

UPDATE ON CONGESTIVE HEART FAILURE

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NBIMU

Disclosures

- Relationships with commercial interests:
 - Grants/Research Support: Bayer, Sanofi, Merck, Pfizer
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 - Consulting Fees: Bayer, Novartis
 - Other: N/A

Learning Objectives

- At the end of this presentation, participants will be able to:
 - Appreciate challenges in heart failure management
 - Apply current therapies used in treatment of heart failure

Mr “Short of Breath”

- 54 year old male
- Increased SOB over 2 months with increasing peripheral edema
- DM2, HTN, previous smoking
- Medications:
 - Rosuvastatin 20 mg daily, Metformin 500 mg bid daily, Perindopril 4 mg daily
- BP 140/90, HR 76 – elevated JVP 8 cm, S3
- Functional class 3 workload

Mr “Short of Breath”

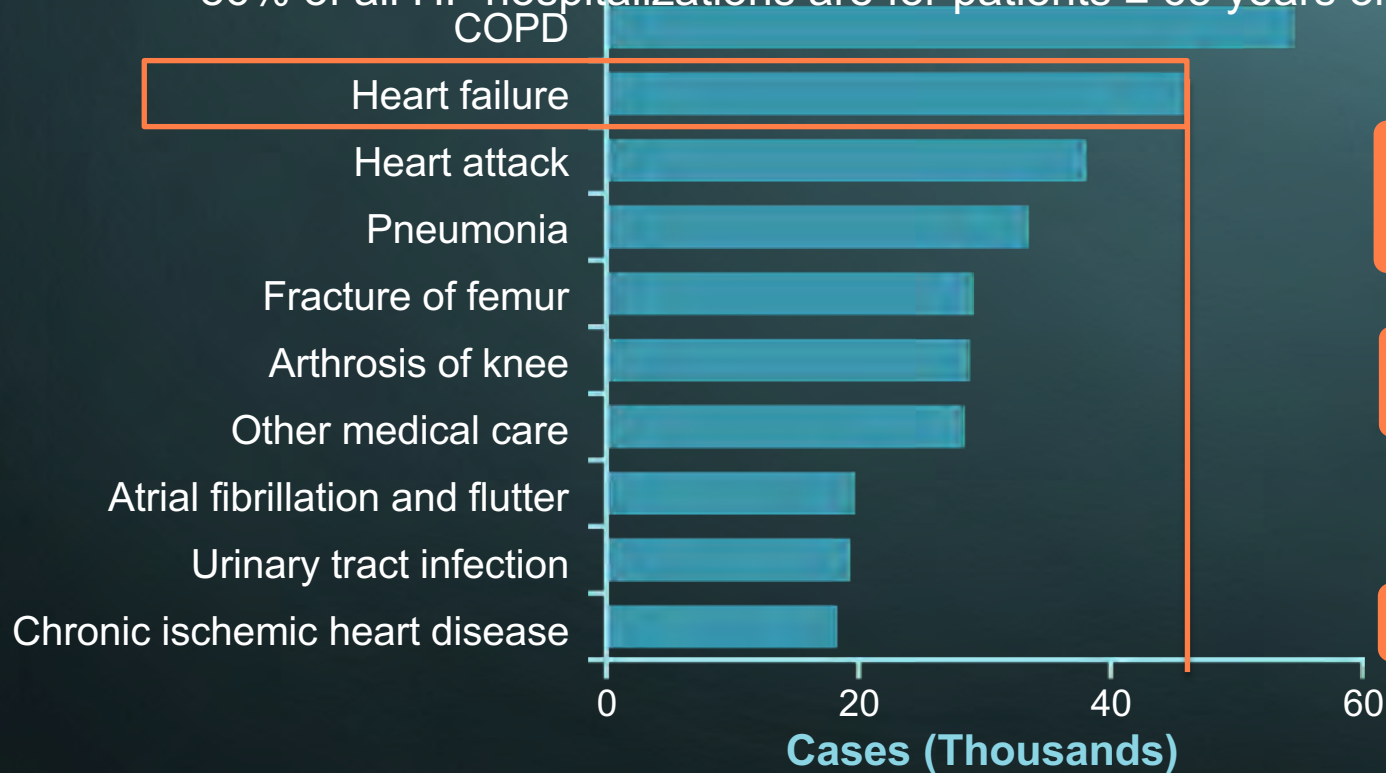
- Started on Furosemide and referred for echo
- Echo revealed severely reduced LV systolic function with EF 20%



HF is the 2nd most frequent diagnosis for hospitalizations in Canada (65+)

Primary cause of hospitalization for patients 65 years old and older in 2011

- 86% of all HF hospitalizations are for patients ≥ 65 years old



Burden in 2013 in Canada

45 428 hospitalizations for HF (primary diagnosis)

