

**Medicare Evidence Development & Coverage Advisory  
Committee (MEDCAC)**  
**Health Outcomes in Heart Failure Treatment Technology  
Studies- RESPONSE TO QUESTION 1**  
**March 22, 2017**

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## Employment:

Employee / Faculty at Baylor College of Medicine and DeBakey Veterans Affairs Medical Center

## Research:

- Clinical Trial Investigator –Baylor College of Medicine Institutional Contract for Patient Enrollment and Coordinator Support: Novartis, modest, < \$ 10,000
- Circulation Associate Editor: modest, <\$10,000
- American Board of Internal Medicine Heart Failure and Cardiac Transplant Question Writing Committee, modest, <\$10,000

## Volunteer Activities (No Financial COI):

- ACC Heart Failure Council Chair
- Member of Heart Failure Society of America Board of Directors

## ACC Conflicts:

- ACC has no conflicts to disclose

# Collaborating Organizations



AMERICAN  
COLLEGE *of*  
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The Society for Cardiovascular  
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HEART FAILURE SOCIETY OF AMERICA

# Q 1: How confident are you that the following are standalone, meaningful primary health outcomes in research studies of HF treatment technologies ?

- Each end point important, but not adequate as stand alone
- Technology needs ALL 3 (not 1) : 1) Device efficacy 2) Device Safety 3) Clinical Outcomes
- Each end-point's value changes according to technology target profile, patient presentation and concordance with other outcomes
- Different patient presentations/ stages of disease such as Stage A,B,C,D or ADHF, shock, chronic HFrEF or HFpEF, advanced / refractory HF require different outcomes

## HF hospitalization

- Patients with prolonged hospital stay or who die have less time at risk for rehospitalization
- Composite of death or HF hospital stay or “days alive and out of the hospital” a better index : combines mortality, LOS of index hospital stay, & subsequent hospital stays
- Time to event analyses censors after the initial event, discounting the clinical burden of multiple or prolonged initial hospital stays.
- HFH should not be discordant with other clinical outcomes such as mortality and CVD death, and safety

## HF hospitalization or equivalent events (outpatient IV therapy )

- Important for trials addressing congestion or decompensation of HF
- Important for hospitalized / ADHF patients
- A composite of death or HF hospitalization or urgent care events or days alive and without requirement for hospitalization or urgent care visit may be a better end point
- Should not be discordant with mortality, other CVD events and safety

## Total Hospitalizations

- Not as a stand- alone
- Important for safety : high risk interventions related to morbidity or risk related to procedure
- Important for additional efficacy : HFpEF where the burden of comorbidities is high
- Should be concordant with improvement in HF end points such as HF hospitalizations
- May be important if targeting a comorbidity causing HF such as HTN



# Discussion

please discuss the appropriate length of follow-up HF intervention for assessing this outcome; important considerations when assessing the merits of composite outcomes hospitalization, or heart failure hospitalization equivalent events

## ADHF Shock Trials

- Hemodynamics
- All cause mortality
- All cause mortality with need for cardiac transplantation
- In-hospital survival
- Subsequent 6 mo or 1 year follow up

## Hospitalized ADHF

- Composite of death or HF re-hospitalization + urgent care events
- 6 months or 1 year

## Stage C Chronic HF

- Composite of death or HF re-hospitalization + urgent care events
- 1 Year or 3 year or 5 years

## Stage D / Advanced HF

- For non-end of life: Composite of mortality + HF re-hospitalization + urgent care events+ need for transplantation
- If end of life: Quality of Life
- 1 year

# Combined End Points

- **Concordant clinical end points with similar treatment effects** for each outcome: Should not combine divergent end points , report end points separately

*examples : A device that increases mortality but reduces hospitalizations*

**Combined clinical composite score:** Clinical hard end points (mortality, hospitalizations) + symptoms (NYHA Class), global assessment (Packer M. J Card Fail. 2001 Jun;7(2):176-82).

*Event rates higher , sample size smaller; but difficult to interpret if effects are not similar for all components or if the effect of treatment is primarily on a more common, less serious component of the composite. Typically only focuses on the first occurring event, which can lead to a substantial loss of information ( J Card Fail. 2005 Oct;11(8):567-75.)*

