

MEDCAC Meeting - Health Outcomes in Heart Failure (HF) Treatment Technology Studies

AdvaMed

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March 22, 2017

Disclosures

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- Abbott employee (major)

Why are we here?

Discuss scientific rationale for using appropriate endpoints in these studies to complement mortality:

- regulatory approval
- assessment of post-approval effectiveness
- coverage and reimbursement of novel clinical devices in heart failure

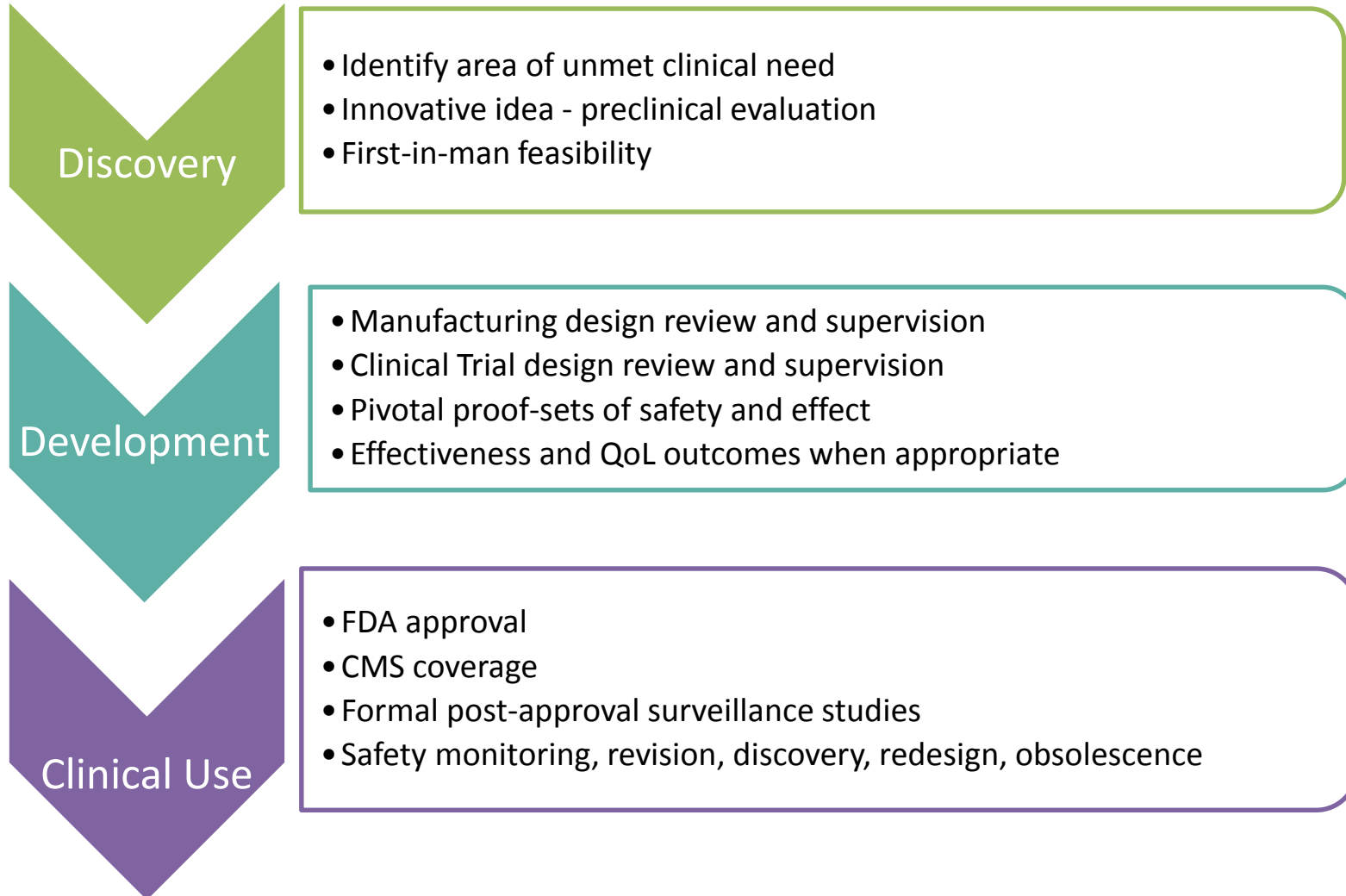
Industry's approach to innovation

- Focus on meaningful patient outcomes and improving patient experience by identifying areas of unmet medical needs
- Produce the highest levels of patient-focused scientific evidence in HF populations
- Improve quality of health care for CMS beneficiaries including reducing hospitalizations in HF patients
 - Support CMS focus on reducing preventable 30-day rehospitalizations in order to improve quality of health care delivery.
 - Applaud the American Heart Association's "Rise Above Heart Failure" campaign to significantly reduce HF hospitalizations by 2020.