Average \$10,970 per hospitalization

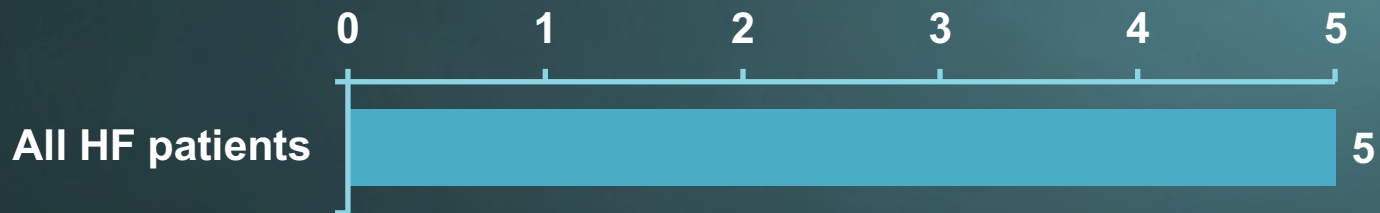


Total \$432 million

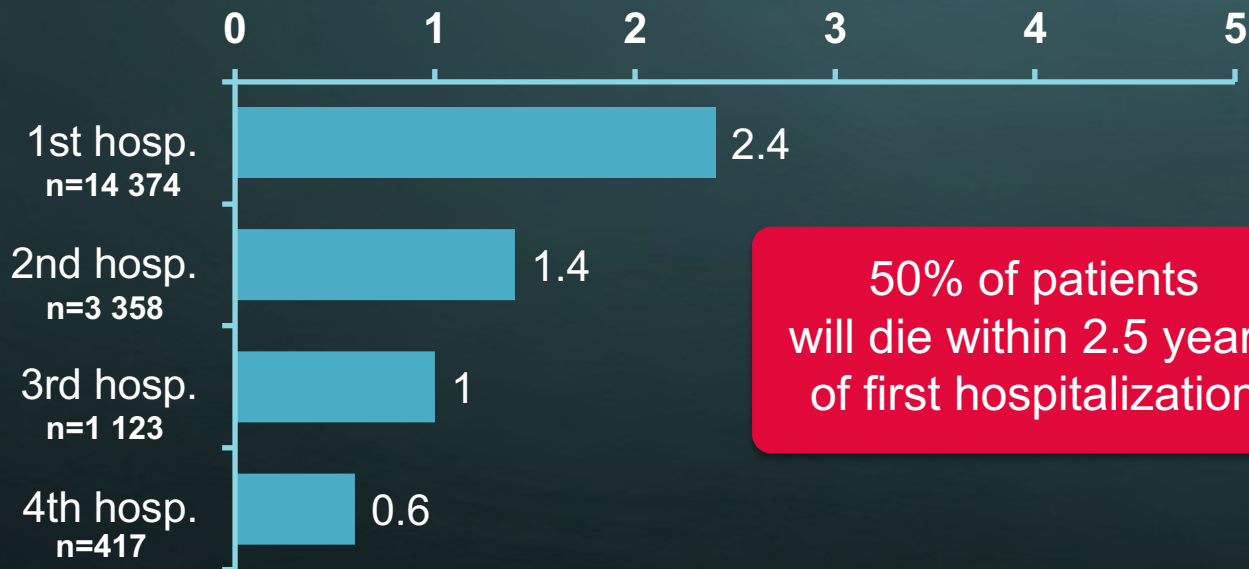


Each hospitalization has a major impact on patient survival

Median survival (Years)



Go et al. *Circulation* 2013; 127: e6–e245.

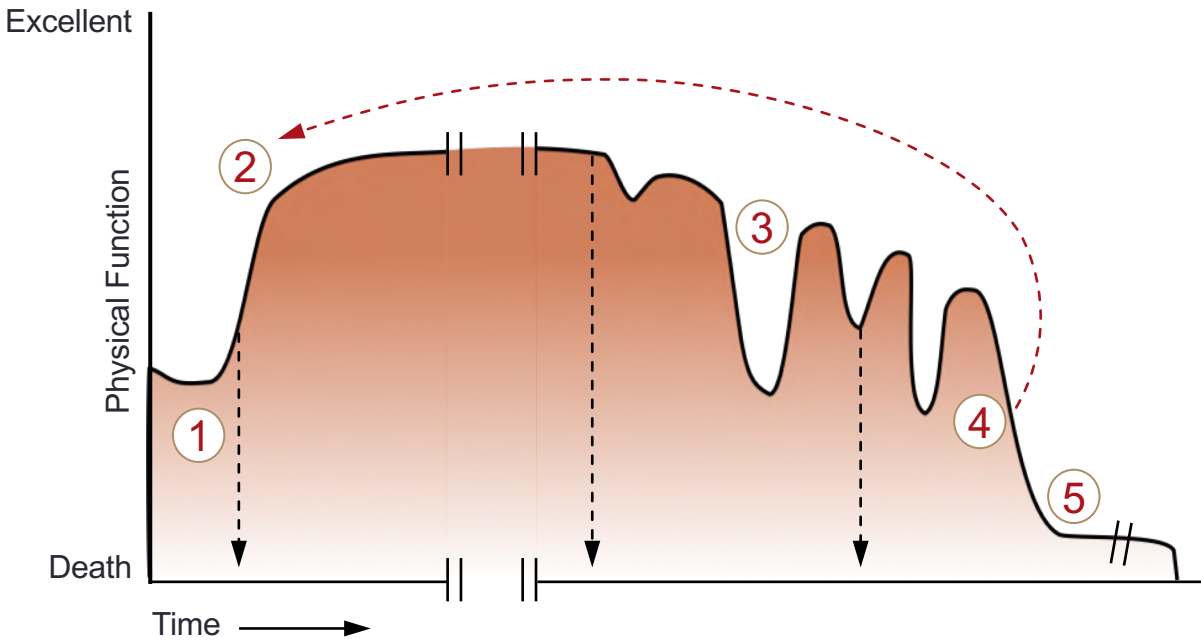


50% of patients will die within 2.5 years of first hospitalization

Whellan & Hamad. *Am Heart J* 2007; 154(2): 203-5.

Heart Failure Trajectory

Palliative and Supportive Care



- Phase ① Initial symptoms of HF develop and HF treatment is initiated
- Phase ② Plateau of variable length reached with initial medical management, or following mechanical support or heart transplant
- Phase ③ Functional status decline with variable slope; intermittent exacerbations of HF that respond to rescue efforts
- Phase ④ Stage D HF, with refractory symptoms and limited function
- Phase ⑤ End of life

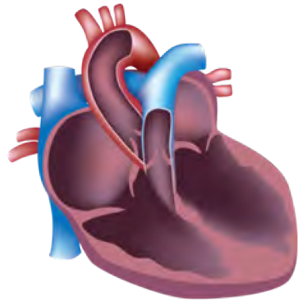
Sudden Death Event - - -
 Transplant or Ventricular Assist Device - - -

Dotted lines represent sudden cardiac death that can occur anytime during the trajectory

• Goodlin SJ. *J Am Coll Cardiol.* 2009;54(5):386-96.

