Reducing Heart Failure Hospitalizations

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Advanced Heart Failure & Cardiac Transplant

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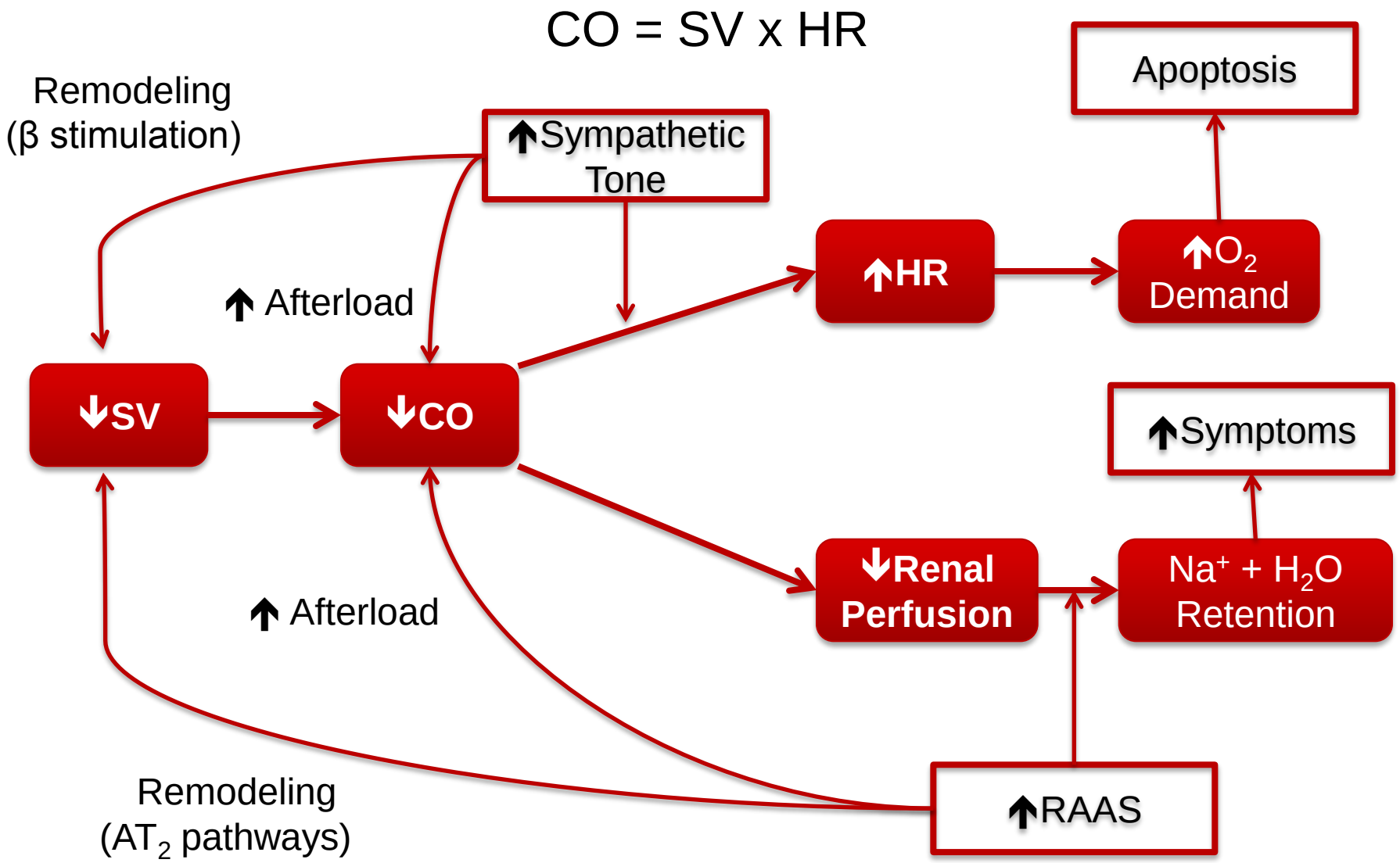
The Ohio State University
Wexner Medical Center

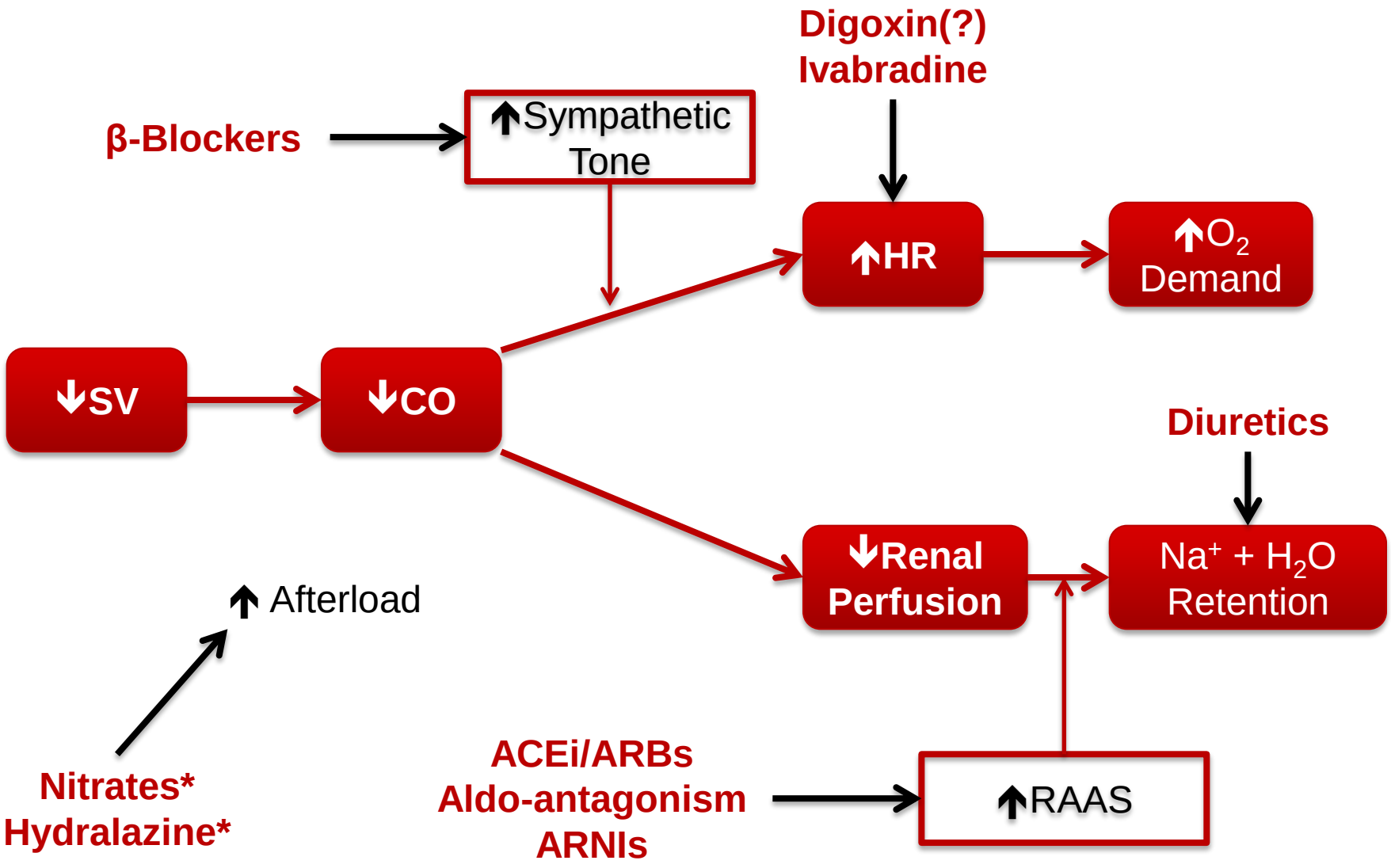
Disclosures

- Thoratec – consultant, grant funding
- St. Jude – consultant, grant funding
- CareDx – medical advisory board
- Abiomed – travel reimbursement

