POPULATION PRECISION MEDICINE AND SECONDARY PREVENTION OF HEART FAILURE

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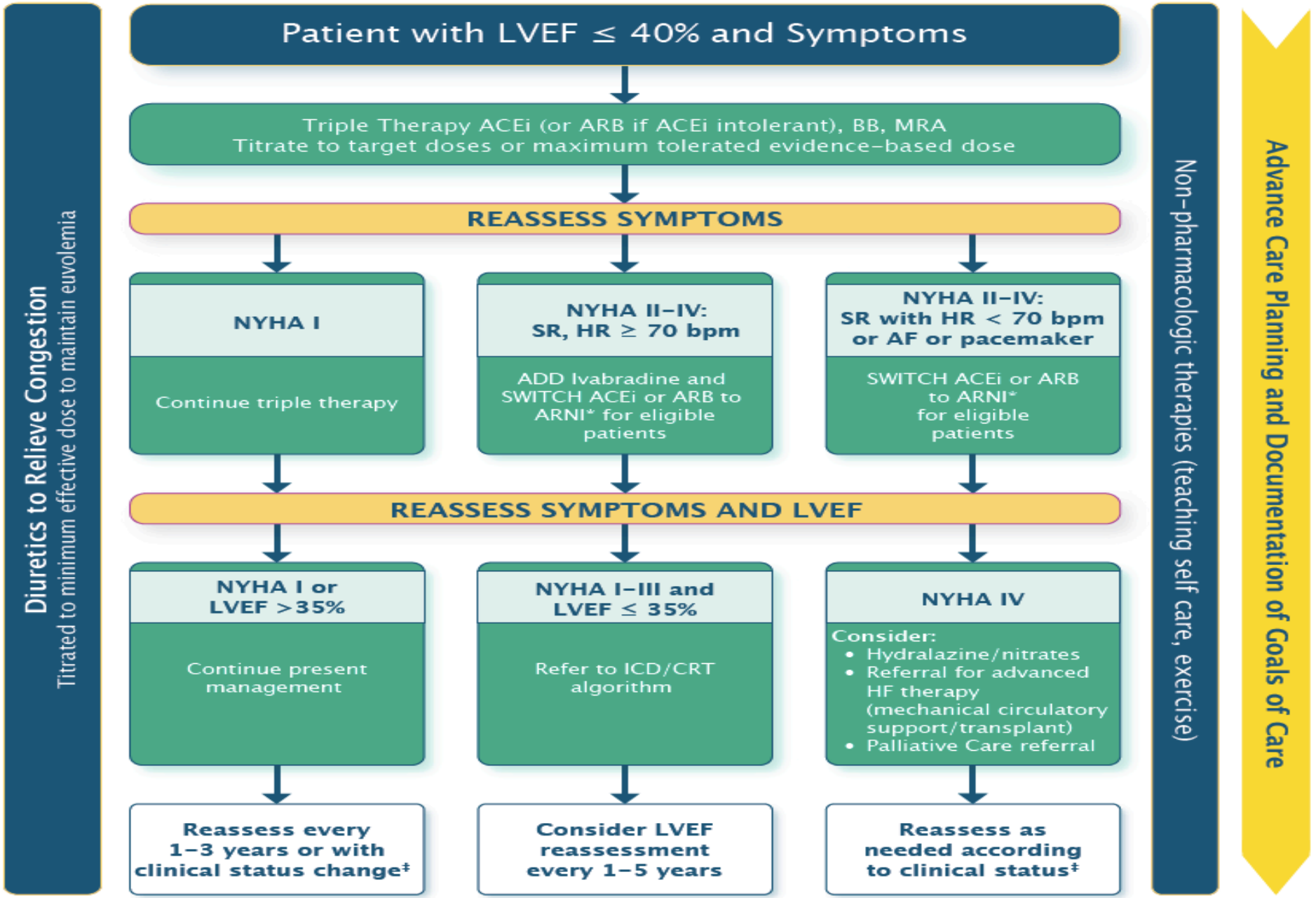
- I will NOT discuss off-label use.