HF_rEF

Heart Failure with reduced ejection fraction - EF ≤ 35–40%



Systolic dysfunction

A condition of volume overload

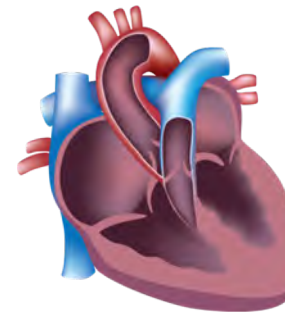
1. Characterized by eccentric hypertrophy
2. Results in globular heart with thinning of LV walls, decreased systolic function and enlarged LV volume

HF_mEF

Heart Failure with mid-range ejection fraction – EF > 50%

HF_pEF

Heart Failure with preserved ejection fraction – EF > 50%

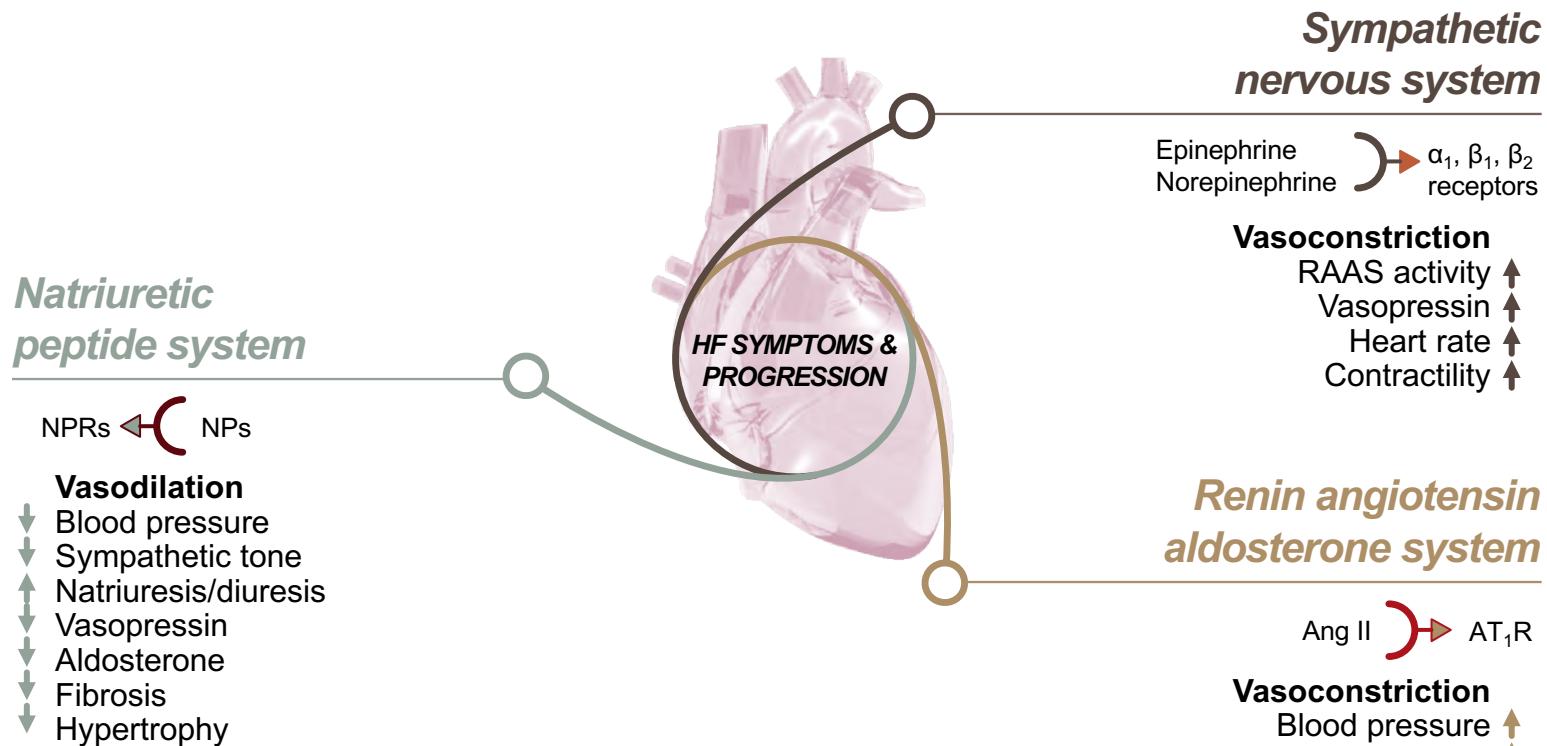


Diastolic dysfunction

A condition of pressure overload

1. Characterized by concentric hypertrophic growth
2. Results in normal sized LV cavity with thickened walls and preserved systolic function

Decline In Systolic Function Leads To Activation Of Three Major Neurohormonal Systems



- Ang=angiotensin; AT1R=angiotensin II type 1 receptor; HF=heart failure; NPs=natriuretic peptides; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system
- Levin *et al.* *N Engl J Med* 1998;339:321–8;
- Nathisuwan & Talbert. *Pharmacotherapy* 2002;22:27–42;
- Kemp & Conte. *Cardiovascular Pathology* 2012;365–371;
- Schrier & Abraham. *N Engl J Med* 2009;341:577–85

Etiology of HF

Echocardiogram, ECG, plus recommended lab testing for all patients (CBC, creatinine, ferritin, TSH, troponin, NP)

HFrEF (and HFmEF)
LVEF \leq 40%, up to 49%

HFpEF
LVEF \geq 50%

Congenital Heart Disease
Pericardial Disease

Common etiologies

Tachyarrhythmia

Valve disease

Known or risk factors for CAD

LVH

CAD work-up*

Hx of HTN?*

Significant CAD (Ischemic)