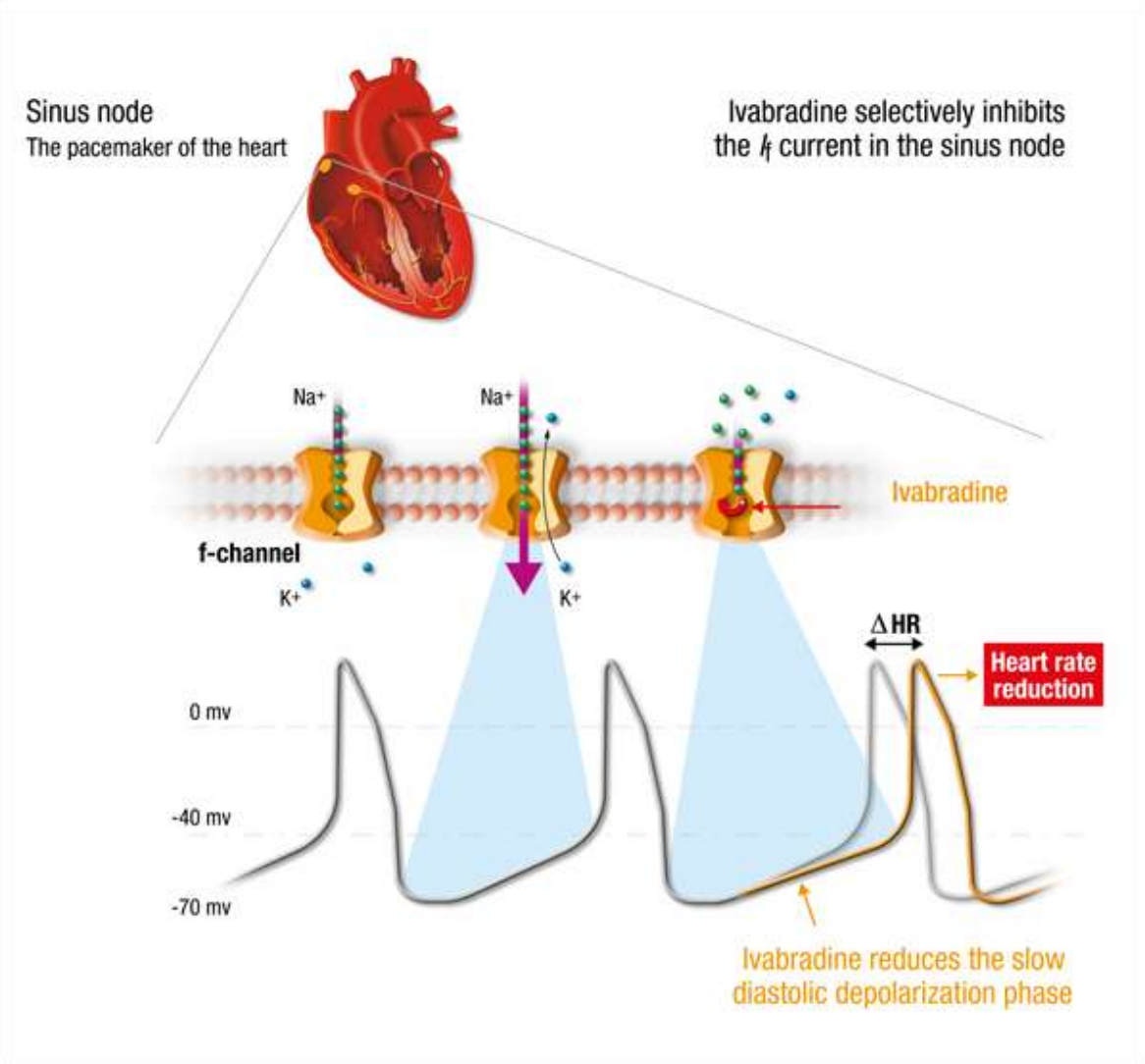
HF Maladaptation (Simplified)



Treating HF (Simplified)



Ivabradine



www.shift-study.com

SHIFT Study: Primary objective

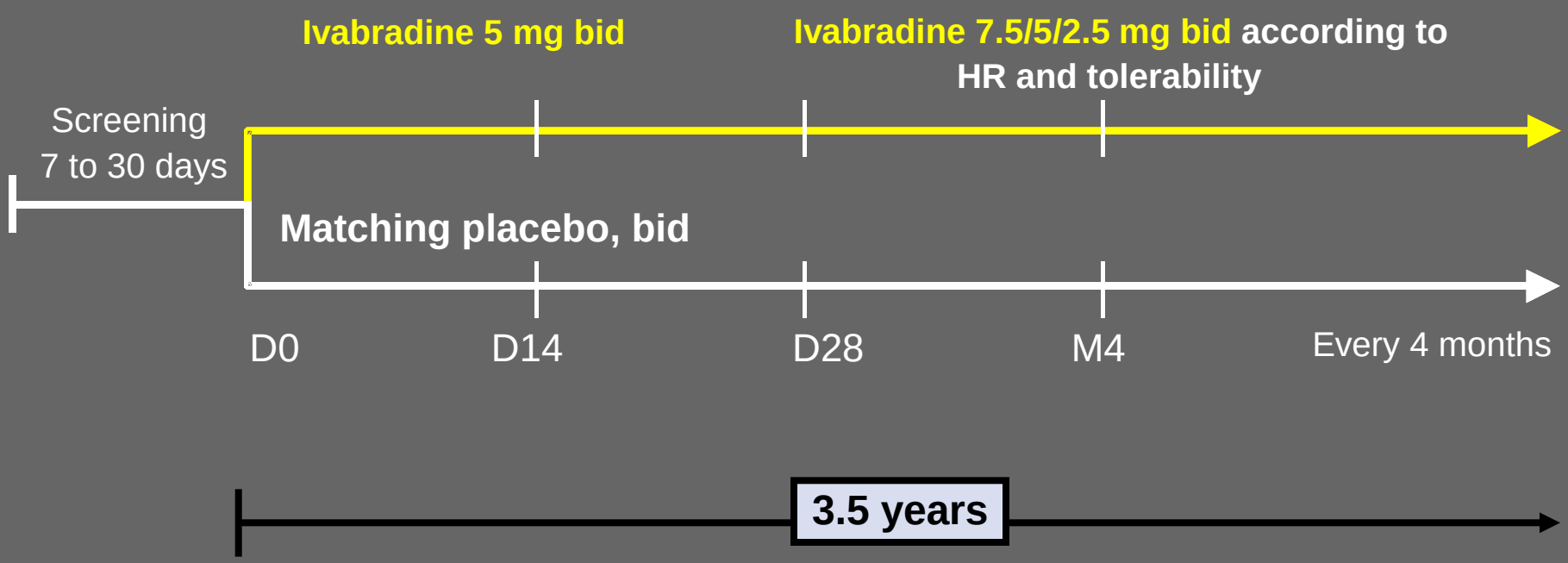
To evaluate whether the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with

1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction ≤35%
3. Heart rate ≥70 bpm in sinus rhythm
4. Best recommended therapy