Can we resolve …

- **Precision medicine**
  - Tailoring a treatment strategy based on patient specific factors
- **Population health**
  - The health outcomes of a group of individuals, including the distribution of such outcomes within the group


Diuretics to Relieve Congestion
Titrated to minimum effective dose to maintain euvolemia
Patient with LVEF ≤ 40% and Symptoms
Triple Therapy ACEi (or ARB if ACEi intolerant), BB, MRA
Titrate to target doses or maximum tolerated evidence-based dose
REASSESS SYMPTOMS
NYHA I
Continue triple therapy
NYHA II–IV:
SR, HR ≥ 70 bpm
ADD Ivabradine and SWITCH ACEi or ARB to ARNI* for eligible patients
NYHA II–IV:
SR with HR < 70 bpm or AF or pacemaker
SWITCH ACEi or ARB to ARNI* for eligible patients
REASSESS SYMPTOMS AND LVEF
NYHA I or
LVEF >35%
Continue present management
NYHA I–III and
LVEF ≤ 35%
Refer to ICD/CRT algorithm
NYHA IV
Consider:
• Hydralazine/nitrates
• Referral for advanced HF therapy (mechanical circulatory support/transplant)
• Palliative Care referral
Reassess every 1–3 years or with clinical status change‡
Consider LVEF reassessment every 1–5 years
Reassess as needed according to clinical status‡
Non-pharmacologic therapies (teaching self care, exercise)
Advance Care Planning and Documentation of Goals of Care

Tailoring treatment for mortality benefit

A few examples

Prognostic Factors	Clinical Factors
Risk Scores	Heart Rate
Hospitalization	Blood Pressure
Natriuretic Peptides	Etiology
Co-morbidity	QRS Duration
	Renal Function and K+
	Anemia

McDonald M et al. Can J Cardiol 33(11):1434-1449

Case: Patient Johan Hulette

- 50ish year old male with ischemic cardiomyopathy, LVEF 28%
  - Status post-surgical and percutaneous revascularization
  - Complex co-morbidities including CKD
  - Persistent NYHA III symptoms with marked fatigue and postural lightheadedness
- Recent hospitalization for AHF with volume overload
  - Diuretics adjusted but the admitting team did not think there was anything additional to add/change to his baseline treatment to improve “hard outcomes”
  - Clinically euvolemic at discharge with BNP of 2100
- HF therapies
  - bisoprolol 2.5 mg po od, ramipril 2.5 mg po od, spironolactone 12.5 and furosemide 80 mg po od
  - ICD for primary prevention
- Notable patient characteristics
  - HR 75 in NSR
  - BP 90/50 with no postural drop
  - eGFR 40
  - K+ 5.4
  - QRS duration of 115ms

Q1 – Precision Medicine

- What can you do to further customize his therapies?

A. Nothing – he's on optimally tolerated medical therapy (OTMT)

B. I would "push" his RAASi and beta-blockers to target doses and cautiously monitor his blood pressure, renal function and K+

C. I would increase his diuretic given the BNP was 2100

D. I would add ivabradine

CCS HF Guideline Recommendations

- **Recommendation 27:** We recommend preferentially using the specific drugs at target doses that have been proven to be beneficial in clinical trials as optimal medical therapy. If these doses cannot be achieved, the maximally tolerated dose is acceptable [Table 11] (Strong Recommendation, High Quality Evidence).