No Significant CAD

Probable hypertensive HF/ hypertensive cardiomyopathy

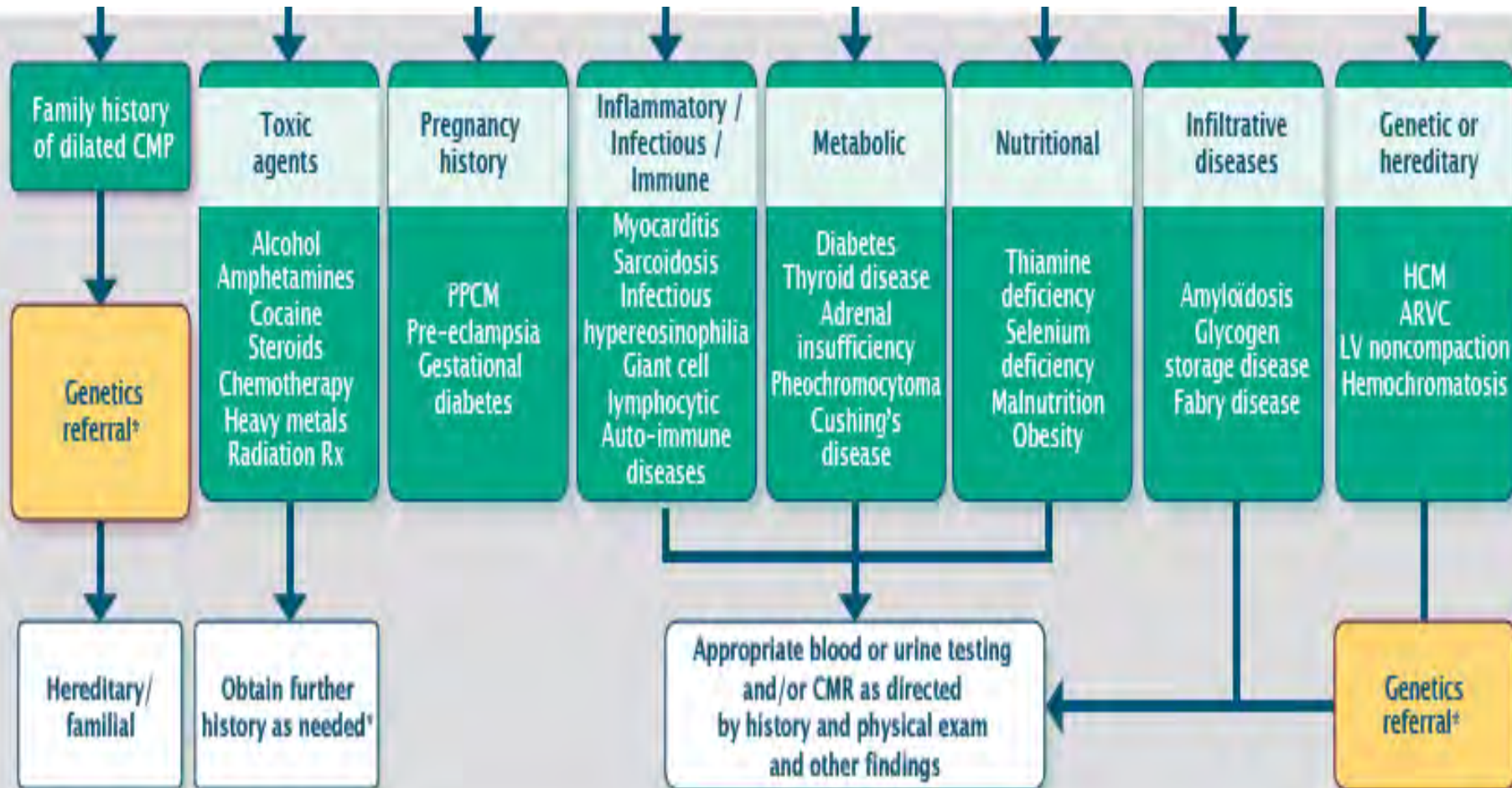
Further work-up and referral as appropriate

MORE COMMON



Other etiology considerations

LESS COMMON



Current Challenges Associated With HF Care In Canada

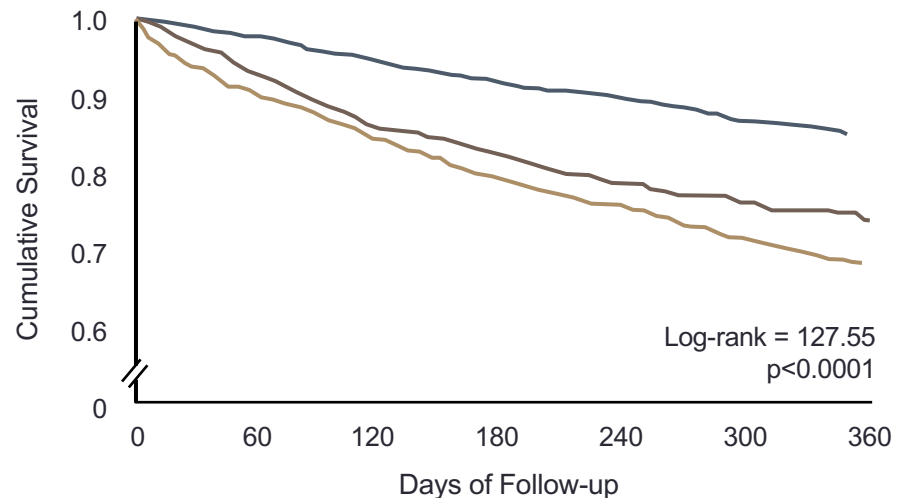
- HF cannot be “cured” by relieving symptoms
 - Often progresses without signs or symptoms
 - Clinical focus has been to control symptoms
- Patients discharged are often unprepared and unsupported
 - Patients unable to self-manage – information overload
 - Frequent returns to emergency
 - 30-day readmission rates are high

Follow-up Cardiovascular Care

- Importance of Follow-up Care:
 - A study of 3,136 patients in Alberta with Heart Failure found those who received regular cardiovascular follow-up visits with a family physician had better outcomes