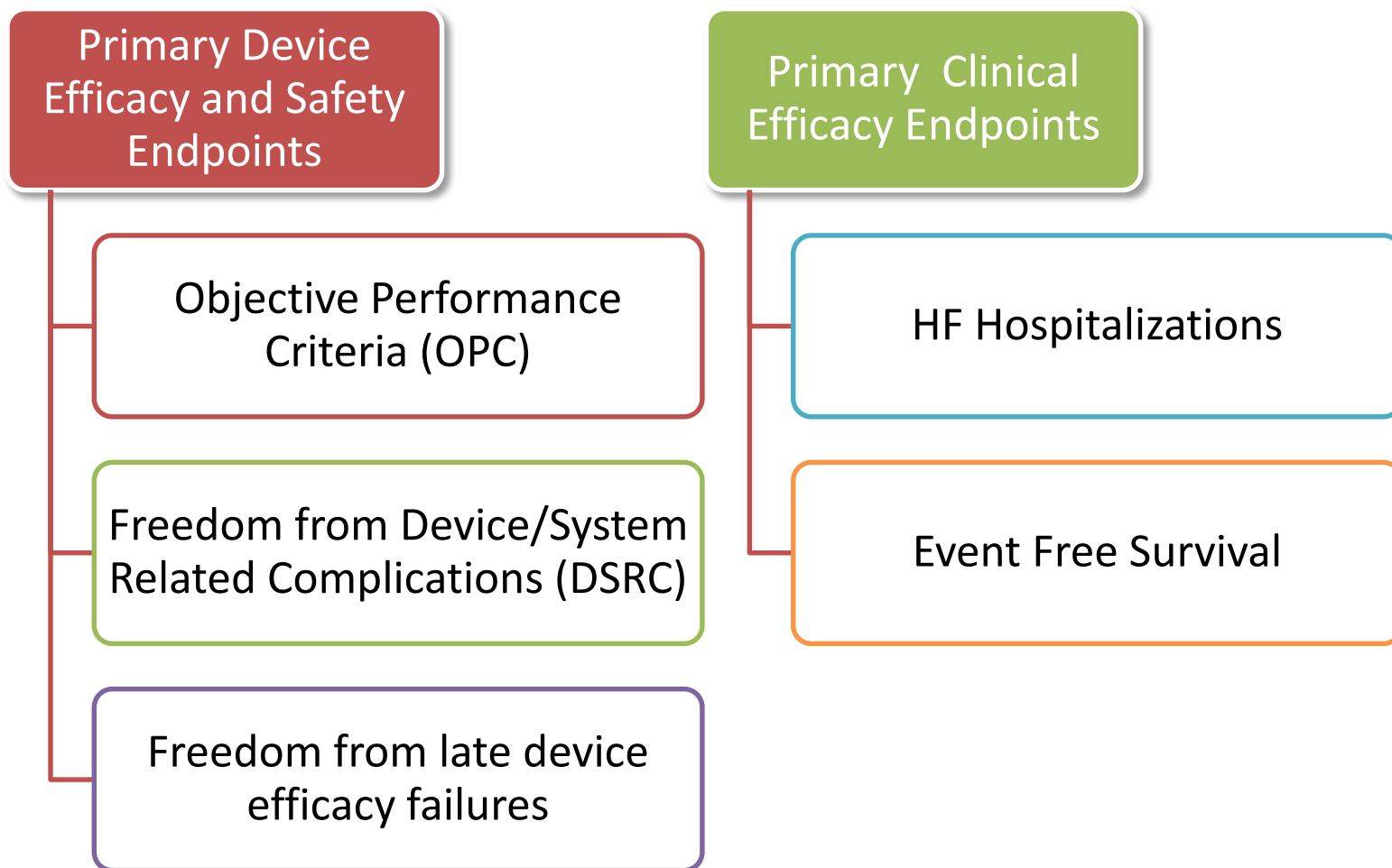
*composite end points reflect the totality of patient experience , not mortality alone. Example :As overall survival with MCSD therapy improves, nonfatal but highly morbid events (such as stroke or device failure) will increasingly be seen as critical to the evaluation of device efficacy and safety*

- **A global ranking approach :** ranks various aspects of the clinical course based on a prespecified hierarchical ranking system, may provide many of the advantages of composite end points while avoiding pitfalls. Example : Gives a hierarchy to time to death then time to hospitalization (J Card Fail. 2008 Jun;14(5):368-72. )

# Outcomes for Different Technologies

Hospitalizations the right outcome for all technologies ?