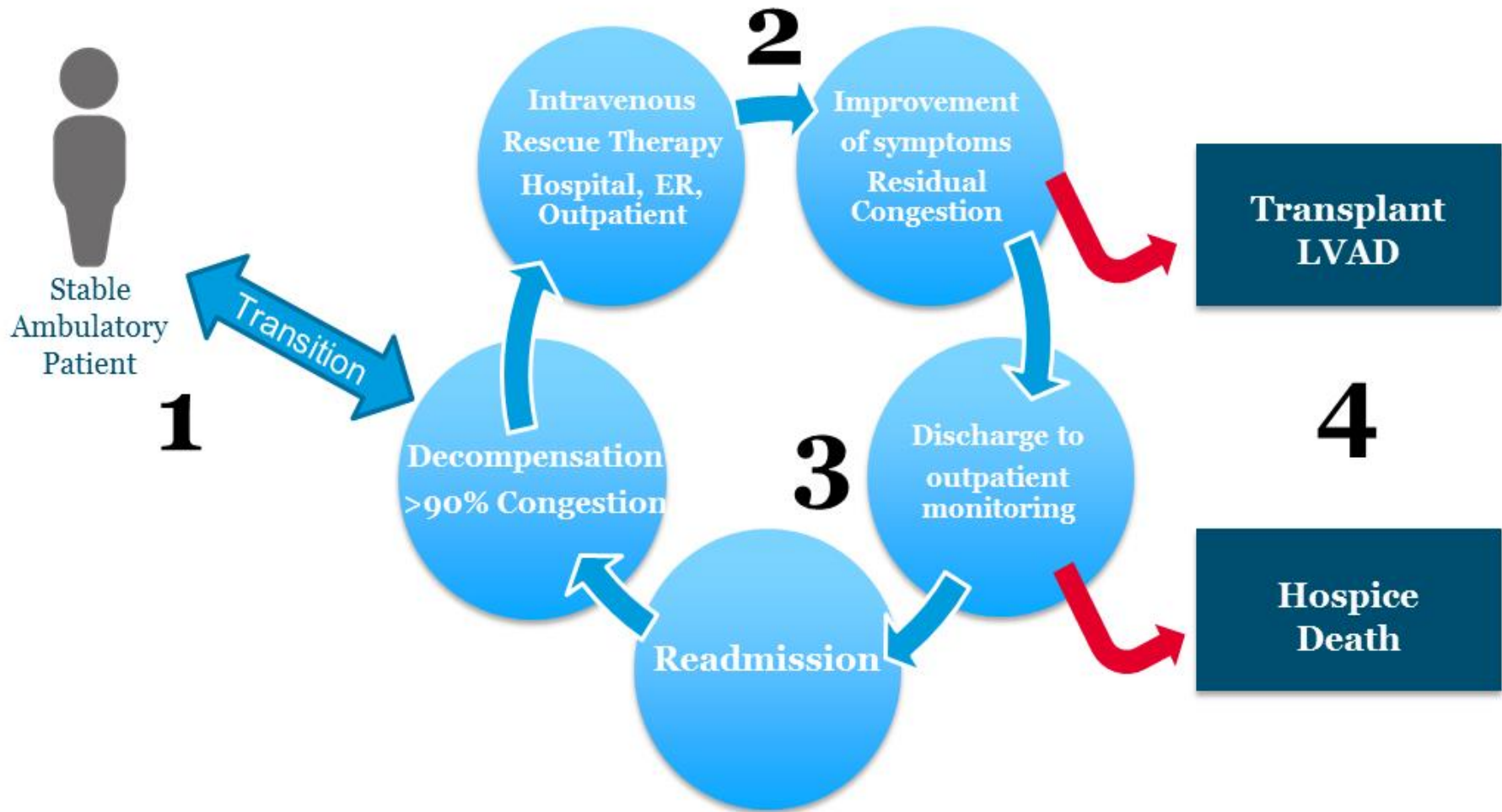
These efforts underscore the importance of reducing HF hospitalizations as a component of primary endpoints in clinical evidence development

Patient-focused product development pathway

Industry's responsibilities for innovative devices



Endpoints specific to the HF journey are dependent on progression of disease and early intervention