    *Maximally tolerated dose of beta-blocker

Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81

Study Design



Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81

Study Endpoints

Primary composite endpoint

- Cardiovascular death
- Hospitalization for worsening heart failure

Other endpoints

§ All-cause / CV / HF death

§ All-cause / CV / HF hospitalization

§ Composite of CV death, hospitalization for HF or non-fatal MI

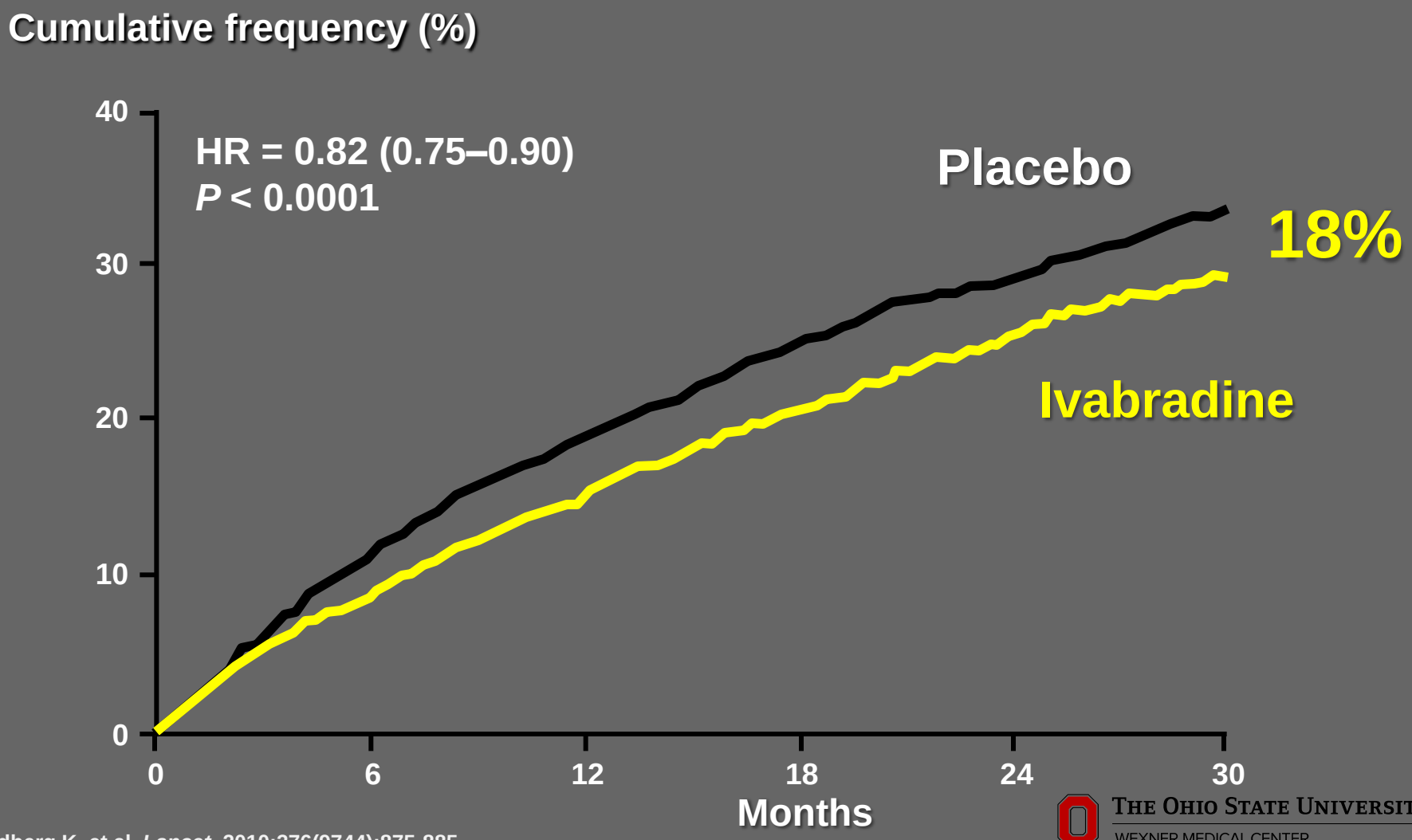
§ NYHA class / Patient & Physician Global Assessment

In total population and in patients with at least 50% target dose of beta-blockers

Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81

Primary composite endpoint

(CV death or hospital admission for worsening HF)



Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

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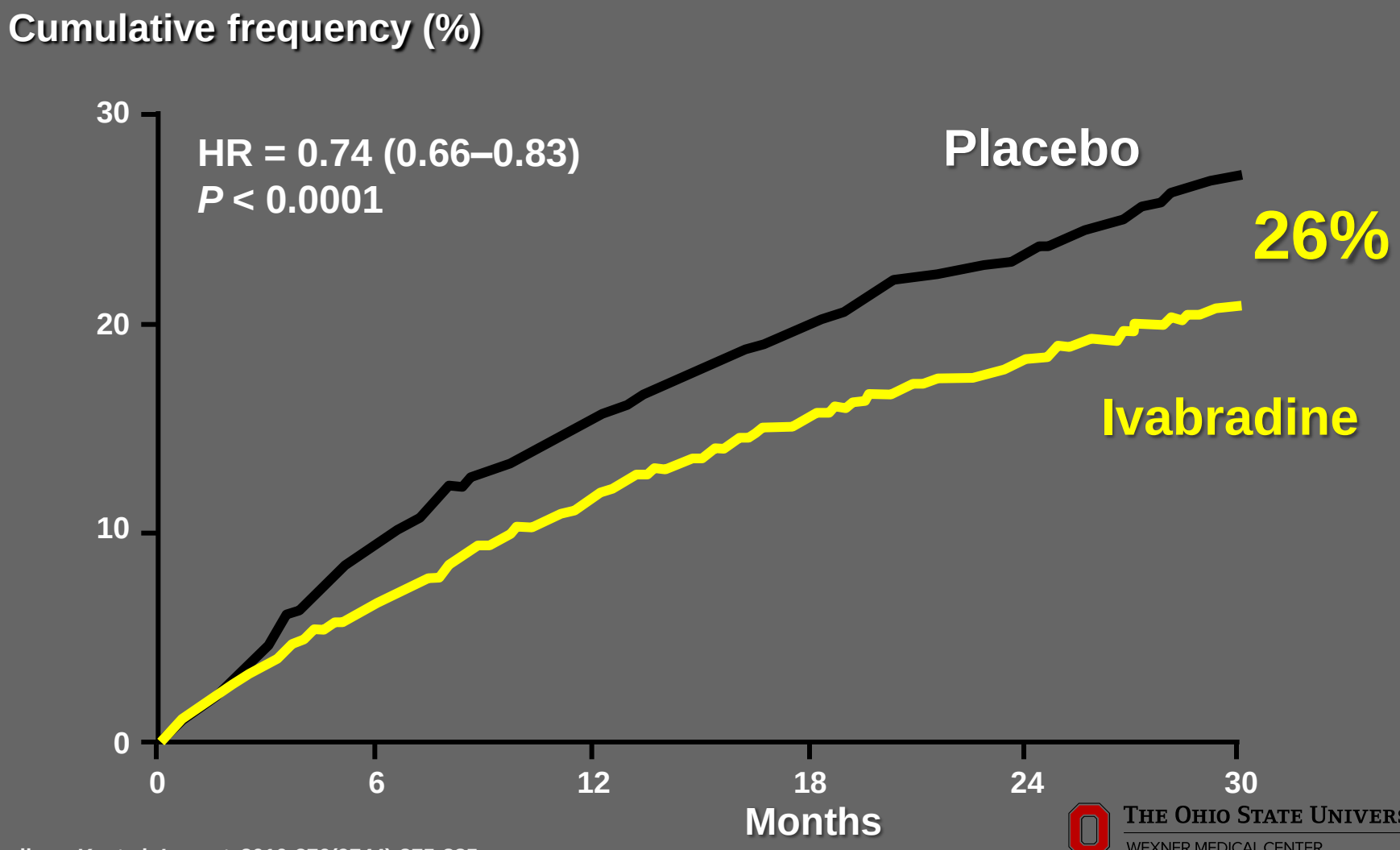
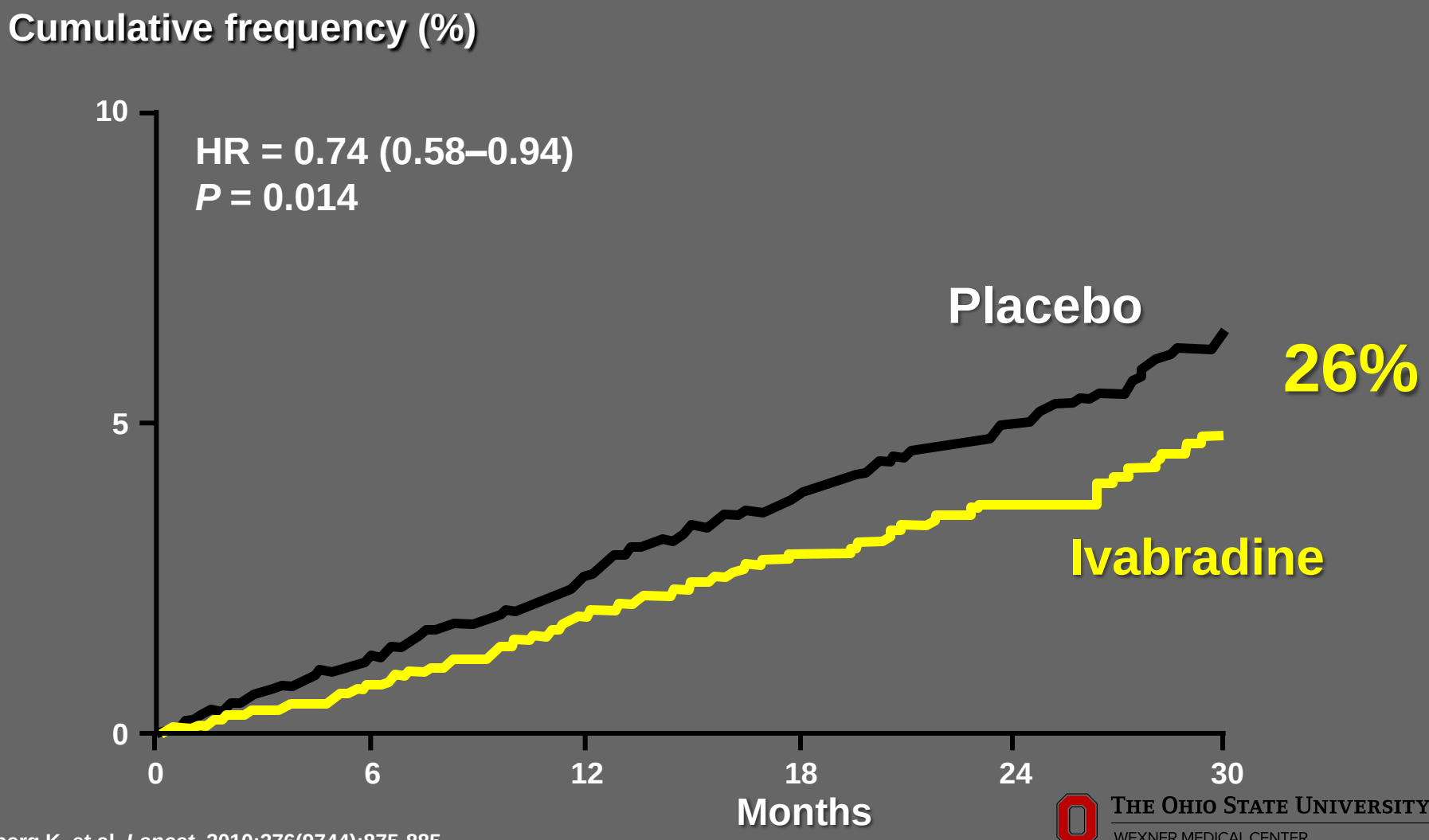
Hospitalization for HF



Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Death from heart failure



Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Ivabradine

- In patients on at least 50% target dose of β-blocker, only hospitalizations were reduced

- In a separate trial, no improvement was seen with ivabradine used for stable CAD without HF
  - Patients with limiting angina may do worse

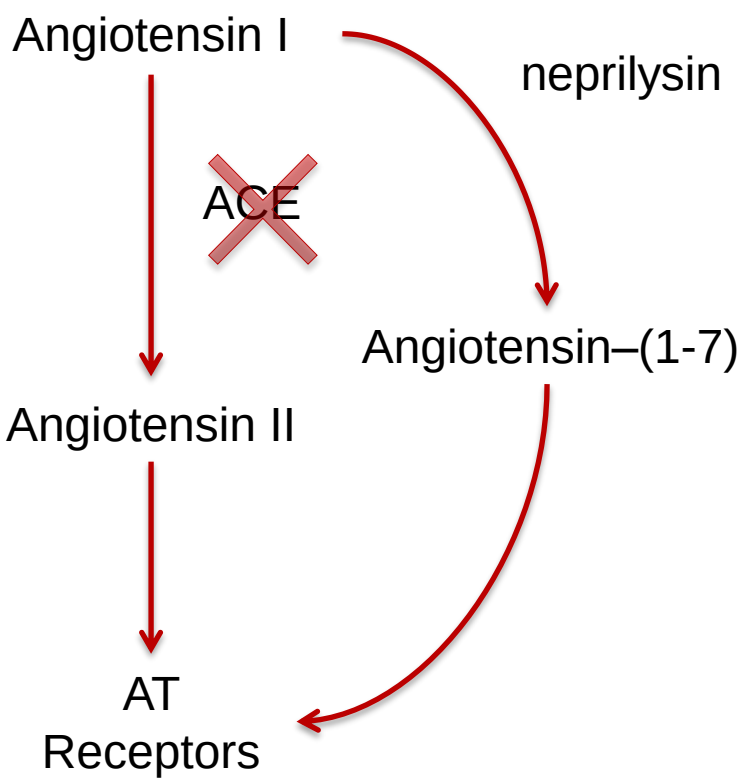
Swedberg K, et al. *Lancet*. 2010;376(9744):875-885
Fox K, *et al*, *NEJM* 2014; 371:1091-1099

Ivabradine

- Approved (April 4, 2015) by FDA
  - *Approved for reduction in HF hospitalizations only*
- Corlanor (Amgen)
- Symptomatic HFrEF (LVEF < 35%) on GDMT
- HR > 70 (max tolerated beta blocker)
- Adverse effects
  - Bradycardia
  - Caution with CYP3A4 inhibitors
  - Caution with drugs prolonging QTc
  - Don’t use with 1st gen Ca Channel blockers
  - Luminous phenomena 14%

Angiotensin-Neprilysin Inhibitors (ARNIs)

- Newest kid on the block
- Originally named LCZ696
- Combination of valsartan + AHU377 (sacubitril)
- AT2 receptor blockade + neprilysin inhibition
- Blocks angiotensin II at receptor / increase natriuretic peptides
- Lower BP, promote sodium excretion,



Ferrario CM, *et al*, *Am J Physio* 2005; H2281-H2290

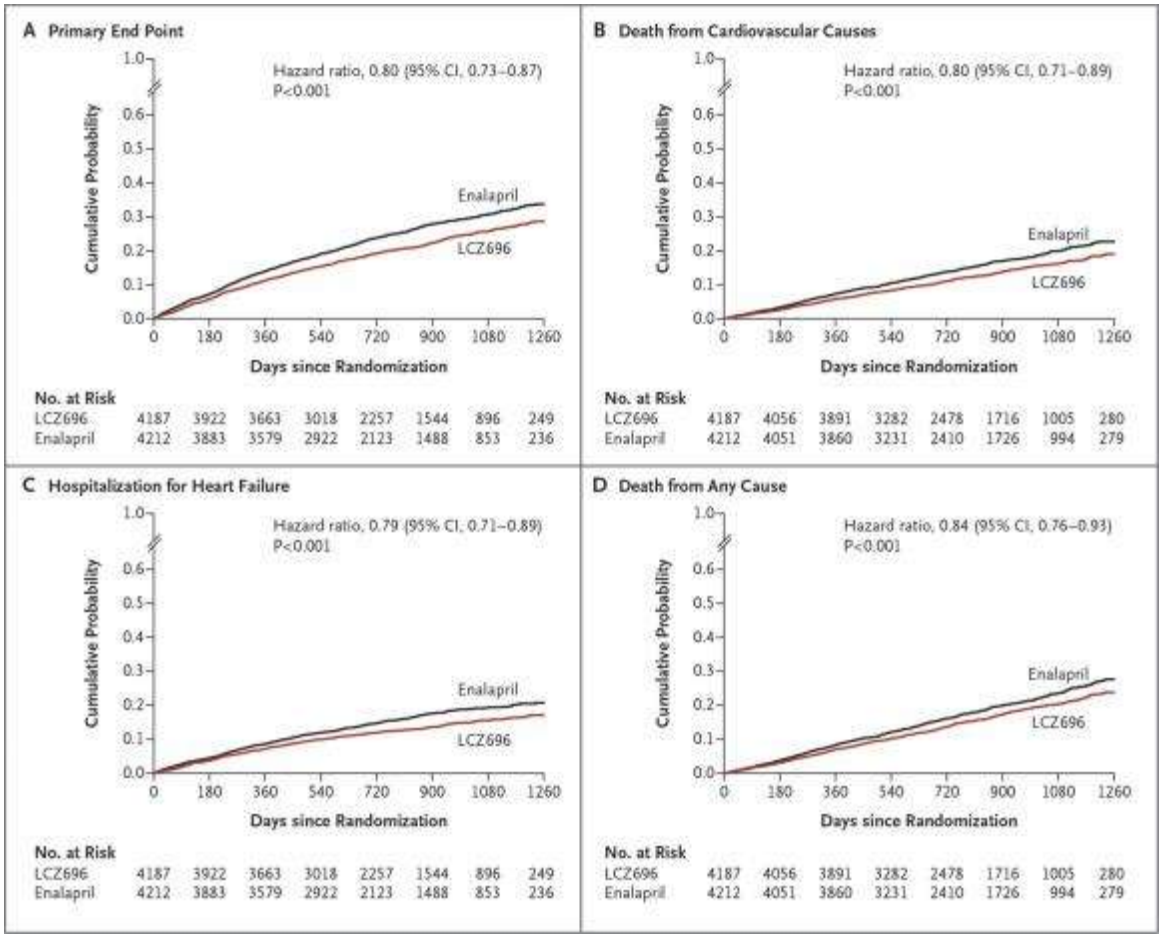
PARADIGM: LCZ696

- December 2009 to March 2014
- > 8000 patients HFrEF
- Received LCZ696 vs enalapril
- Primary: CV death or HF hospitalization
- Secondary: overall mortality