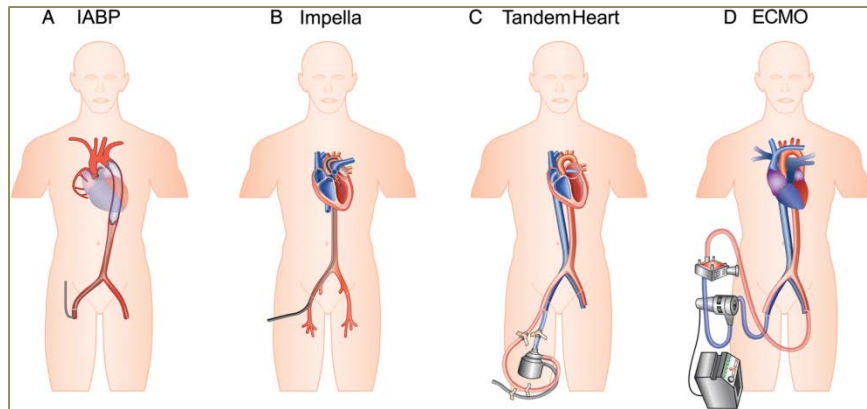
## Yin / Yang of Technology



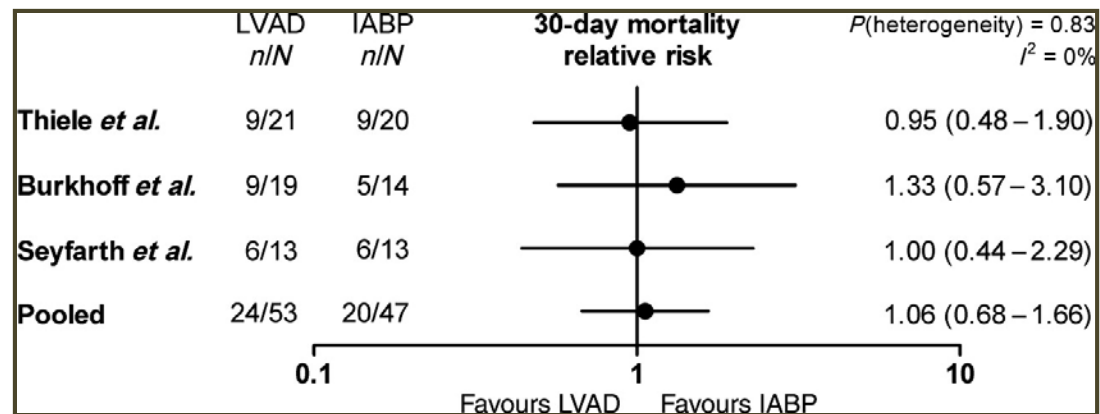
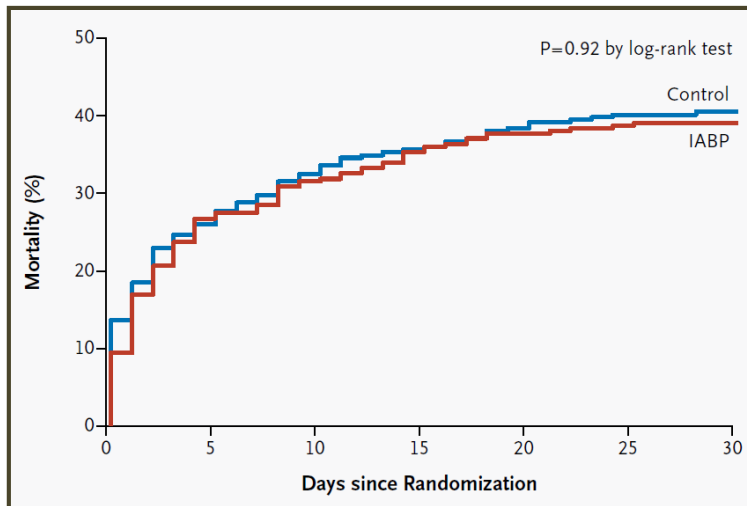
# Outcomes for Different Technologies

Hospitalizations the right outcome for all technologies ?

**Outcome for Technology for Shock/Acute HF Recovery or Bridge : 3 OUTCOMES NEEDED :**  
**1) DEVICE EFFICACY: HEMODYNAMICS 2) DEVICE SAFETY 3) CLINICAL OUTCOME: MORTALITY**



|                             | IABP                    | ECMO      | Tandem Heart | Impella          |
|-----------------------------|-------------------------|-----------|--------------|------------------|
| Afterload                   | Reduced                 | Increased | Increased    | Neutral          |
| LV stroke volume            | Slight increase         | Reduced   | Reduced      | Reduced          |
| Coronary perfusion          | Slight increase         | Unknown   | Unknown      | Unknown          |
| LV pre-load                 | Slightly reduced        | Reduced   | Reduced      | Slightly reduced |
| PCW pressure                | Slightly reduced        | Reduced   | Reduced      | Slightly reduced |
| Peripheral tissue perfusion | No significant increase | Improved  | Improved     | Improved         |



