors on Survival in Patients With Chronic Heart Failure

**CONSENSUS Trial**

- Placebo
- Enalapril
- 27% ↓ in risk
- P<0.001

**SOLVD Treatment Trial**

- Placebo
- Enalapril
- 16% ↓ in risk
- P=0.004

Angiotensin II  

Norepinephrine  

ACE inhibitors  

β-blockers  

Cardiac injury and remodeling
Early Placebo-Controlled β-Blocker Trial in Symptomatic Patients with Heart Failure

Randomized double-blind

Baseline

Carvedilol 25-50 mg BID (n=33)

Placebo (n=16)

Krum, Packer et al., Circulation 1995; 92:1499-1506
Effect of Carvedilol on Cardiac Function and Exercise Tolerance After 12-16 Weeks

Krum, Packer et al., Circulation 1995; 92:1499-1506
Effect of Carvedilol on Combined Risk of Death or Worsening Heart Failure

Krum, Packer et al., Circulation 1995; 92:1499-1506
US Carvedilol Trials (n=1094)

All-Cause Mortality

Death or CV Hospitalization

Event-Free Survival

Days

65% ↓ in risk
P < 0.0001

38% ↓ in risk
P = 0.0007

COPERNICUS Trial

All-Cause Mortality

% Survival

Carvedilol

Placebo

35% ↓ in risk
P = 0.00013

Angiotensin II
Aldosterone
Norepinephrine
Cardiac injury and remodeling
Effect of Mineralocorticoid Receptor Antagonists on Survival in Heart Failure

**EMPHASIS-HF**

HR 0.76 (0.62-0.93)  
P = 0.008

**RALES**

HR 0.70 (0.60-0.82)  
P < 0.001


What Is Biological Antagonism?

Endogenous compensatory peptides
(bradykinin, natriuretic peptides, adrenomedullin, angiotensin [1-7])

Modulation of many neurohormonal systems

Renin-angiotensin system

Direct benefits on heart, vasculature, kidney and nervous system

Neprilysin

Inactive metabolites
Neprilysin Activity Is Increased in Heart Failure and Has Adverse Prognostic Significance

Cardiovascular death or heart failure hospitalization

- Lower neprilysin activity
- Higher neprilysin activity

P = 0.03

Cardiovascular death

- Lower neprilysin activity
- Higher neprilysin activity

P < 0.001

JACC 2015:65:657–65
Increased Neprilysin Is the Next Neurohormonal Frontier in the Treatment of Heart Failure

Sympathetic nervous system

Renin-angiotensin system

Aldosterone

Neprilysin
Omapatrilat

Dual inhibitor of ACE and neprilysin

Combined ACE-neprilysin inhibition with omapatrilat once daily

% Activity

0 12 24 hours

NEP
ACE
OVERTURE Trial

All-Cause Mortality

ACE-Neprilysin Inhibition With Omapatrilat

Combined ACE-neprilysin inhibition with omapatrilat once daily

Failure to inhibit neprilysin for 24 hours

Modest (10%) reduction in risk of cardiovascular events

Transient simultaneous enzyme inhibition causes excessive bradykinin

Excess risk of serious angioedema
Evolution of Angiotensin Neprilysin Inhibition

LCZ696 (sacubitril/valsartan)

- Omapatrilat
  - Inhibition of aminopeptidase
  - Inhibition of ACE

24-hr inhibition of neprilysin (sacubitril)

Angiotensin receptor blockade (valsartan)
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

Aim of the PARADIGM-HF Trial

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE
PARADIGM-HF: Study Design

Randomization

Double-blind

Strategy to switch to and achieve target doses of enalapril (n=4212)

Strategy to switch to and achieve target doses of sacubitril/valsartan (n=4187)

10,521 patients receiving subtarget doses of ACE inhibitors or angiotensin receptor blockers chronically
PARADIGM-HF: Study Design

10,521 patients receiving subtarget doses of ACE inhibitors or angiotensin receptor blockers chronically

Randomization

Single-blind

Demonstration of tolerance to target doses of enalapril for 2 weeks

Demonstration of tolerance to target doses of sacubitril/valsartan for 2-4 weeks

Double-blind

Strategy to switch to and achieve target doses of enalapril (n=4212)