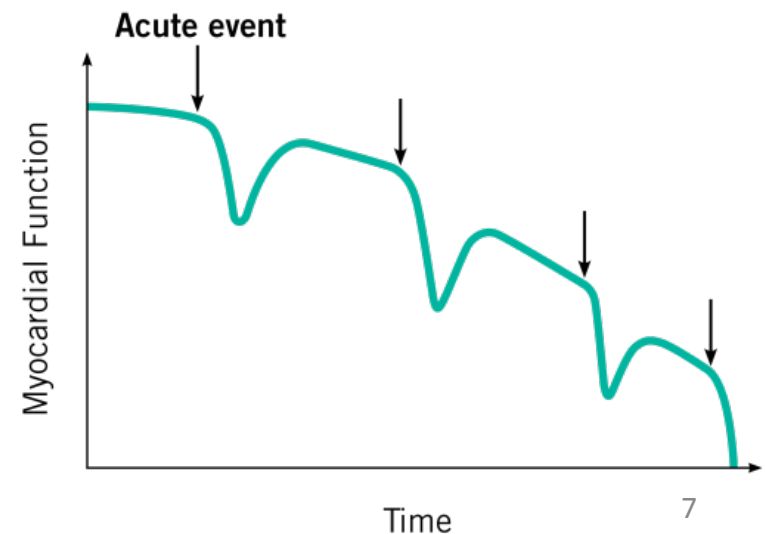


Why is decompensation lethal?

Each event leads to disease progression

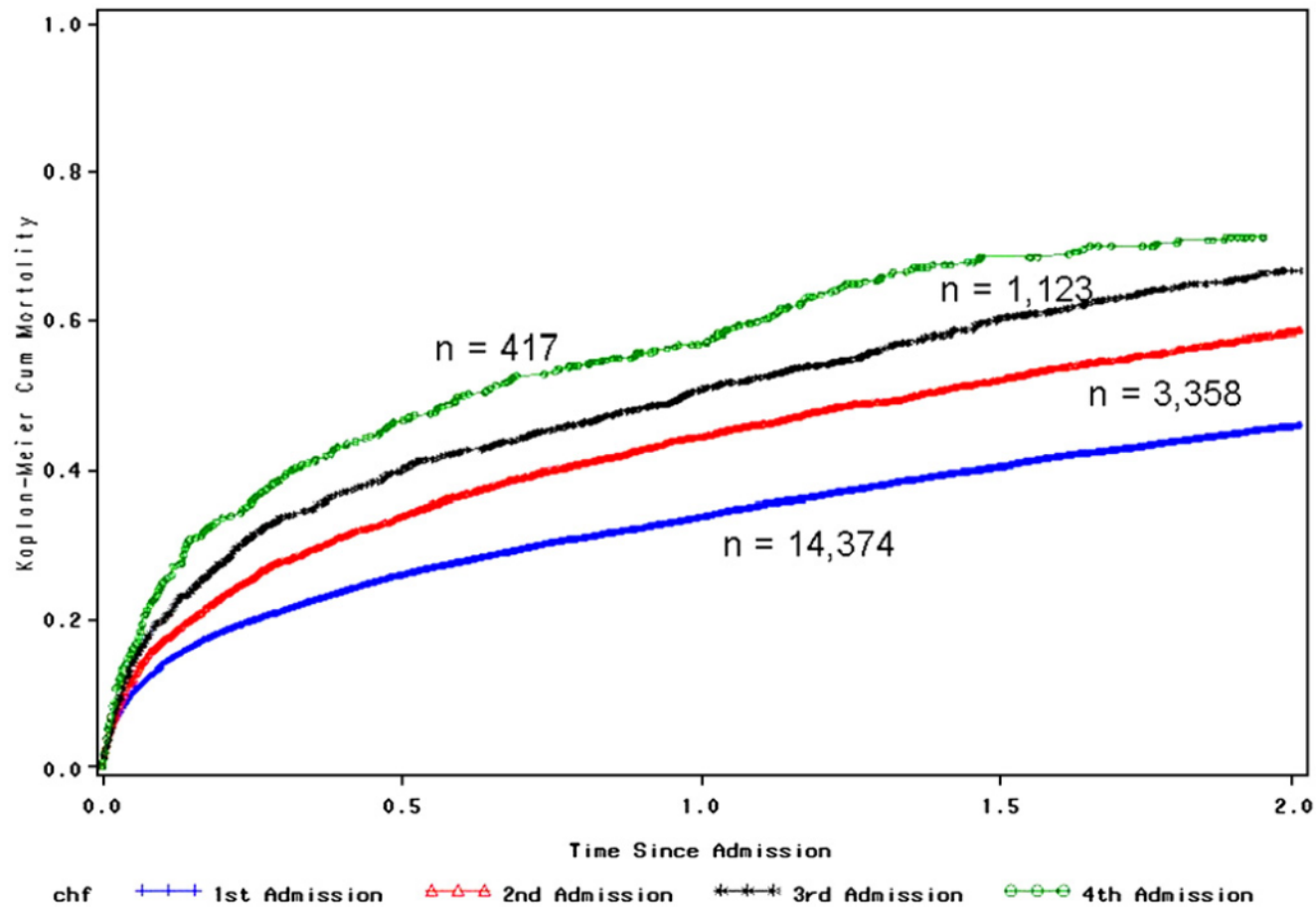
- Worsening of already abnormal stress/strain relationship
- Microinfarction suggested by elevated troponin levels
- Adverse neurohormonal activation – inflammatory reaction
- Worsening functional mitral regurgitation
- Progression of adverse myocardial and vascular remodeling leading to chronically elevated filling pressures
- Progression of renal dysfunction
- Reduction in systemic perfusion