Kaplan–Meier Survival Curves For Care Received, by Ambulatory Specialty

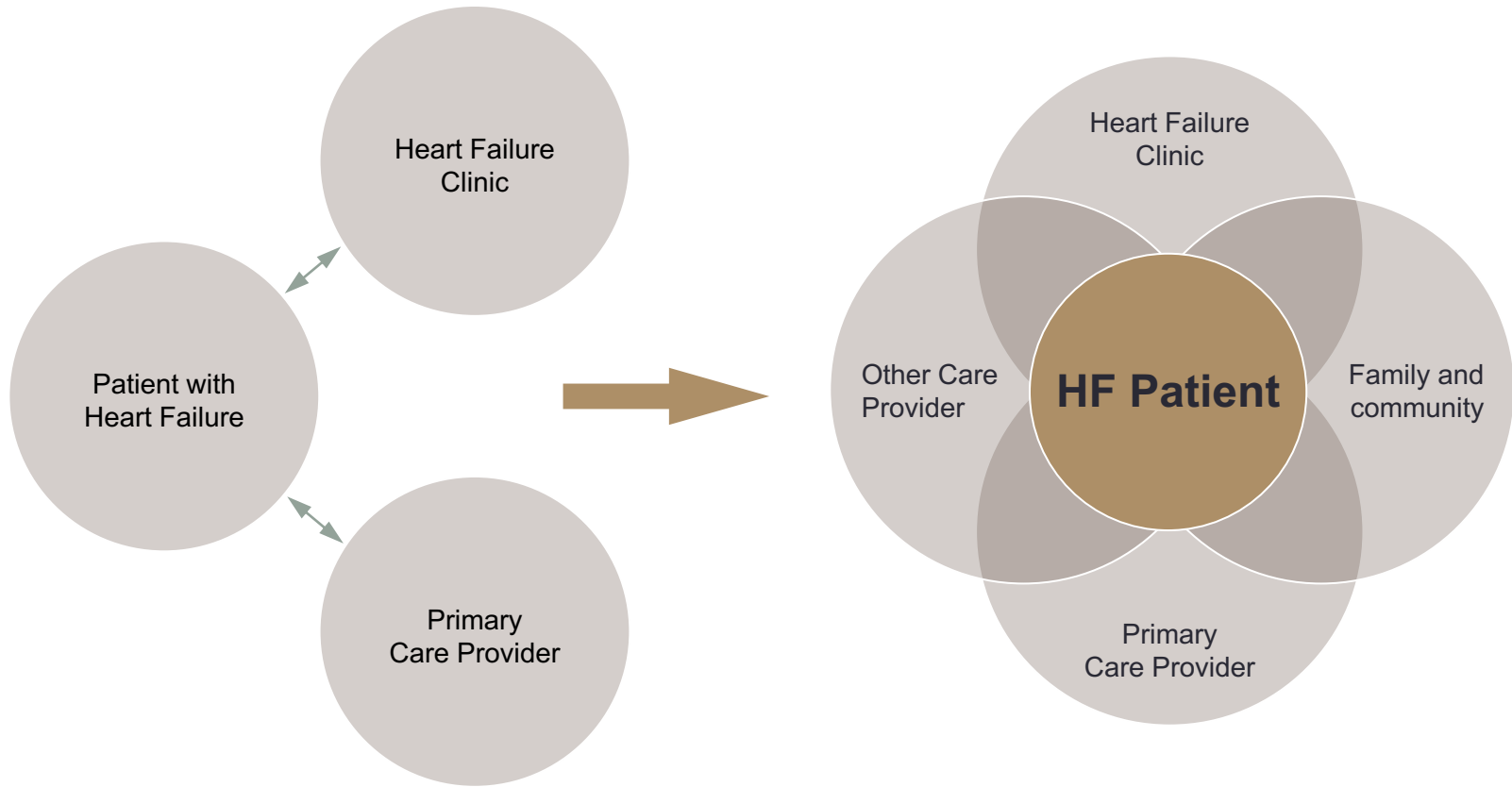
- Combined care (both specialist and family physician)
- Care by family physician only
- No follow-up care



- Ezekowitz JA, *et al.* Impact of specialist follow-up in outpatients with congestive heart failure. CMAJ 2005;172:189-94.

Model For Future Disease Management Of HF

From this  To this!



Incremental benefit in HF treatment

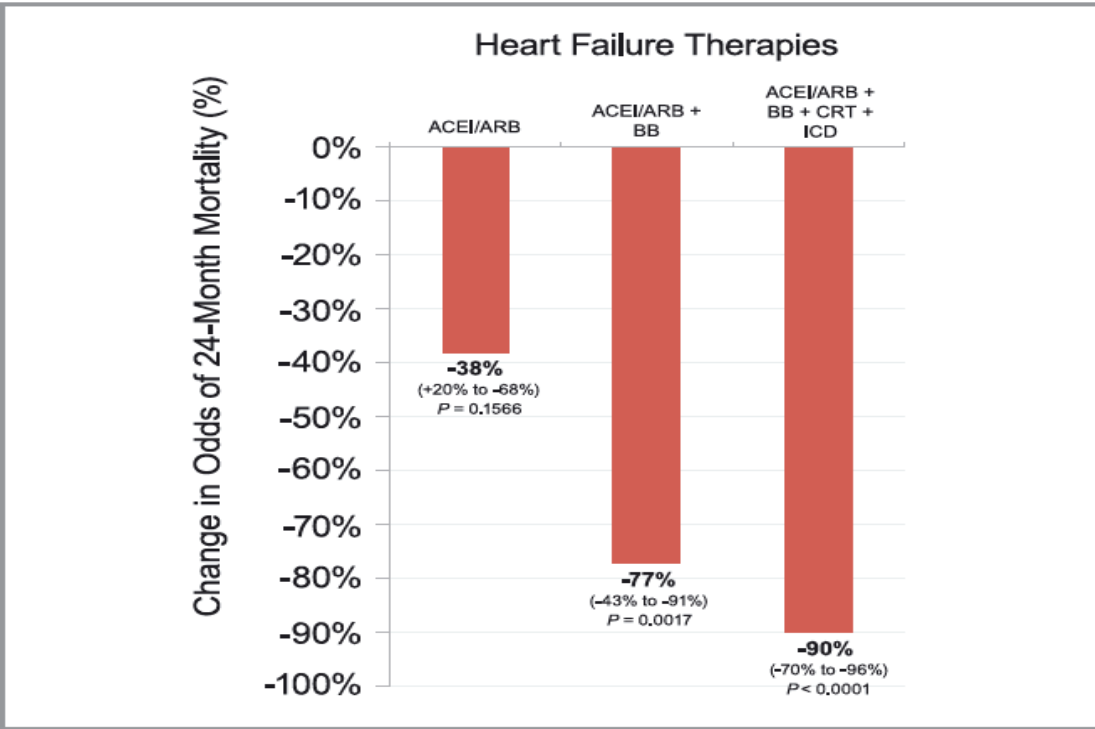


Figure 4. Cumulative percent reduction in odds of death at 24 months associated with sequential treatments compared with no treatment. Analysis includes only patients eligible for all 4 therapies (N=368). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