McMurray J, *NEJM* 2014; 371:993-1004

PARADIGM: LCZ696

Results showed improvement in primary and secondary endpoints



McMurray J, *NEJM* 2014; 371:993-1004

PARADIGM Conclusions

- Angiotensin receptor – neprilysin inhibition:
  - Reduces CV death and hospitalization for HF
  - Reduces overall mortality
  - Reduces symptoms and improves physical function

McMurray J, *NEJM* 2014; 371:993-1004

LCZ696 – A Game Changer?

Excitement because trial was stopped early

- Met pre-specified end-points
- “Boundary for overwhelming benefit with LCZ696 had been crossed”

LCZ696 – Concerns

- Hypotension due to more vasodilation
- 10,500+ patients screened
- 1100 discontinued during ACEi run-in phase
- Almost 1000 discontinued during ARNI run-in phase
- Angioedema not an issue in this trial
  - But was with previous neprilysin inhibitors
- Cough and hyperkalemia no different than enalapril group.
  - Hyperkalemia more of an issue with previous ANRIs

McMurray J, *NEJM* 2014; 371:993-1004

ARNIs

- FDA approved sacubitril/valsartan on July 7, 2015
  - Approved to reduce HF hospitalizations and CV death
- Brand name: Entresto
- If patients are on ACEi's, must stop at least 36 hours prior to starting ARNI
- Neprilysin breaks down BNP
  - ARNIs may elevated BNP levels
  - Unclear if BNP threshold will be useful
  - Consider NT-proBNP or ST-2

Entreso PI, www.novartis.com
Emani S, *et al*, *Future Cardio* 2015

Remote monitoring

- The next major development in HF management?
- Help prevent hospitalizations?
- Prevent negative effects of playing “catch-up?”

(Thanks to Dr. William Abraham for slides)

What Do We Need to Monitor to Accomplish This Goal?

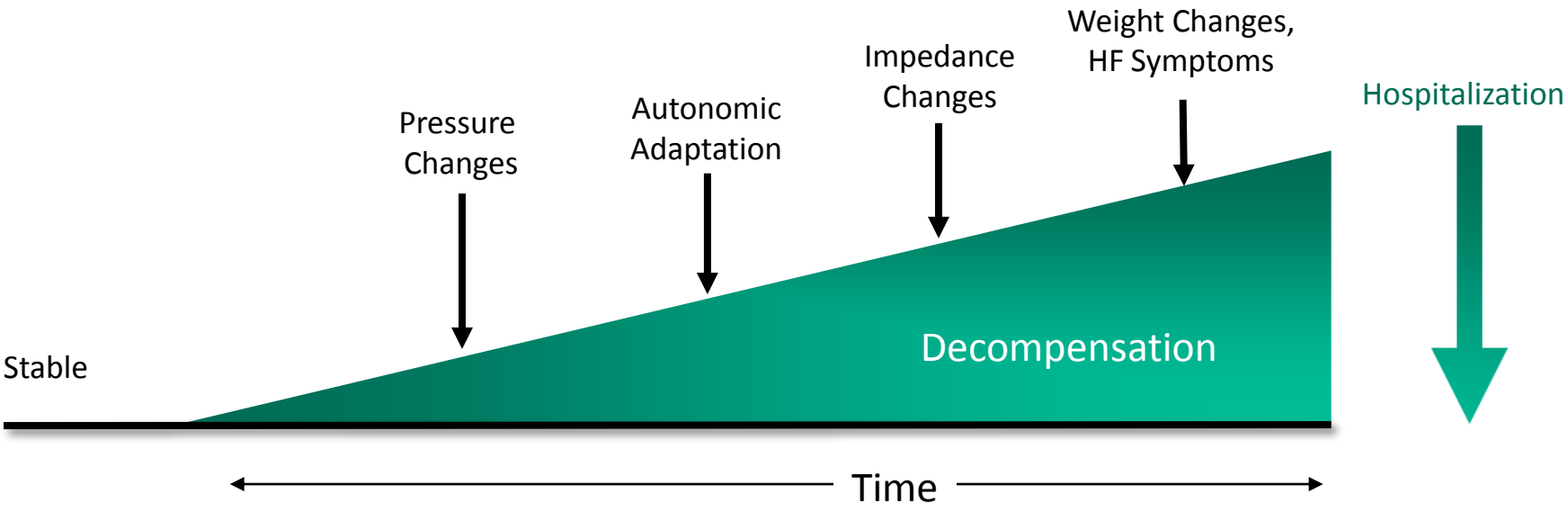
- Fluid in the lungs / pressures in the heart
- How do we currently assess these in patients with chronic heart failure?
  - Symptoms
  - Daily weights
  - Physical examination
  - Device-based diagnostics
  - Biomarkers

} Surrogates for fluid retention and increased filling pressures

- How well do these assessments perform?
  - Not very well

The Development of Acute Decompensation

Physiologic markers of the development of acute decompensation:



Unreliability of Weight Change in Identifying Heart Failure Decompensation

Weight change has **low sensitivity** for identifying decompensation

	Sensitivity	Specificity
2 kg weight gain over 48-72 hrs[1]	9%	97%
2% weight gain over 48-72 hrs[1]	17%	94%
3 lbs in 1 day or 5 lbs in 3 days[2]	22.5%	-

Lewin, 2005. N=77[1]

Abraham, 2011. N=156[2]

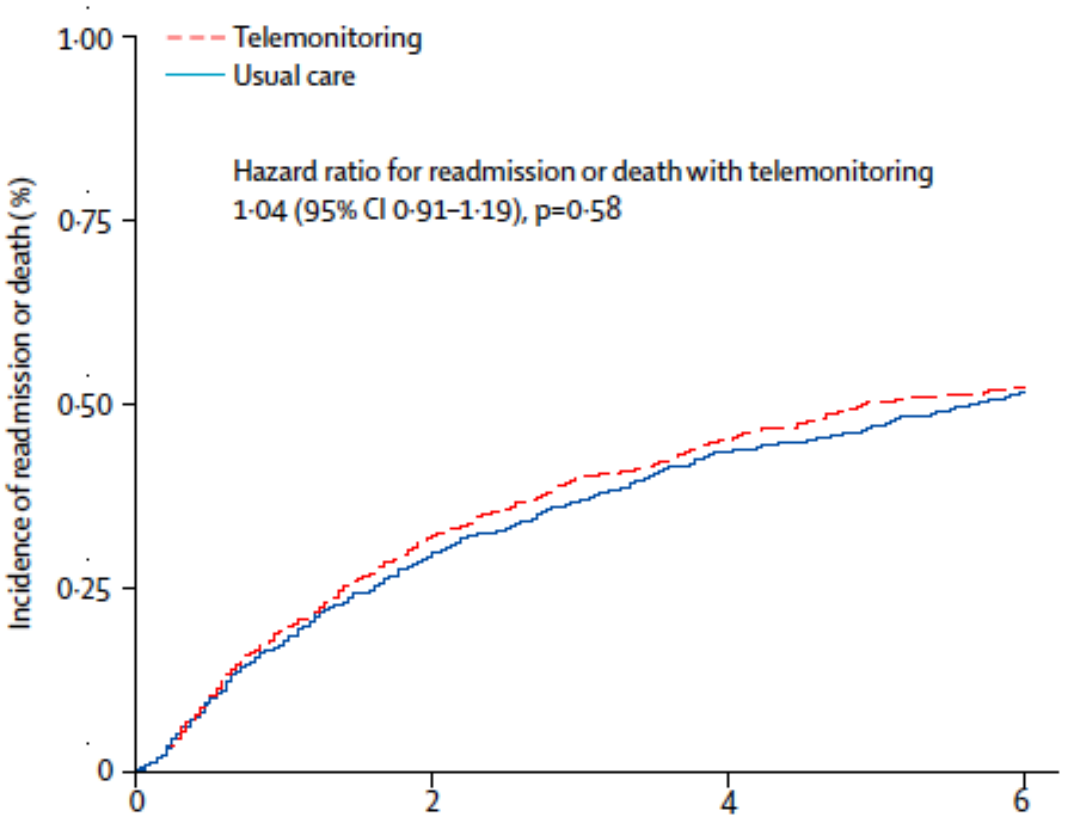
1. Lewin J, et al. Eur J Heart Fail 2005
2. Abraham WT, et al. Congest Heart Fail 2011