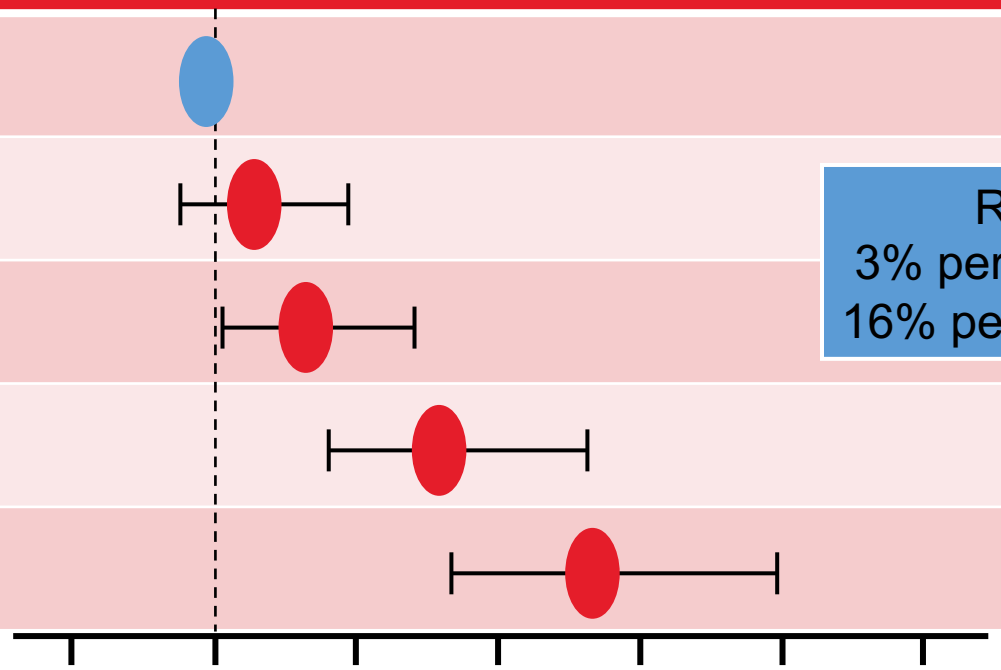
- **Practical Tip:** If a drug with proven mortality or morbidity benefits does not appear to be tolerated by the patient (eg, low blood pressure, low heart rate or renal dysfunction), other concomitant drugs, including diuretics, with less proven benefit should be carefully re-evaluated to determine whether their dose can be reduced or the drug discontinued.

Ezekowitz et al. Can J Cardiol 33(11):1342-1433

The higher the HR …

the higher the risk of CV mortality and HF hospitalization

HR at baseline (bpm)	HR
70 - < 72	1.00
72 - < 75	1.15
75 - < 80	1.33
80 - < 87	1.80
≥ 87	2.34



Böhm et al. *Lancet* 2010; 376: 886-94

Early impact of HR at discharge:
High discharge HR is associated with worse outcomes

	Heart rate at discharge (bpm)				
	40-60	61-70	71-80	81-90	>90
Patients (%)	14.6%	23.9%	28.9%	18.7%	13.9%
Hazard ratio for 30-day mortality	1.06	Referent	1.21	1.70	1.88
p-value	0.720	Referent	0.185	<0.001	<0.001