HF hospitalizations is a valid endpoint for measuring decompensation



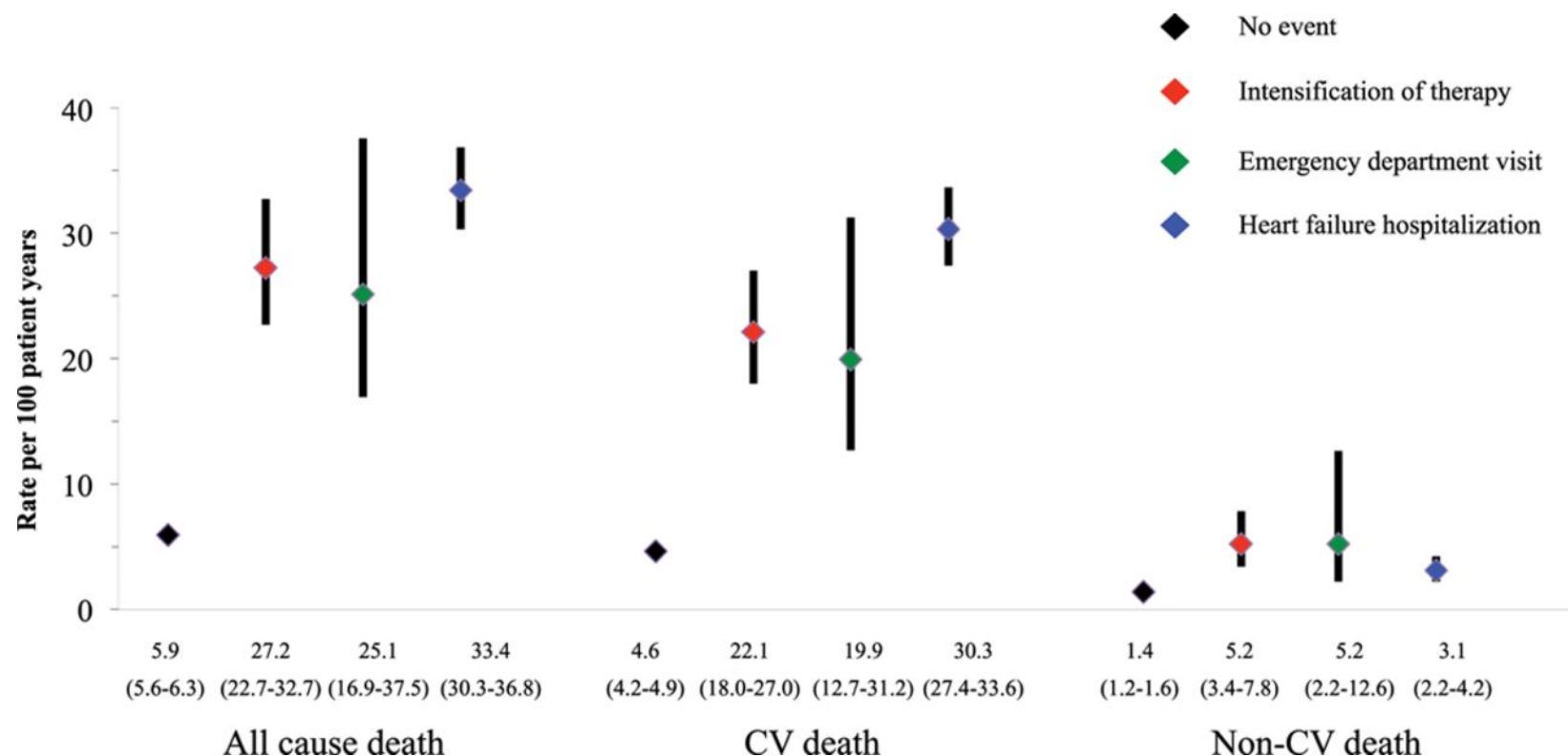
Long-term mortality risk increases with multiple hospitalizations