TELE-HF Trial: Telemonitoring of Weight Changes and Heart Failure Symptoms

- NIH-sponsored randomized controlled trial of 1653 patients
- Primary endpoint: readmission for any reason or death from any cause within 180 days after enrollment
- Control group: usual care (no telemonitoring)
- Treatment group: telemonitoring of symptoms and weight by telephone-based interactive voice-response system
- Result: no difference in number of deaths, readmissions, or days in hospital

Chaudhry SI, et al. N Engl J Med 2010

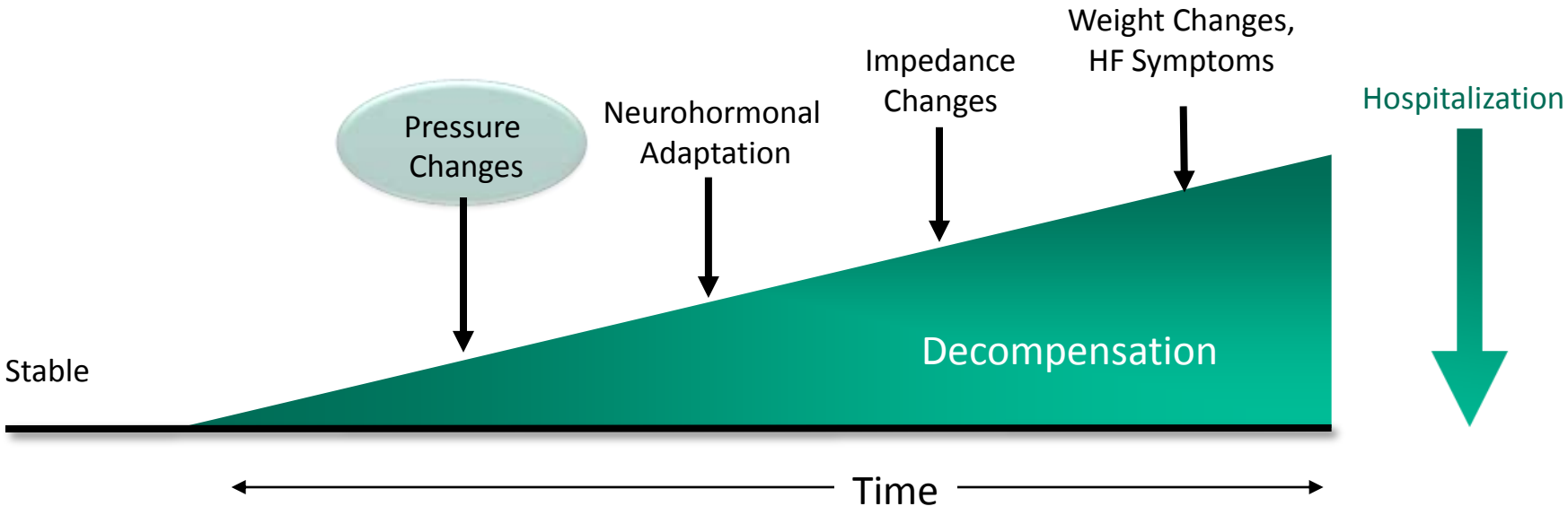
TELE-HF Trial: Telemonitoring of Weight Changes and Heart Failure Symptoms



Chaudhry SI, et al. N Engl J Med 2010

Is There Value in Monitoring Pressure Changes?

HF decompensation leads to increase in intracardiac and pulmonary artery pressures



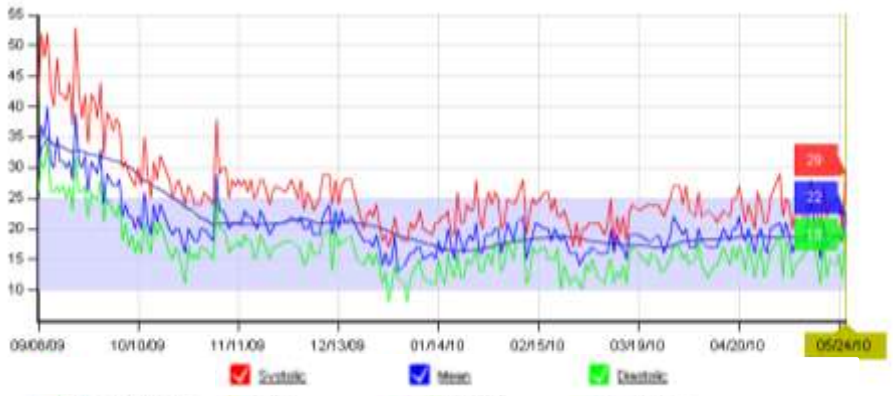
The Pulmonary Artery Pressure Measurement System*