**Mortality challenging, hospitalization prolonged**

Burkhoff D. *et al* Am Heart J. 2006 Sep;152(3):469.e1-8.; M Seyfarth, *et al.* A RCT to evaluate the safety and efficacy of a pLVAD vs. IABP for treatment of cardiogenic shock caused by MI J Am Coll Cardiol. 2008;52(19):1584-1588; Thiele H, *et al.* RCT comparison IABP with a pVAD in patients with AMI complicated by cardiogenic shock. Eur Heart J 2005;26:1276-1283. PROTECT: Dixon SR, *et al.* A prospective feasibility trial investigating the use of the Impella 2.5 in patients undergoing high-risk PCI. J Am Coll Cardiol Interv 2009;2:91-96.; Cheng JM, *et al.* Percutaneous LVAD vs. IABP counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J; doi:10.1093/eurheartj/ehp292



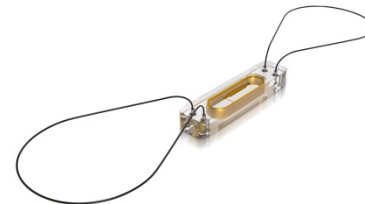
# Outcomes for Different Technologies

Hospitalizations the right outcome for all technologies ?

## Cardiac implantable electronic devices (CIEDs) :

1) Device efficacy :Hemodynamics 2) Safety 3) Clinical outcomes: HFH or Combined End Points

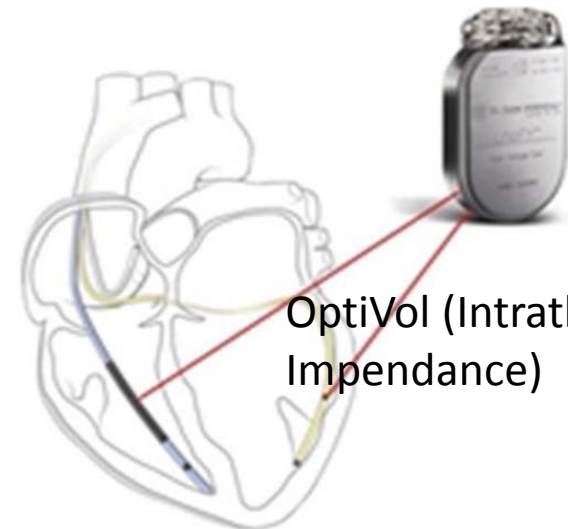
| Sensor                         | Examples   |
|--------------------------------|--|
| Currently available sensors    |  |
| Heart rate derivatives         | Mean heart rate, nocturnal heart rate<br>Heart rate variability (SDAAM, SDANN)<br>HRV footprint  |
| Accelerometers                 | Physical activity level  |
| Impedance monitors             | RV-Can (OptiVol)<br>LV-RV, LV-can impedance<br>Minute ventilation  |
| Hemodynamic                    | Right ventricle pressure (Chronicle IHM)<br>RV $dP/dt_{max}$ (ePAD)<br>Left atrial pressure (HeartPOD)<br>Pulmonary artery pressure (Champion) |
| Cardiac output                 | Doppler<br>RV $O_2$ saturation monitor   |
| Heart sounds                   | Peak endocardial acceleration  |
| Emerging modalities            |  |
| Chemicals                      | $PO_2$ , $PCO_2$ , pH<br>Electrolytes, glucose   |
| Biomarkers                     | Natriuretic peptides (BNP, NT-proBNP, ANP)<br>Inflammatory markers (TNF- $\alpha$ , IL-6, hsCRP)<br>Troponin                                   |
| Metabolomic/signaling cascades | Apoptosis/caspase signaling<br>Glycolysis<br>Microtubule assembly pathways   |



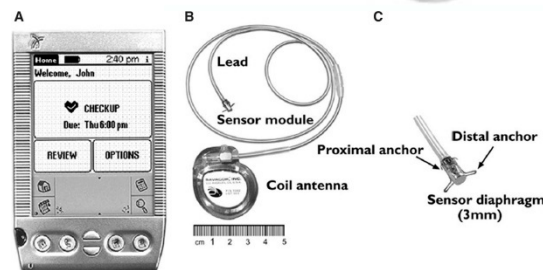
CardioMEMs (PA)



Chronicle (RV)



OptiVol (Intrathoracic Impedance)