Selected Approaches To Improve Patient Adherence In HF And Chronic CVD

• Provider-driven Strategies

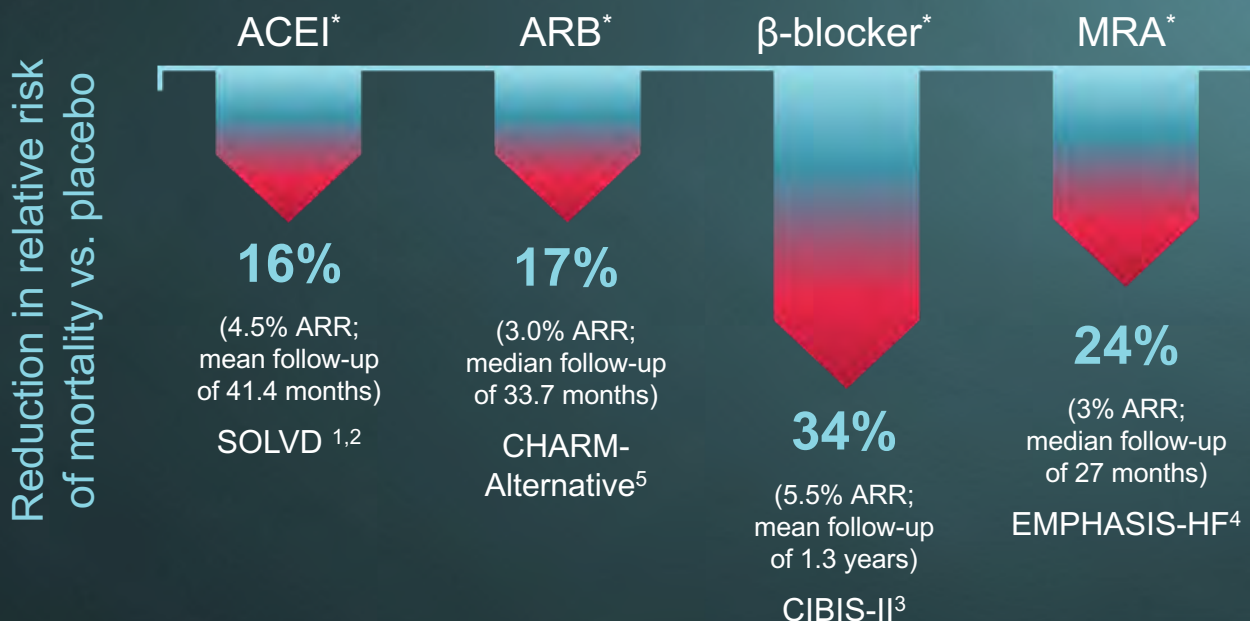
- In hospital initiation of medication
- Nurse or pharmacist-led interventions
- Simplification of drug regimen
- Avoidance of medications with known side effects
- Improved communication between provider and patients
- Heightened awareness of the possibility of poor adherence

• Patient-driven Strategies

- Improved knowledge about medication and disease state; patient education
- Self-monitoring (e.g., daily weight, blood pressure)
- Reduced complexity of dosing schedule
- Active participation in disease management program



Mortality of HFrEF patients has improved with contemporary therapies, but residual risk remains high



*On top of standard therapy at the time of the study (except in CHARM-Alternative where background ACEI therapy was excluded), patient populations varied between trials and, as such, relative risk reductions cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) enrolled chronic HF patients with LVEF ≤ 35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF ≤ 40%.

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist

1. McMurray et al. *Eur Heart J* 2012;33:1787–847; 2. SOLVD Investigators. *N Engl J Med* 1991;325:293–302; 3. CIBIS-II Investigators. *Lancet* 1999;353:9–13; 4. Zannad et al. *N Engl J Med* 2011;364:11–21; 5. Granger et al. *Lancet* 2003;362:772–6; 6.

Evidence Based Heart Failure Drugs and Doses* (mg) for Patients with Systolic LV Dysfunction

4

Drug	Start Dose	Target Dose
ACE inhibitors		
Captopril	6.25-12.5 mg TID	25-50 mg TID
Enalapril	1.25-2.5 mg BID	10 mg BID
Lisinopril	2.5-5 mg OD	20-35 mg OD
Perindopril	2-4 mg OD	4-8 mg OD
Ramipril	1.25-2.5 mg BID	5 mg BID
Trandolapril	1-2 mg OD	4 mg OD
Beta-blockers		
Bisoprolol	1.25 mg OD	10 mg OD
Carvedilol	3.125 mg BID	25 mg BID**
Metoprolol CR/XL	12.5-25 mg OD	200 mg OD
ARBs		
Candesartan	4 mg OD	32 mg OD
Valsartan	40 mg BID	160 mg BID
Mineralocorticoid receptor antagonists		
Spirolactone	12.5 mg OD	50 mg OD
Eplerenone	25 mg OD	50 mg OD
Vasodilators		
Hydralazine	37.5 mg TID	75 mg TID
Isorbide dinitrate	20 mg TID	40 mg TID