Strategy to switch to and achieve target doses of sacubitril/valsartan (n=4187)
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

**Enalapril**
\[n=4212\]

**Sacubitril valsartan**
(LCZ696) \[n=4187\]

HR = 0.80 (0.73-0.87)

\[P = 0.0000004\]

Self-contained trial during first chronological half (Nov 2009 – Dec 2011)

N=3489
HR= 0.76 (0.62-0.91)
P=0.004

Self-contained trial during second chronological half (Jan 2012 – Mar 2014)

N=4910
HR= 0.82 (0.70-0.95)
P=0.009
PARADIGM-HF: Cardiovascular Death

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Enalapril
(n=4212)

Sacubitril•valsartan
(n=4187)

HR = 0.80 (0.71-0.89)
P = 0.00008
Life extension: 1.5-2.0 years

18.9 mg daily

0
180
360
540
720
900
1080
1260

0 4 8 16 24 32

Angiotensin Neprilysin Inhibition Doubles the Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
Can Physicians Delay the Replacement of ACE Inhibitors With Sacubitril•Valsartan?

- Advantages of sacubitril•valsartan over enalapril seen within 30 days of initiation of treatment in stable patients with mild-to-moderate symptoms

- Sacubitril•valsartan (vs enalapril) reduced:
  - Cardiovascular death by 20% (P=0.00008)
  - Resuscitated and nonresuscitated sudden cardiac death by 22% (P=0.002)
  - Sudden cardiac death in patients with an ICD by 51% (RR 0.49 [95% CI 0.25–0.98])
Progress Until the Present

1675-1975
Fluid retention

1975-1990
↓ Cardiac function

1990-2015
Neuro-hormonal activation

Diuretics

Inotropic drugs
Vasodilators

Angiotensin neprilysin inhibitors
β-receptor blockers
Aldosterone antagonists
Survival in Class III Heart Failure

Assessment of Progress During Past 4 Decades
Survival in Class III Heart Failure

Assessment of Progress During Past 4 Decades

% Survival

100
90
80
70
60
50
40
30
20
10
0

Months

1985
1975

0 3 6 9 12 15 18
Survival in Class III Heart Failure

Assessment of Progress During Past 4 Decades

Survival in Class III Heart Failure

Assessment of Progress During Past 4 Decades
Survival in Class III Heart Failure

Assessment of Progress During Past 4 Decades
Survival in Heart Failure in the Community

Fluid retention

↓ Cardiac function

Neuro-hormonal activation

Failure of adoption of evidence-based therapies

Future Challenges
How We Think About Cancer and Heart Failure

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<th>Physician tells the patient #1</th>
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<td>We will do everything to kill every cancer cell. You are worried; that makes you a great patient</td>
<td>Your ejection fraction is lower than I would like. We will give you a few meds to help. You shouldn’t worry.</td>
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### How We Think About Cancer and Heart Failure

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<td>We are going to do exactly what was done in clinical trials</td>
<td>Clinical trials represent an ideal universe that we will never replicate</td>
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<th>Physician tells the patient #2</th>
<th>Cancer</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>We will do everything to kill every cancer cell. You are worried; that makes you a great patient</td>
<td>Your ejection fraction is lower than I would like. We will give you a few meds to help. You shouldn’t worry.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician’s attitude towards treatment</th>
<th>Cancer</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start with target doses; reduce dose only with intolerable toxicity</td>
<td>Start with subtherapeutic doses; increase dose only when convenient</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician’s attitude towards evidence</th>
<th>Cancer</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>We are going to do exactly what was done in clinical trials</td>
<td>Clinical trials represent an ideal universe that we will never replicate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician’s long-term view</th>
<th>Cancer</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>We will not let you die of cancer, no matter what</td>
<td>If you get worse, we would love to replace your heart</td>
<td></td>
</tr>
</tbody>
</table>
Future Challenges

- Fluid retention
- Cardiac function
- Neuro-hormonal activation

- Failure of adoption of evidence-based therapies
1675-1975

Fluid retention

1975-1990

↓ Cardiac function

1990-2015

Neuro-hormonal activation

2015-

I don’t care

Future Challenges

Failure of adoption of evidence-based therapies

Shift to replacement therapy

? Transplant

? Devices

? Stem cells