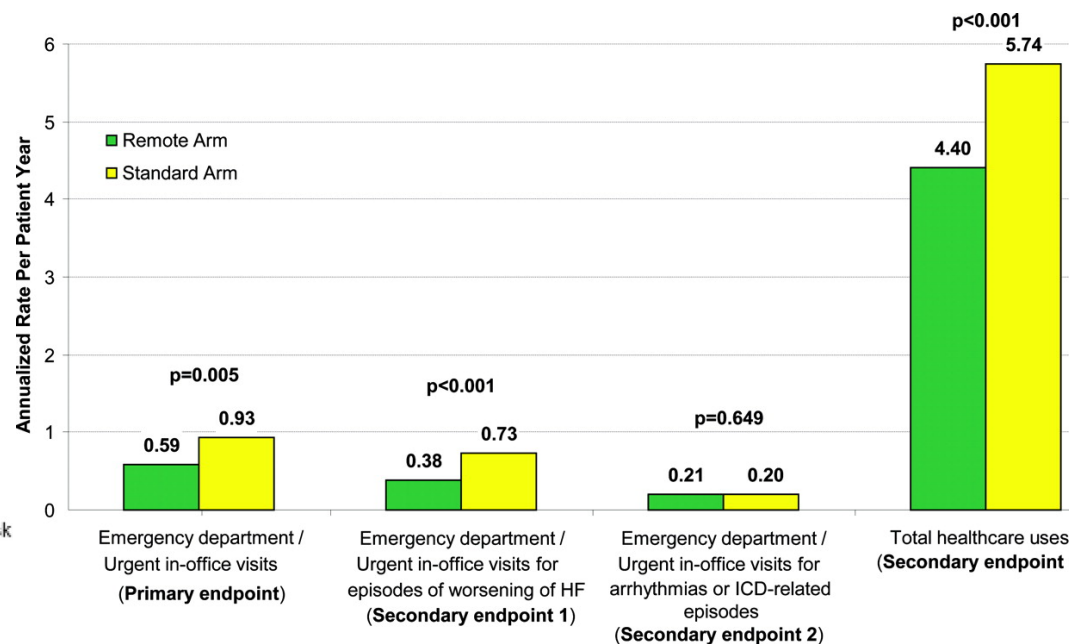
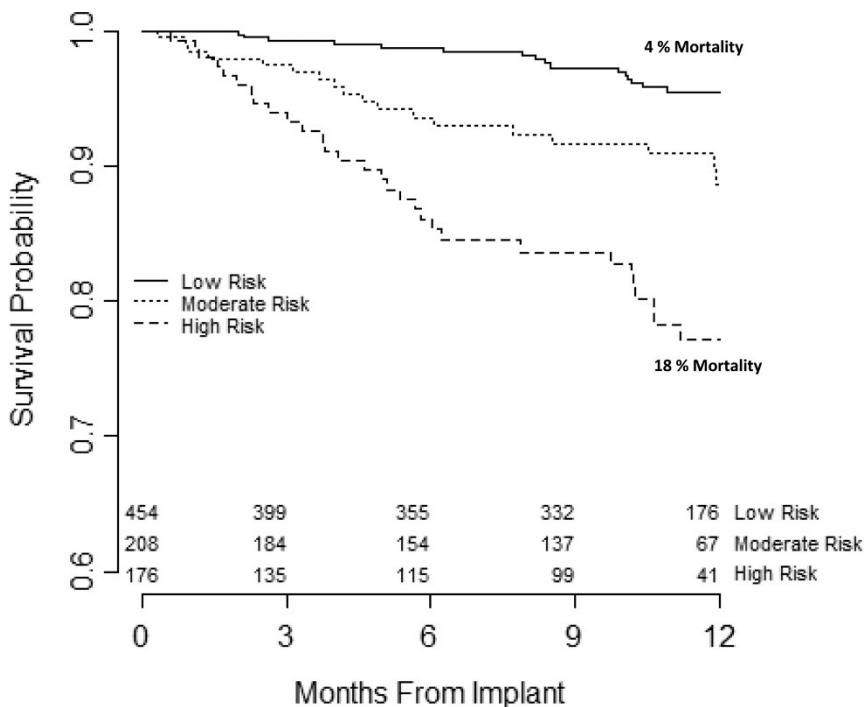


HeartPOD (LA)



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# Technology needs to take the background therapy changes into consideration: Remote monitoring by ICD / CRT-D- standard of care ?