Preventing HF hospitalizations improves survivability



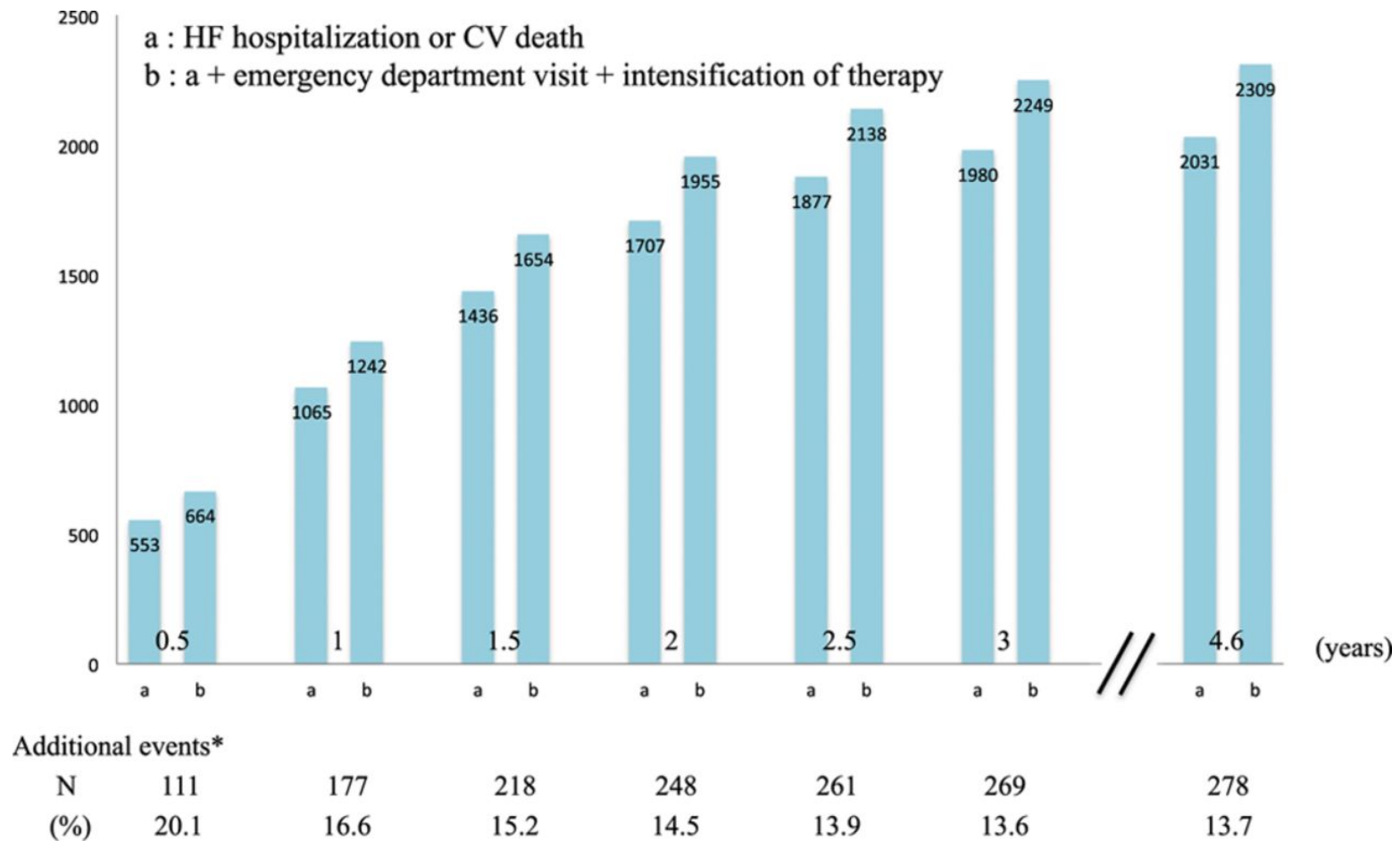
Kaplan-Meier cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.

Decompensation events requiring more intensive therapy are associated with higher mortality risk