Catheter-based delivery system

MEMS-based pressure sensor

Home electronics

PA Measurement database

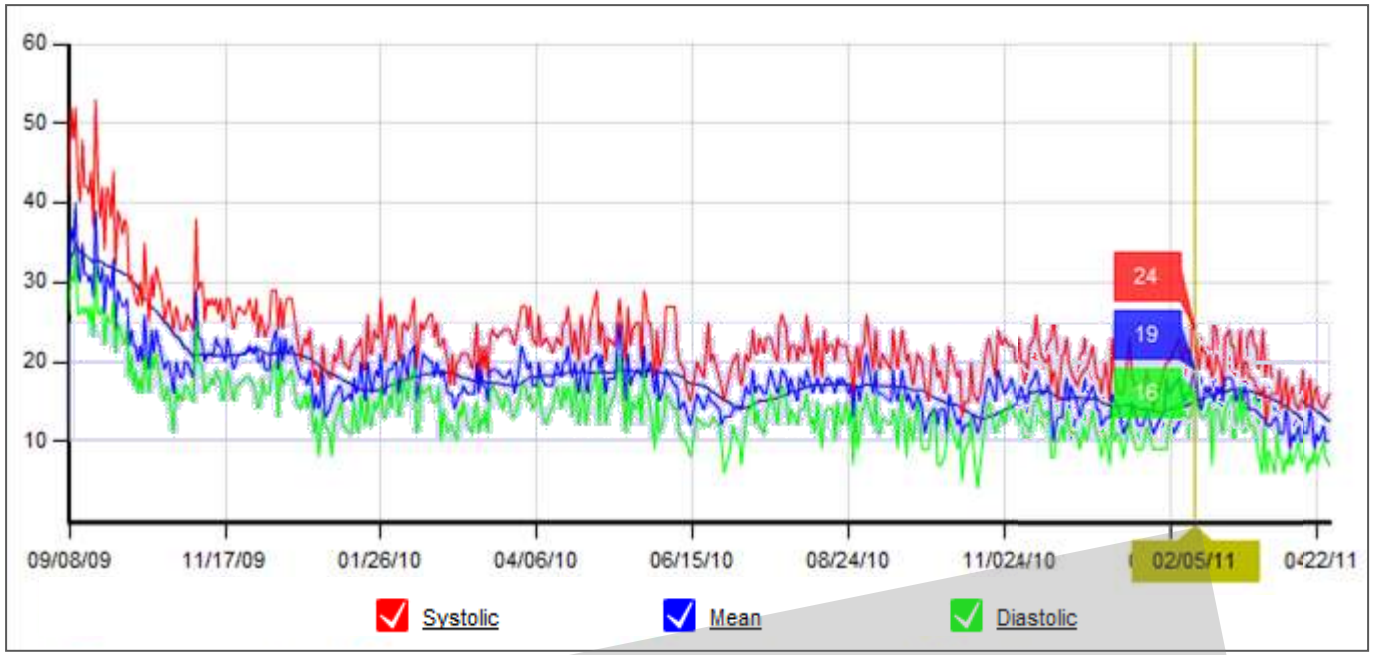


*CardioMEMS Inc., Atlanta, Georgia, USA

Patient Management Database

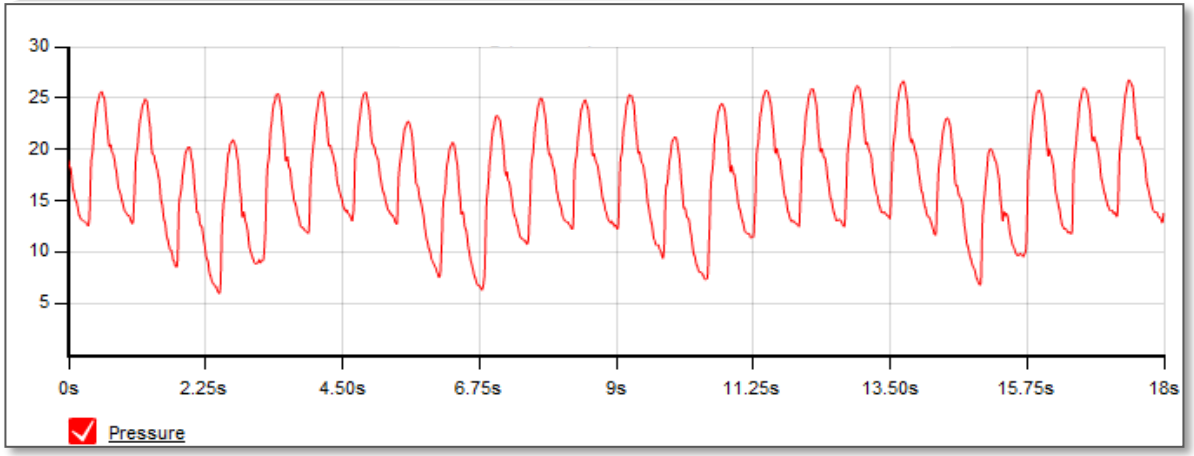
Trend Data

- Easy-to-read
- Physician alerts
- Home transmission
- Secure, encrypted web-based access



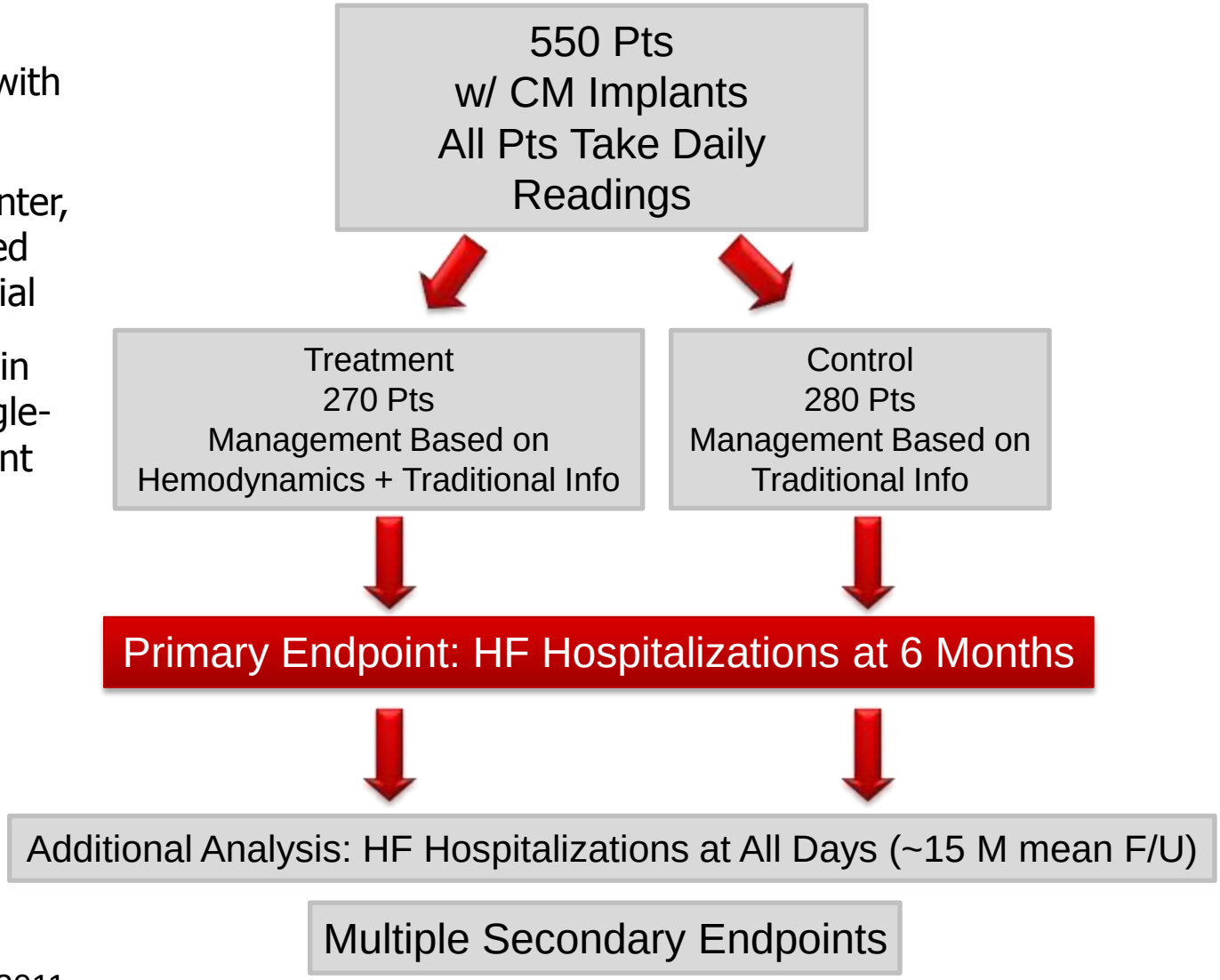
Discrete Data

Reading	
Systolic:	24
Mean:	19
Diastolic:	16
Heart Rate:	81



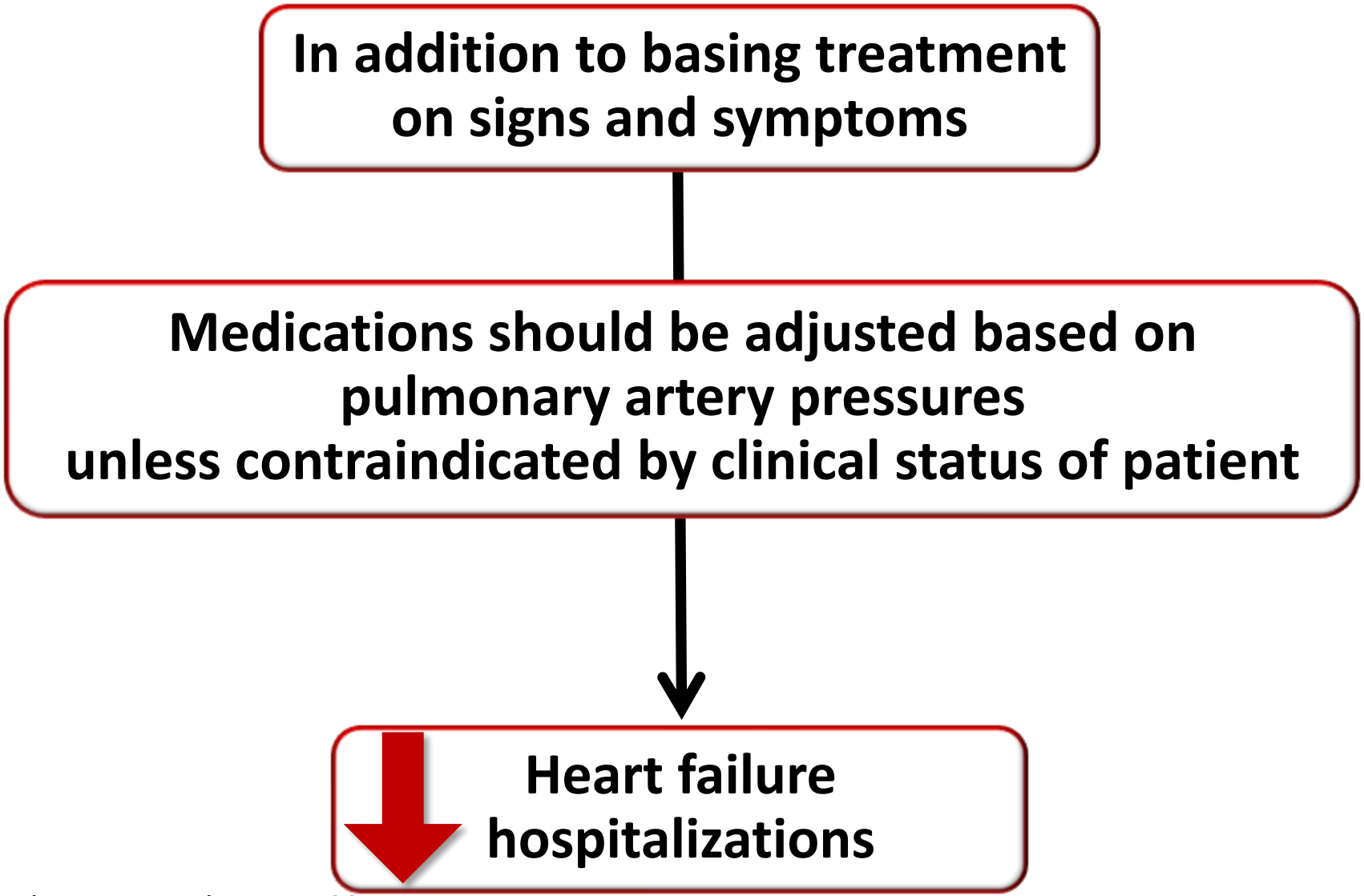
CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients

- Trial Designed by Steering Committee with active FDA input
- Prospective, multi-center, randomized, controlled single-blind clinical trial
- All subjects followed in their randomized single-blind study assignment until the last patient reached 6 months of follow-up
- 64 US Centers



Abraham WT, et al. Lancet 2011

Hypothesis of the CHAMPION Trial



Abraham WT, et al. Lancet 2011

Protocol Guidelines: PA Pressure Management

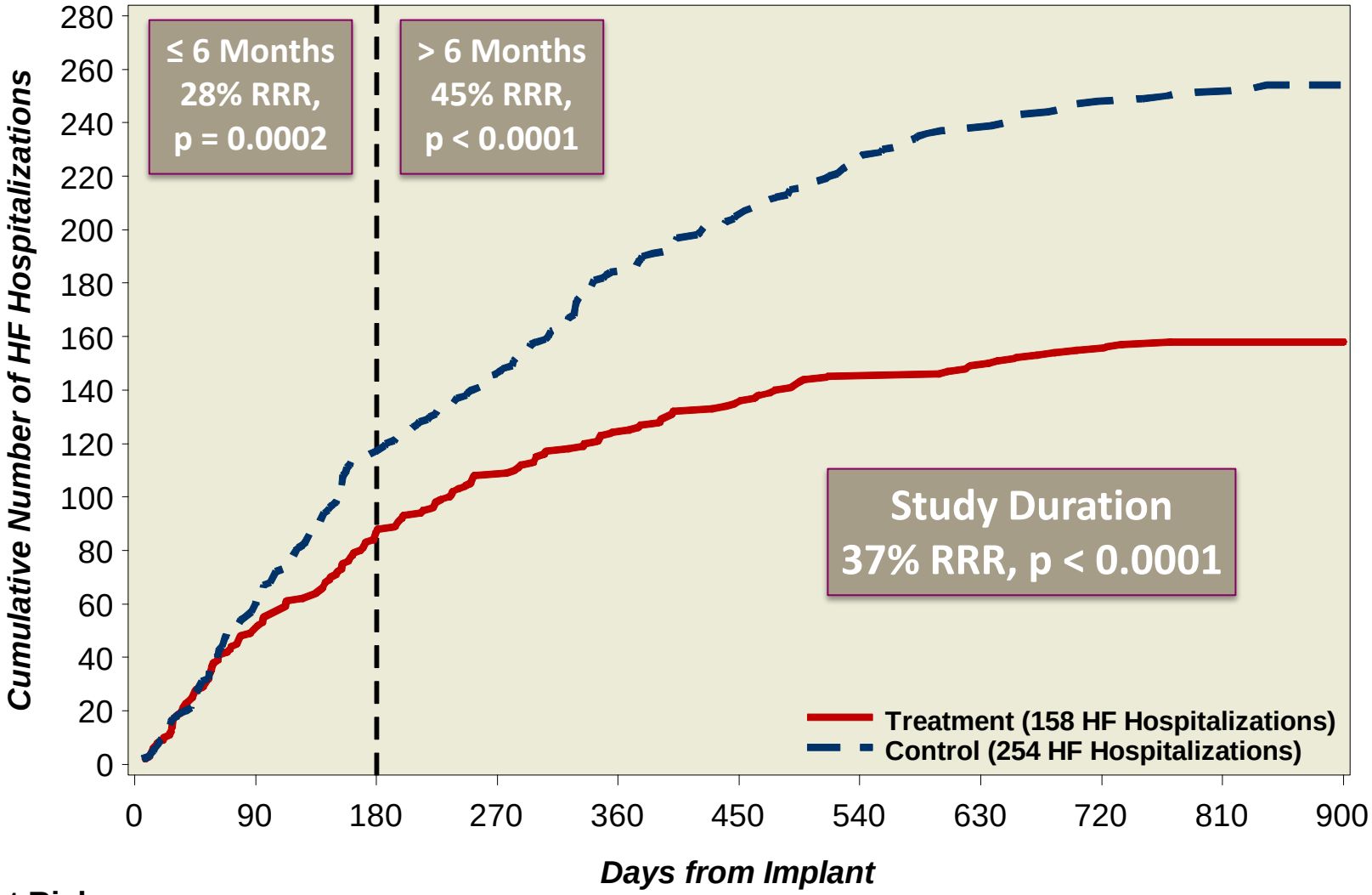
Treatment Recommendations for Elevated PA Pressures

- Add or increase diuretic
  - increase/add loop diuretic
  - change loop diuretic
  - add thiazide diuretic
  - IV loop diuretic
- Add or increase vasodilator
  - add or increase nitrate

Abraham WT, et al. Lancet 2011

Cumulative HF Hospitalizations Reduced

At 6 Months and Full Duration of Randomized Study



No. at Risk											
Treatment	270	262	244	210	169	131	108	82	29	5	1
Control	280	267	252	215	179	137	105	67	25	10	0

Primary Efficacy Endpoint Met

	Treatment (n=270)	Control (n=280)	Relative Risk Reduction	p-value[1]	NNT
Primary Efficacy Endpoint: HF Related Hospitalizations (Rate for 6 months)	84 (0.32)	120 (0.44)	28%	0.0002	8
Supplementary Analysis: HF Related Hospitalizations (Full Duration - Annualized Rate)	158 (0.46)	254 (0.73)	37%	<0.0001	4

[1]p-value from negative binomial regression
NNT = Number Needed to Treat

Abraham WT, et al. Lancet 2011

Summary

- Implantable hemodynamic monitors provide direct and actionable measurements of intra-cardiac and pulmonary artery pressures
- Management guided by such monitors reduces the risk of heart failure hospitalizations
- This approach promises to revolutionize the management of heart failure patients
  - Crisis management ➔ Stability management

CardioMEMS: Current Status

- Approved for use in NYHA III HF patients

- Intended to:
  - Reduced HF hospitalizations
  - Improved QoL
  - No indication to improved survival

Challenges with Hemodynamic Monitoring

- Implantation
  - Minimal challenges
  - Need anticoagulation for 30 days

- Reimbursement
  - Implant is covered (generally)
  - New CPT codes
  - Data monitoring not really reimbursed

Hemodynamic Monitoring: Stress on System

- Beneficial when monitoring routinely & frequently
  - Not once every 30 days
- Requires patient compliance with transmission
- Requires medical staff to read/interpret/act upon data
- Need to have medical options to act upon data

Ohio State CardioMEMS Work-Flow

- Remote hemodynamic program is evolving
- Currently ~40 patients being followed
- More automation of system/smart data analysis needed

Thank you