Habal et al. Circ Heart Fail. 2014 Jan 1;7(1):12-20

SHIFT Trial

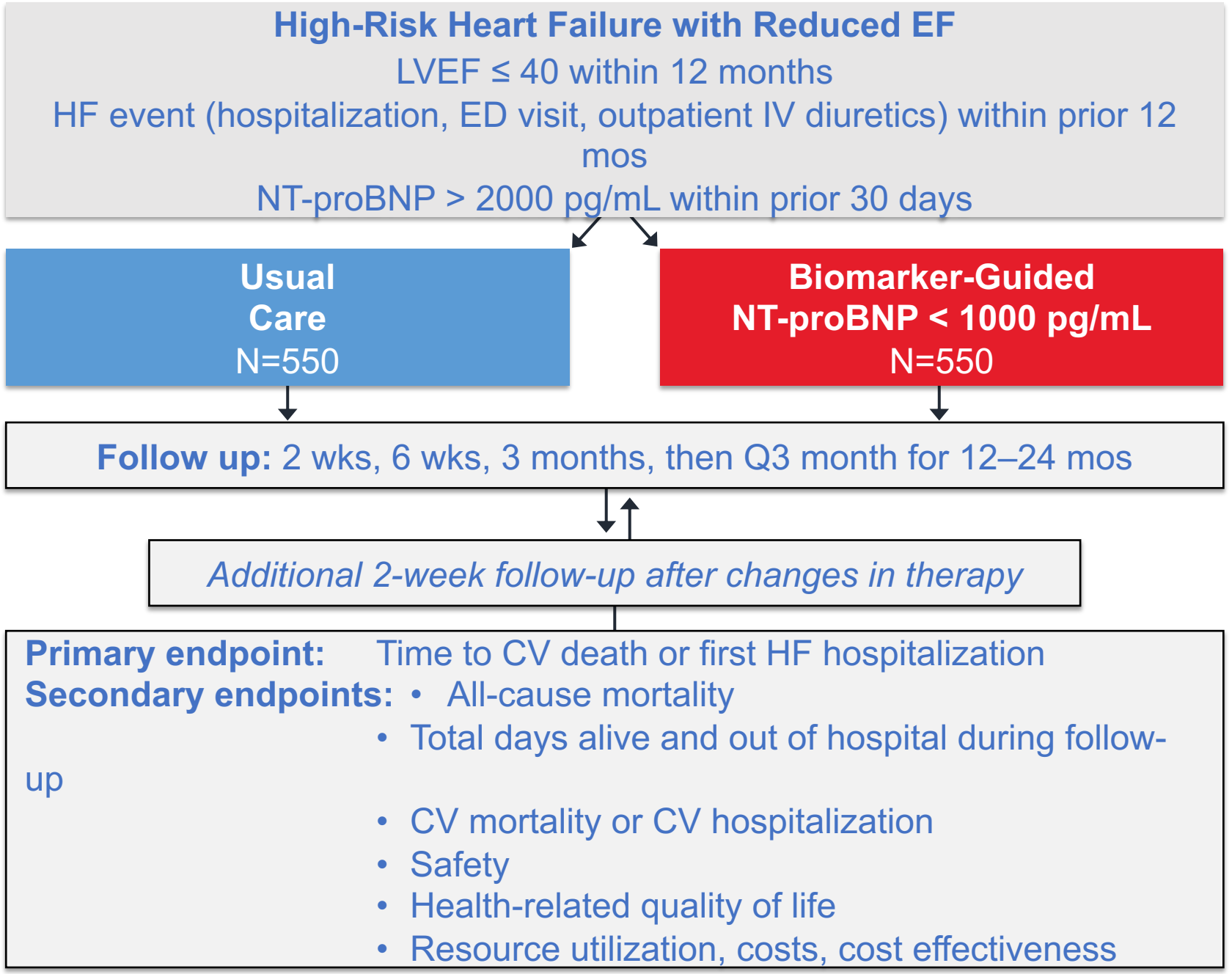
Prespecified Endpoints	Heart rate at trial entry	
	≥ 70 bpm	≥ 77 bpm
Primary endpoint		
CV death or hospital admission for worsening HF	18% (p<0.0001)	25% (p<0.0001)
Mortality endpoints		
All-cause mortality	-	19% (p=0.0074)
Cardiovascular mortality	-	19% (p=0.0137)
Death from HF	26% (p=0.014)	39% (p=0.0017)
Other endpoints		
All-cause hospital admission	11% (p=0.003)	18% (p=0.0002)
Any CV hospital admission	15% (p=0.0002)	21% (p<0.0001)
Hospital admission for worsening of HF	26% (p<0.0001)	31% (p<0.0001)

Swedberg et al. *Lancet* 2010; 376: 875-85

Meta-regression:
Evaluating the effect of individual covariates on mortality in beta-blocker trials