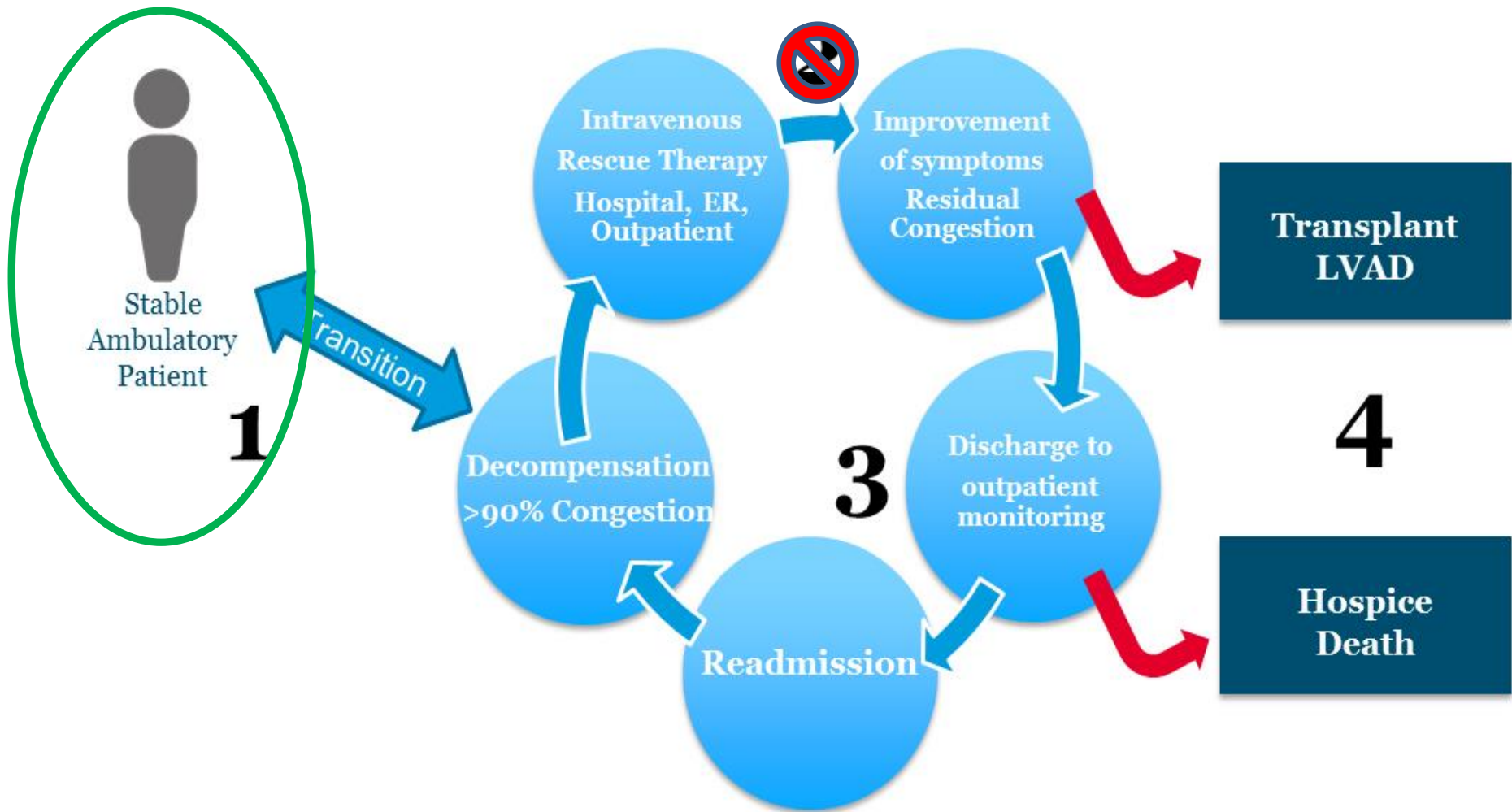
Naoki Okumura et al. *Circulation*. 2016;133:2254-2262