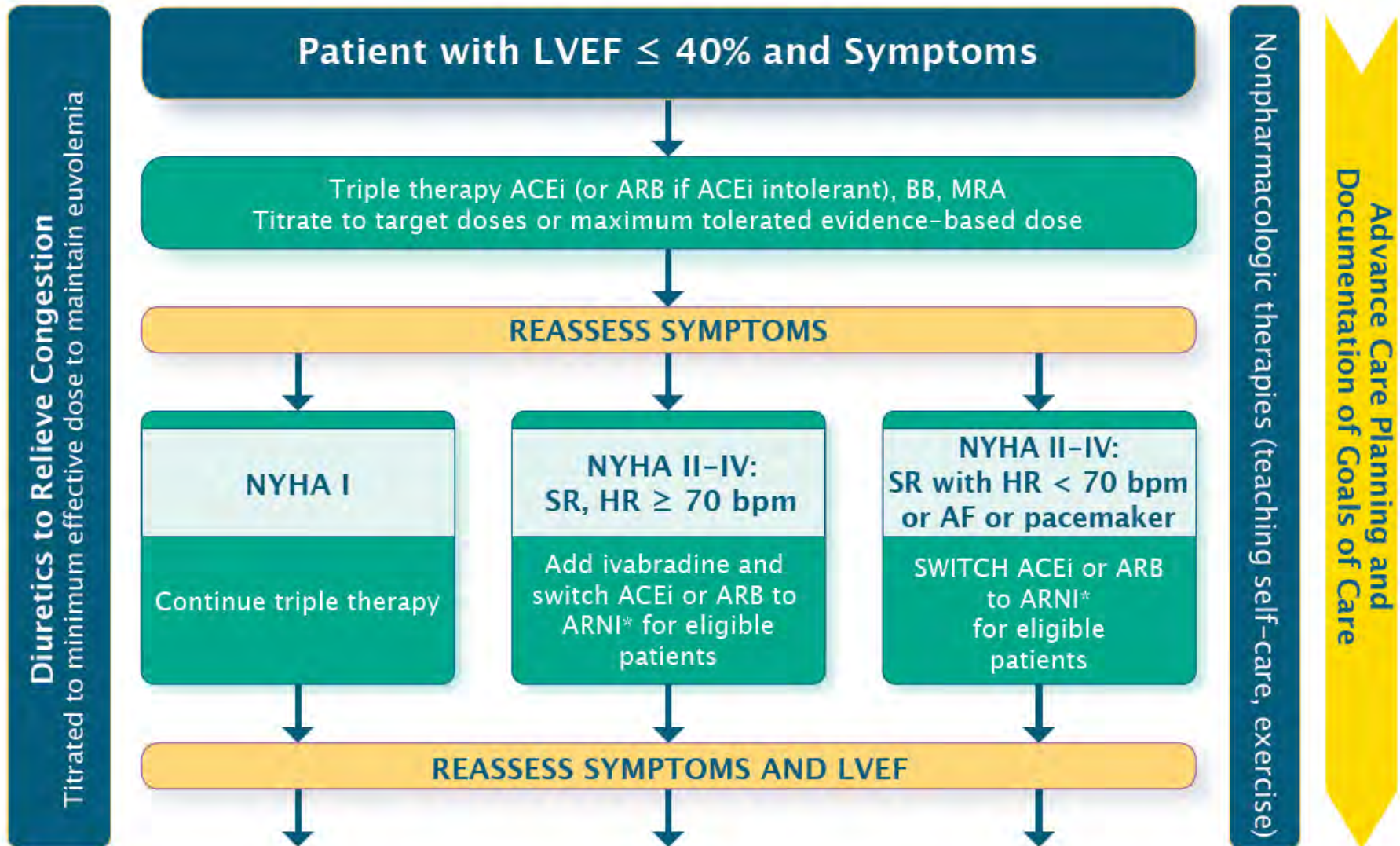
* Drugs and doses may vary and depend upon the clinical scenario. ** 50 mg BID if weight is > 85 kg