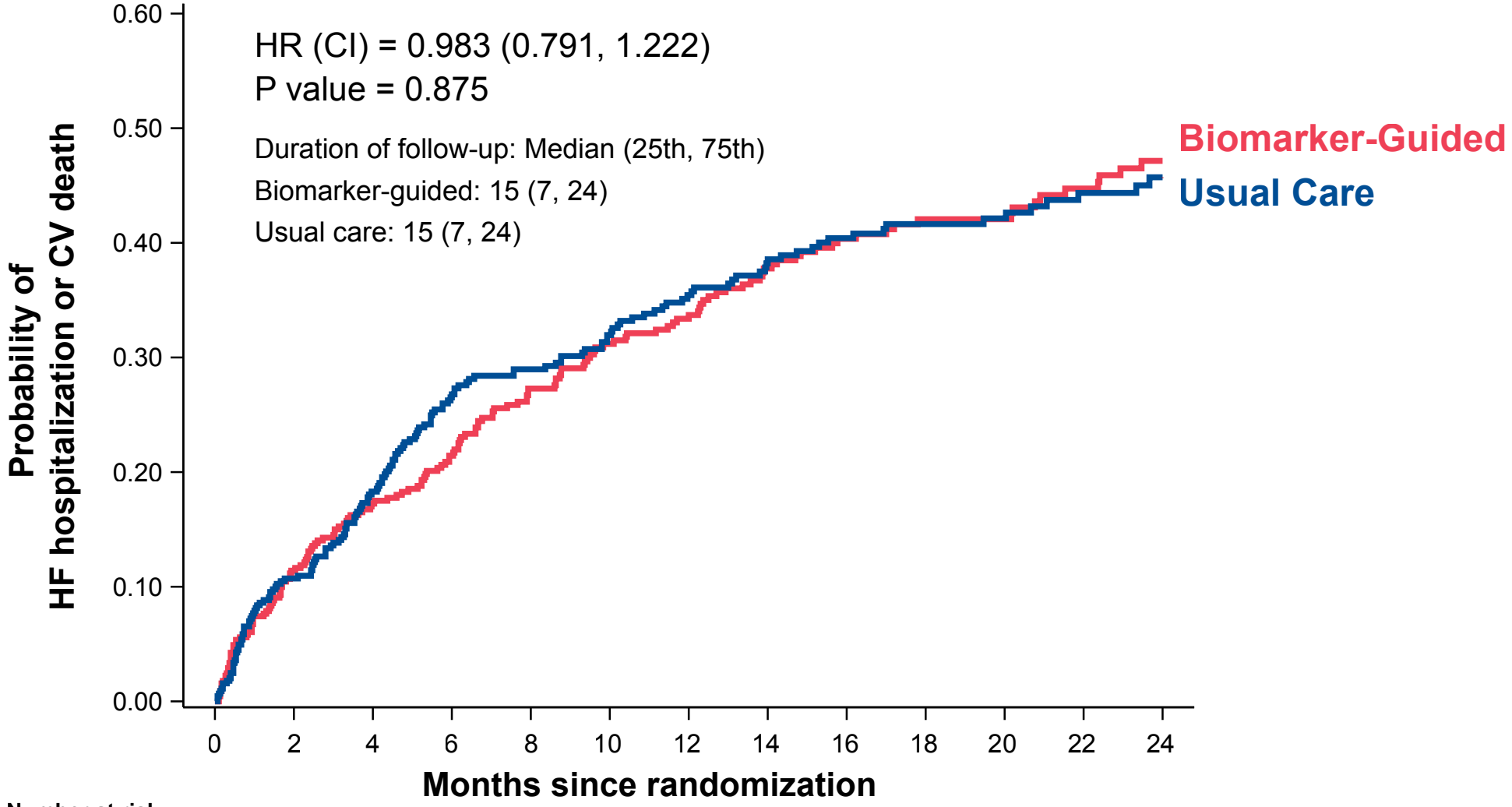
Potential Modifier	Trials, n	Patients, n	Ratio of Relative Risks (95% CI)	p Value
Baseline heart rate	19	17 981	1.07 (0.88-1.32) per 5 beats/min	0.47
Heart rate reduction*	17	17 831	0.82 (0.71-0.94) per 5 beats/min	0.006
β-blocker dose	17	17 660	1.02 (0.93-1.10) per increment	0.69
Mean baseline SBP	17	17 516	1.00 (0.73-1.35) per 20 mmHg	0.99
Mean SBP reduction	10	5 462	1.02 (0.87-1.20) per 2 mmHg	0.78
Agent	21	18 773	---	---
Carvedilol	---	---	Reference	---
Bisoprolol	---	---	1.05 (0.82-1.35)	0.68
Metoprolol	---	---	1.03 (0.77-1.38)	0.85
Atenolol	---	---	0.89 (0.29-2.76)	0.83
Bucindolol	---	---	1.36 (1.09-1.69)	0.009
Nebivolol	---	---	1.30 (0.99-1.71)	0.056