Evolving utilization of non-hospitalization based rescue therapies



* Expanded composite compared with primary composite

Focus shifts to proactively preventing decompensation and maintaining stability



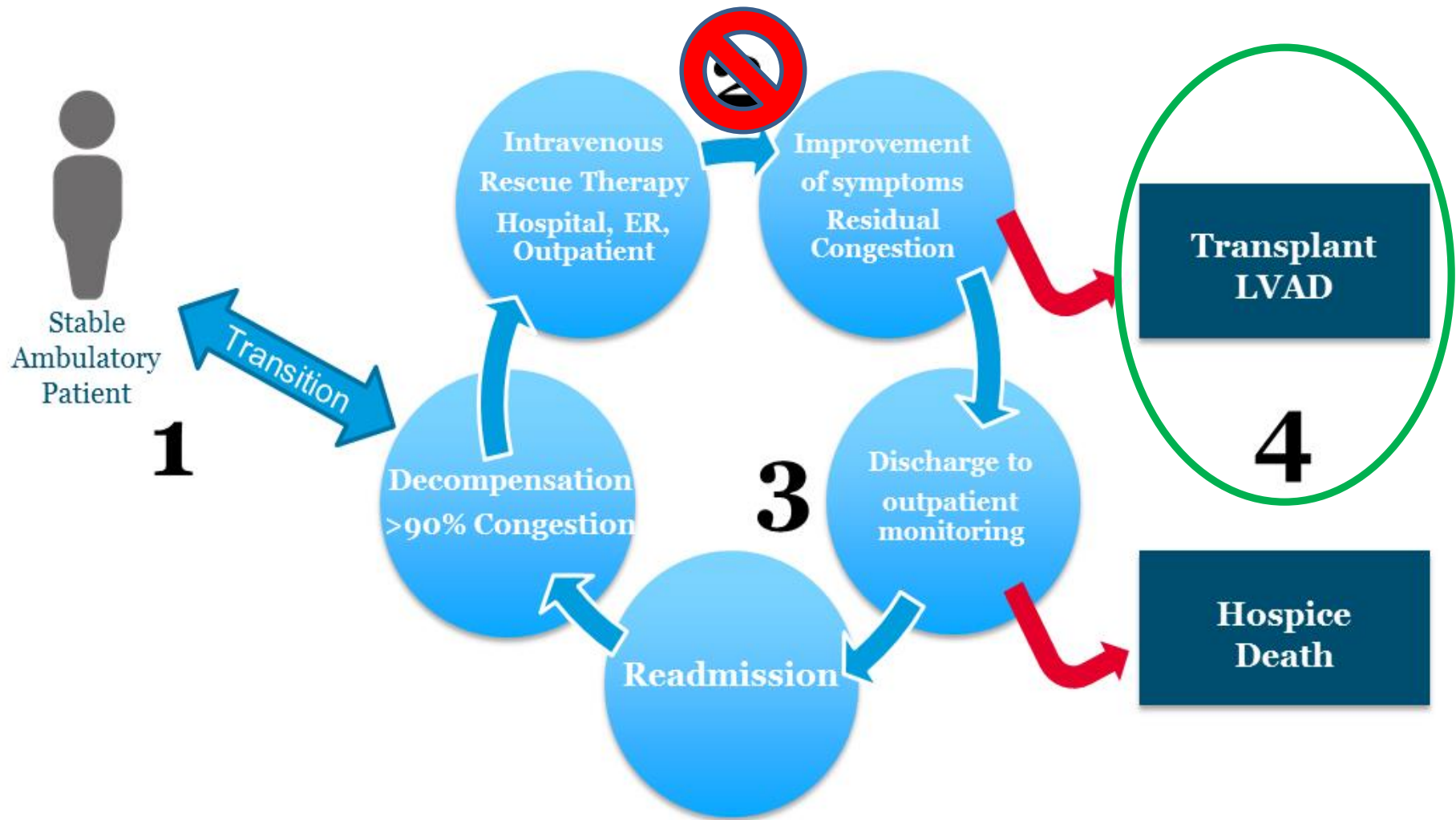
Maintaining stability and preventing decompensation

What are the expected outcomes of novel interventions?

- Remaining well and staying home is a highly desired patient outcome
- As such, prevention strategies should reduce decompensation.
- Successful reduction of adjudicated HF hospitalizations and possibly including reduction in ER visits and/or urgent outpatient rescue therapy events is appropriate
- Mortality should be monitored to ensure safety and may be included as an endpoint
- Reduction in decompensation events directly relates to improved survival

HF hospitalizations are robust and appropriate endpoints for clinical trials that capture clinically important life events for patients

Mortality is important, but it does not ensure patients are doing functionally well



Treating “advanced” refractory patients

What are the expected outcomes of novel interventions?

- Immediate need to prevent death
- After advanced therapy (LVAD or Transplant), decompensation risks dramatically decline
- Quality of life and functional capacity are important outcome measures
- Outcomes and endpoint should focus on prevention of long-term complications

QoL measures for HF research are valid tools

Appropriateness of measures vary by disease state and novel technology

- KCCQ scores and MLWHFQ are the most widely studied and validated measures of quality of life in chronic heart failure (16)
- Improvements in KCCQ and MLWHF are independent predictors of favorable outcomes (17, 18)
- Patient experience is increasingly recognized as one of the three pillars of quality healthcare alongside clinical effectiveness and patient safety
- Length of follow-up is important when generalizing QoL effectiveness

QoL measures are meaningful endpoints for HF clinical trials

Functional assessments provide additional insights to patient experience

- 6MWT is a simple test that can be conducted easily and is a good physiological measure of functional capacity and exercise intolerance
- 6MWT is a prognostic marker of subsequent cardiac death in patients with mild to moderate HF (20)
- VO2max is an objective measure of exercise capacity. Despite inherent challenge, when performed properly with appropriate oversight by a core lab, it is a valid endpoint for HF clinical trials
- VO2max is a prognostic marker of subsequent mortality in HF patients (HF Action)