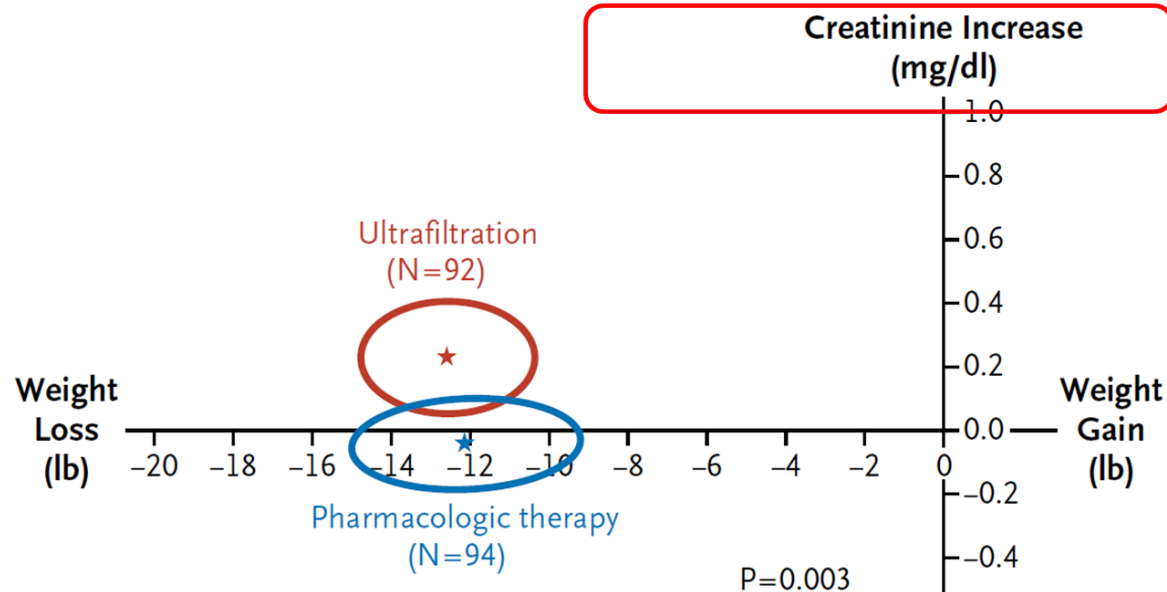
Risk score based on 4 simple sensor-derived parameters (SDANN, HRV footprint, HR, and physical activity) for long-term mortality. From Singh JP, et al . Device diagnostics and long-term clinical outcome in patients receiving cardiac resynchronization therapy. Europace. 2009;11:1647–1653.

Evolve Study. Landolina et al. Circulation. 2012;125:2985-2992



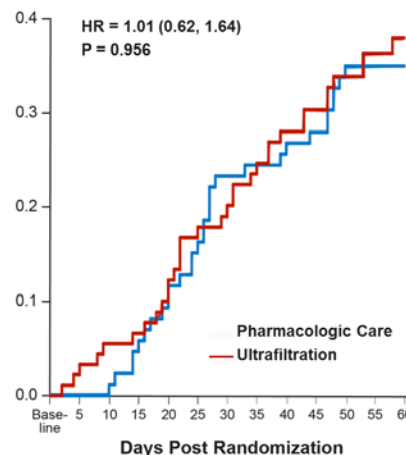
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# Combined End Points for Safety and Efficacy Need to be Unique for Device Type and Target

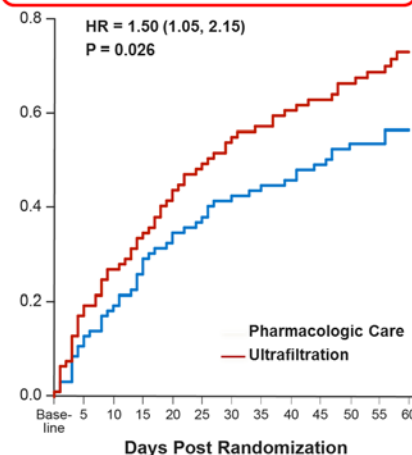


Creainine (mg)

Death or HF Rehospitalization



Death or Serious Adverse Event





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# Outcomes Need to Take the Background Changes in Care into Consideration : HF Hospitalizations as an Outcome

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Impacted by differences in practice patterns : increased use of observation stay / ER and the use of IV medications in heart failure clinics, penalties and incentives or QI

## Hospitalizations of older adults with heart failure as the principal diagnosis

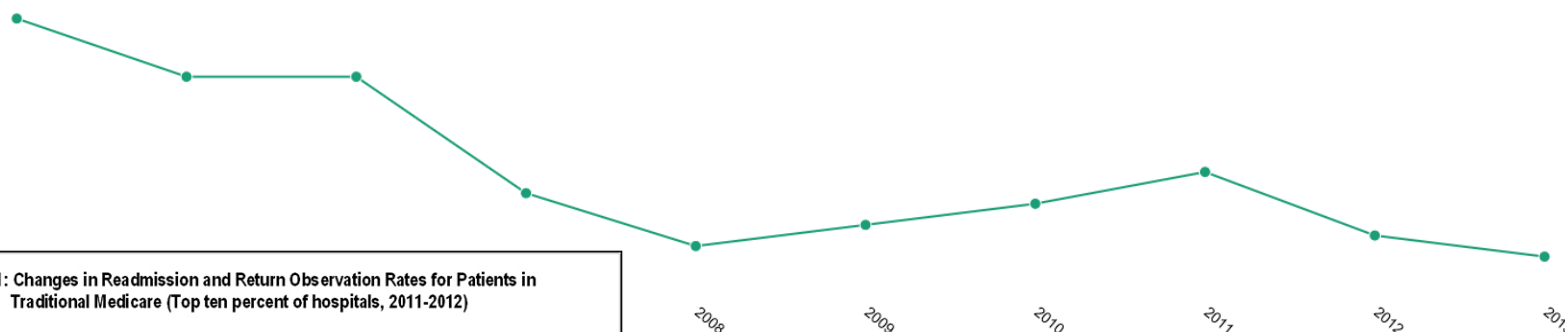
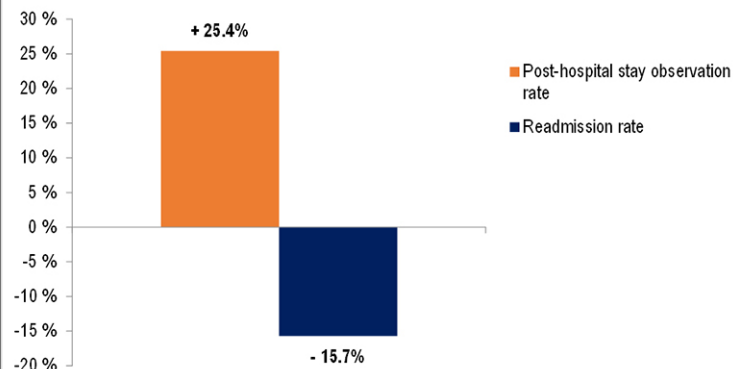