adapted from McAlister et al. *Ann Intern Med* 2009; 150 (11): 784-94


High-Risk Heart Failure with Reduced EF
LVEF ≤ 40 within 12 months
HF event (hospitalization, ED visit, outpatient IV diuretics) within prior 12 mos
NT-proBNP > 2000 pg/mL within prior 30 days
Usual Care
N=550
Biomarker-Guided
NT-proBNP < 1000 pg/mL
N=550
Follow up: 2 wks, 6 wks, 3 months, then Q3 month for 12–24 mos
Additional 2-week follow-up after changes in therapy
Primary endpoint: Time to CV death or first HF hospitalization
Secondary endpoints:
• All-cause mortality
• Total days alive and out of hospital during follow-up
• CV mortality or CV hospitalization
• Safety
• Health-related quality of life
• Resource utilization, costs, cost effectiveness
Screening
Randomization
Follow-up
Endpoints

GUIDE-IT: Primary Endpoint

Time to CV death or HF Hospitalization



Number at risk

Biomarker-guided	446	405	376	355	331	315	293	272	254	242	225	218	202	185	175	166	152	135	128	128	128	100	93	85	78
Usual care	448	401	381	359	330	301	278	263	257	243	227	210	199	185	175	169	153	138	138	138	115	104	90	90	77

Case: Patient Johan Hulete– Part II

- You initiate ivabradine at the first post-discharge visit
  - Before you can up-titrate the dose or follow-up with the patient, he re-presents to hospital with AHF
  - Apparently, he was unable to afford his medications
- In hospital, he is diuresed and discharged home
  - There are no changes to his HF therapies
- After his second admission, he is referred to the HF Clinic at discharge
  - Follow-up appointment within 2 weeks per CCS Companion Recommendations
- Discharge Summary
  - “Hopefully the HF Clinic can help ensure a seamless transition to the community … and the patient would benefit from the multidisciplinary team approach”

Q2 – Population Health

- What provider type(s) are essential for a multidisciplinary HF clinic (assuming they are working within their *scope of practice*)? i.e. what is the gold standard?

A. Nurse
B. Physician and nurse
C. Physician, nurse and nurse practitioner
D. Physician, nurse, nurse practitioner and pharmacist
E. Physician, nurse, nurse practitioner, pharmacist and dietician
F. Depends on the size of the community and available services

CCS HF Guideline Recommendations

- **Recommendation 175:** We recommend that specialized outpatient HF clinics or disease management programs provide access to an interprofessional team ideally including a physician, a nurse, and a pharmacist with experience and expertise in HF (Strong Recommendation, High Quality Evidence).

- **Recommendation 176:** We recommend that all patients with recurrent HF hospitalizations, irrespective of age, multimorbidity, or frailty, should be referred to a HF disease management program (Strong Recommendation, High Quality Evidence).

Ezekowitz et al. Can J Cardiol 33(11):1342-1433

Supporting the Patient Journey:
Defining the Optimal Model for HF Care in Canada

- Define each level of HF care by provider type and the core competencies associated with each role (i.e. level of training, scope of practice).
- Describe the key services and resources (human and structural) that must be in place at each level of care as well as the tools necessary to support optimal patient care at each stage (e.g. care plans/protocols, educational resources, quality assurance strategies)
- Describe how and what should travel with patients between levels (hubs) of care to provide seamless transitional care and to optimize the patient and provider experience of care.

Precision Public Health:
Precision medicine and population health

- Precision public health is providing the right intervention to the right population at the right time
  - More accurate methods for measuring disease severity allows for development of precision and targeted policies for programs that are tailored to each population's unique characteristics
    - Dr. Milan Khoury (Director, Office of Public Health Genomics at the CDC)

- Population and public health policy is based on process improvement that direct resources to those at highest risk
  - Precision medicine approaches help us identify those at high risk, while clinical trials help us to understand whether we can modify their outcomes