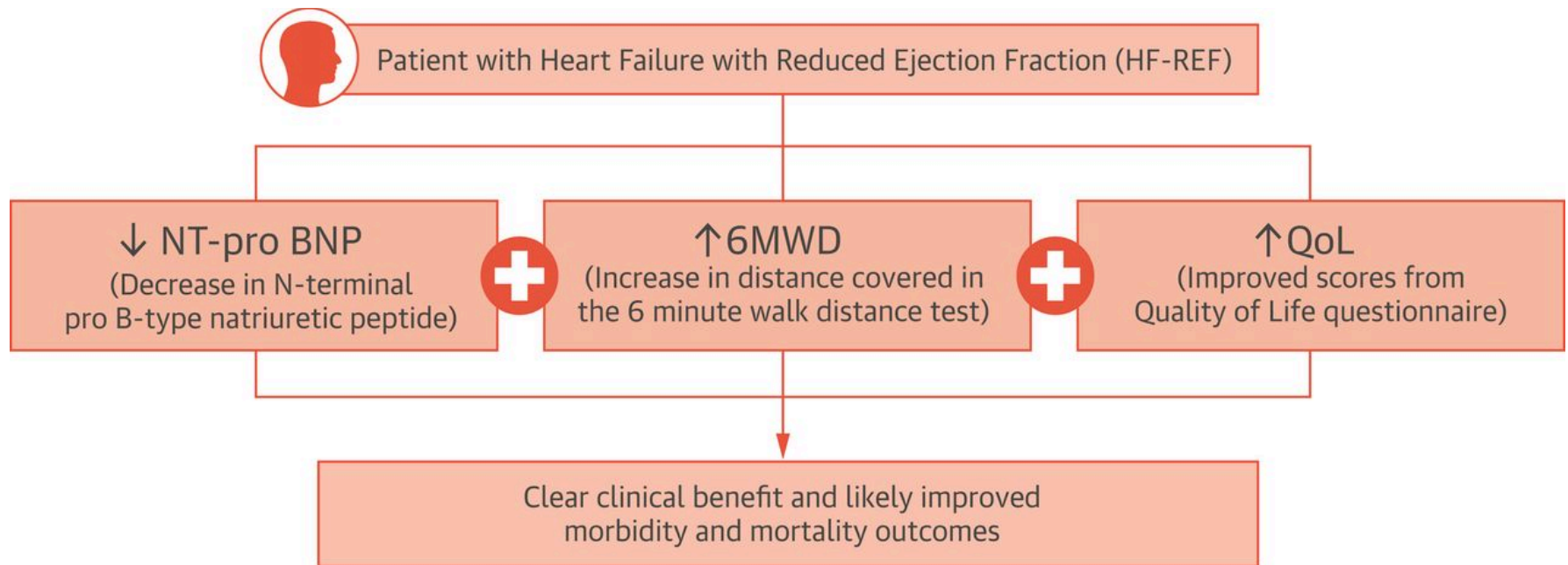
Although there are inherent limitations (e.g., comorbidities) with these tests, when performed properly, functional assessments should be considered as valid endpoints

Surrogate and intermediate endpoints can be considered as valid endpoints

- Reduction in mitral regurgitation
 - Particularly important for therapies treating functional MR
- Reversal of adverse ventricular remodeling
 - Correlates directly with improved survival
- Ejection Fraction
 - Improvement has prognostic significance
- Biomarkers (e.g. BNP, NT-pro BNP, ST2)
 - Prognostic value is clear and changes over time correlate with clinical outcomes
- FDA Expedited Access for Premarket Approval Program for severe diseases (i.e. heart failure) recognizes the importance of surrogates that predict future survival benefit

Surrogate endpoints are valid when utilized as a hierarchical composite endpoint for expedited regulatory review

Proposed use of intermediate and surrogate endpoints in clinical trials for patients with HF-REF



Other Data Considerations:

Real-world data (RWD) complement clinical trials and continues opportunities for coverage with evidence development

- Generalize and corroborate findings from RCTs
- Cultivated cohorts from databases may provide appropriate comparator groups
- Provides long-term follow-up for clinical effectiveness
- Refine clinical decision support efforts



Disease-state specific outcomes are scientifically sound to evaluate novel devices

- **Rate of heart failure hospitalizations along with readmissions, ER visits or outpatient stays that include IV rescue therapies**
 - Capture clinically important life events for patients and are scientifically valid endpoints to support approval and coverage
- **QoL measures for HF research**
 - Important measures of patient experience complementing primary endpoints
 - Length of follow-up for QoL measurements is important and should include innovative trial design
- **Functional assessments and surrogate endpoints**
 - May serve as a composite of primary outcomes and provide mechanistic information to support outcomes
 - May serve as appropriate composite endpoints for expedited FDA reviews
- **Additional Considerations**
 - Alignment on endpoints between FDA and CMS is critical to continued innovation
 - Post-approval innovation assessments should embrace linkage of real-world databases to confirm generalizability and proof of effectiveness

Thank you!

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