Figure 1: Changes in Readmission and Return Observation Rates for Patients in Traditional Medicare (Top ten percent of hospitals, 2011-2012)



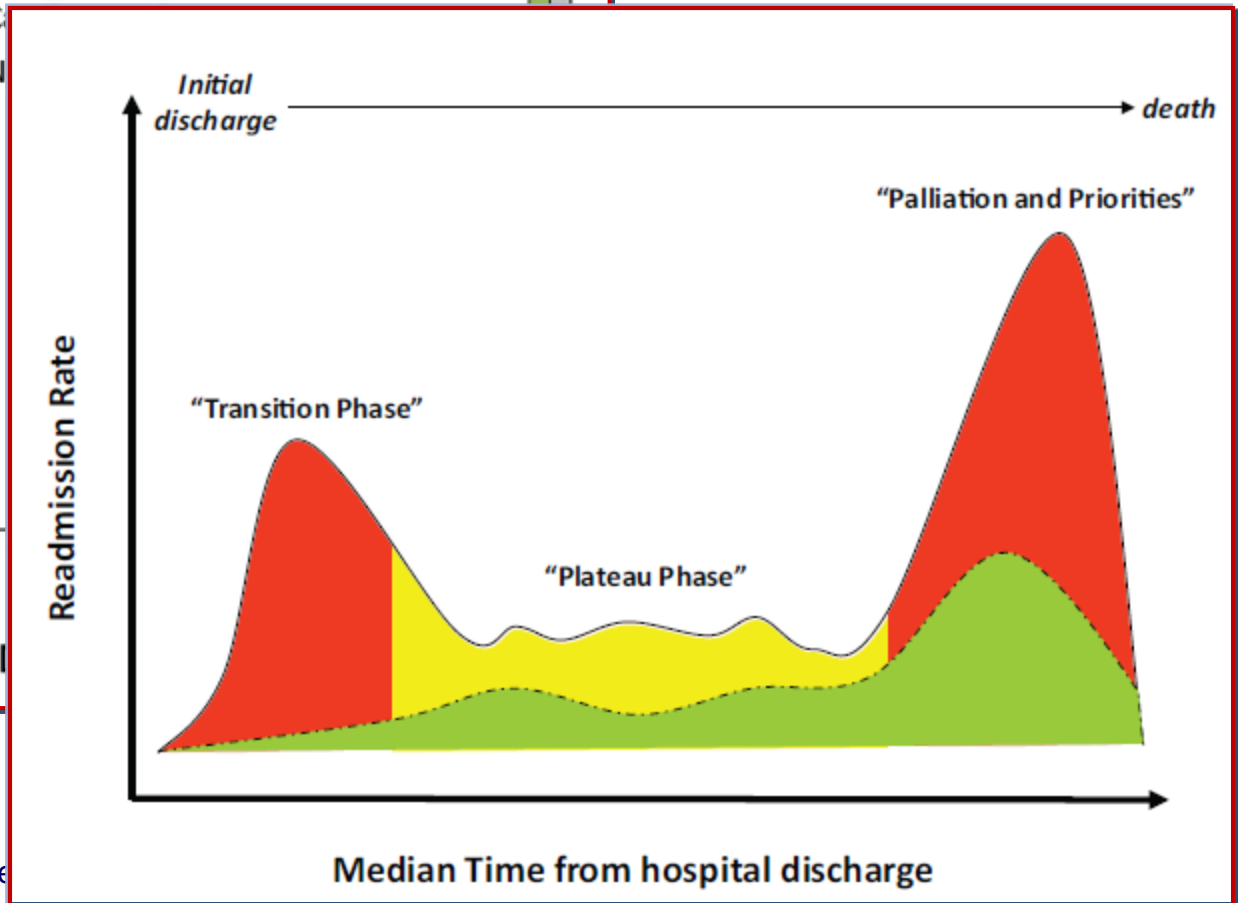
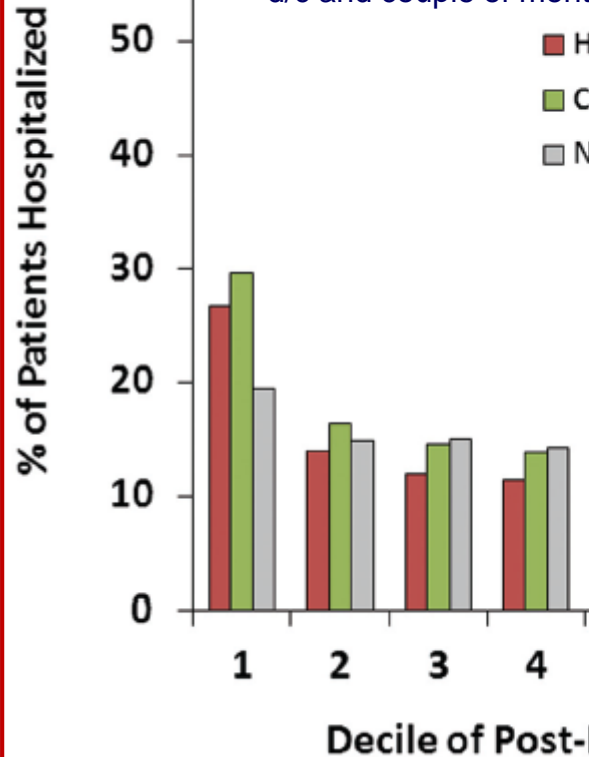
Source: AARP Public Policy Institute Re-analysis of Medicare Data (Medicare & Medicaid Research Review 2014:v4, no.1, p.E1-E13)



Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives. Protecting People.™

# Outcomes Should Differ According to Population Being Targeted: HFH Episodes Differ with Stage

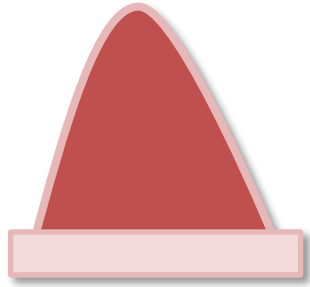
8000 Canadian new onset HF pts,  
readmissions clustering immediately following  
d/c and couple of months before death



Chun et al. Circ Heart Fail. 2012 Jul 1;5(4):414-21. Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure.

Desai and Stevenson. Circulation. 2012 Jul 24;126(4):501-6

# Different Outcomes According to Disease Stages



## ADHF Shock

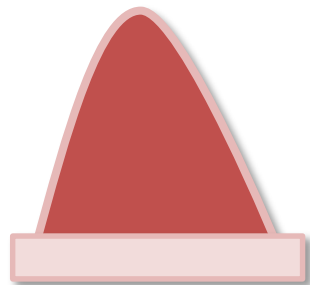
- In-hospital survival rate
- Days alive at 6 mo or 1 year
- Days alive and freedom from requirement for transplant at 6 mo or 1 year



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# Different Outcomes According to Disease Stages

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## ADHF hospitalization episode without shock

- Composite of death or HF hospitalization or urgent care events at 6 months or 1 year
- Event free survival, days alive and out of the hospital

# Different Emphasis According to Presentation Type



## Chronic (Stage B,C) HF

- Composite of death or HF hospitalization or urgent care events
- Days alive and without requirement for hospitalization or urgent care visit
- Concordant improvement in all individual outcomes
- 6 months, 1 year, 3 year or 5 year (depending on effect of technology: example ICD , remote monitoring )



# Different Emphasis According to Presentation Type



## Stage D-

- QOL, Reduction in all cause hospitalizations
- Non-acute care utilization
- Composite of death or HF hospitalization or urgent care events
- Days alive and without requirement for hospitalization or urgent care visit

# Summary

- One end-point would not be appropriate for all HF technology studies, technology needs to fulfill device efficacy, device safety outcomes as well as clinical outcomes
- End-points should differ according to technology target profile, patient presentation and stages of disease
- Composite of death or HF hospitalization & urgent care events may be a better end-point for most chronic HF studies
- Time to event approach may mask later events
- In combined end-points, outcomes should be comparable in direction and magnitude of effect
- In technology: safety as well as efficacy should be considered
- Background changes in care, secular trends in practice need to be taken into consideration