† Not available in Canada

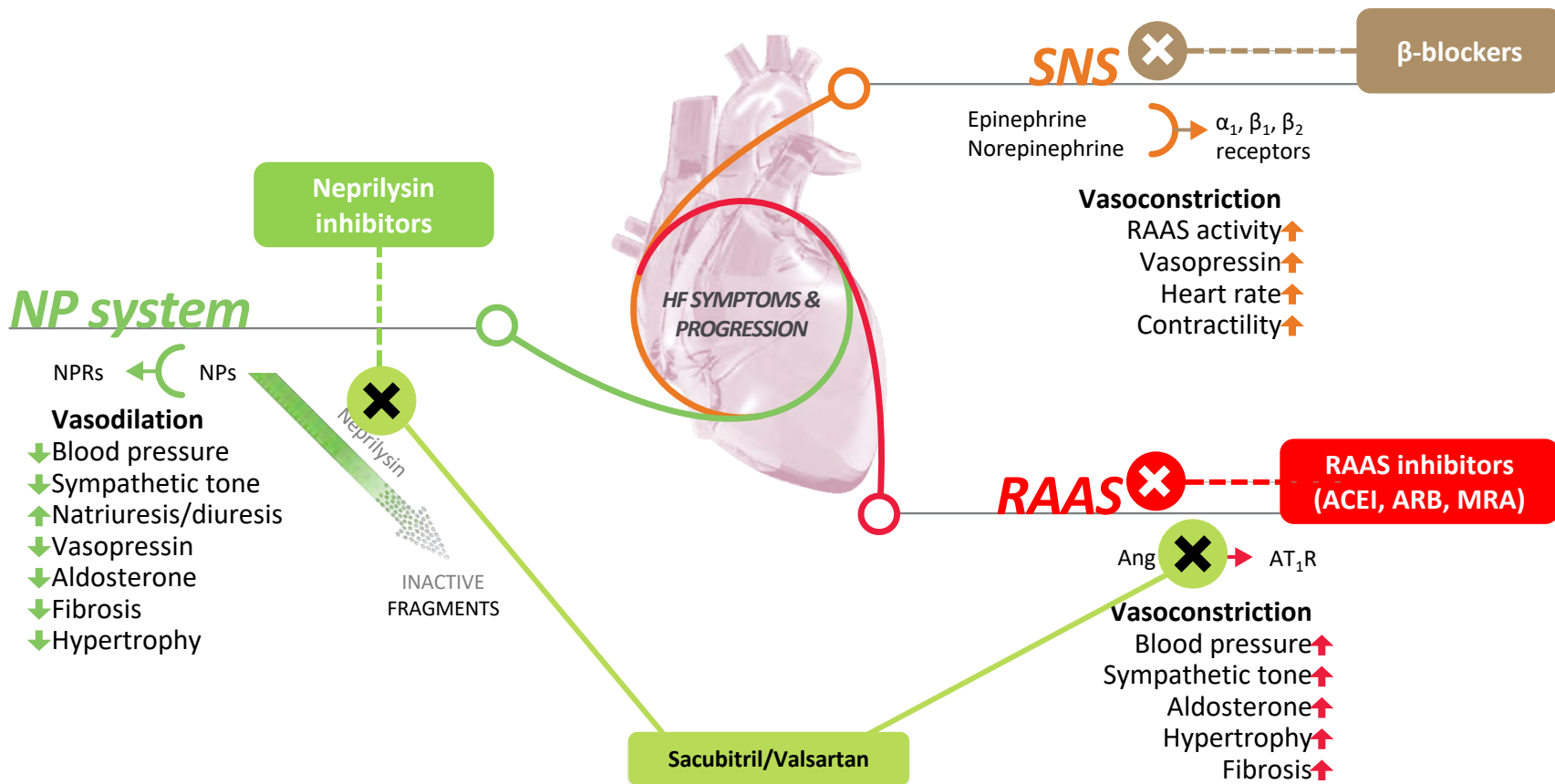
Back to case

- Decreased EF 20%
- Referred for cath – normal coronaries
- Normal TSH, Ferritin and negative HIV
- Started on beta-blocker, ACE-I and MRA and able to achieve target dosing over 3 months
- Still complains of SOB at FC 2 workload
- What now?

Therapeutic Approach to Patients With HFrEF



Sacubitril/Valsartan is the Alternative to an ACEI or ARBs in Patients with HFrEF



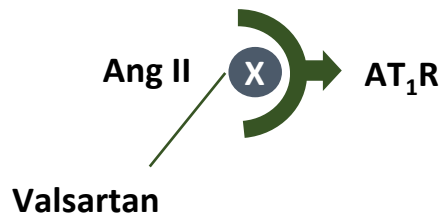
Sacubitril/Valsartan: Increase level of natriuretic peptide and other vasoactive peptides, with simultaneous RAAS suppression

The Combination of Valsartan and Sacubitril Ensures Dual Mode of Action

Effect of Valsartan:



INHIBITS
angiotensin II
through AT₁ receptor blockade

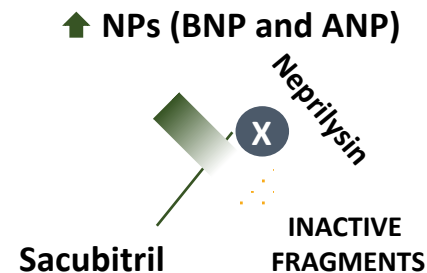


Vasodilation, inhibition of renin/aldosterone release

Effect of Sacubitril:



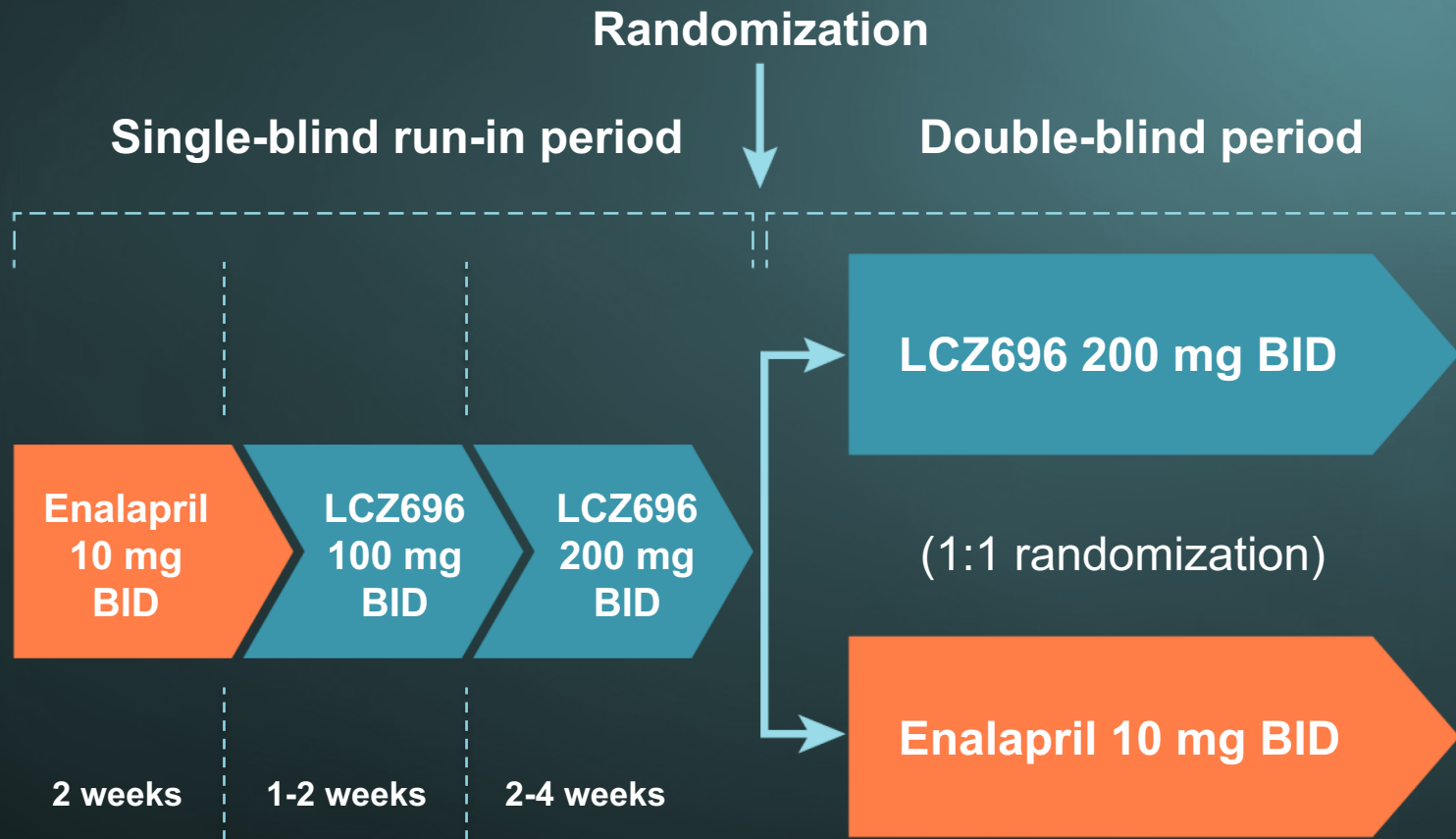
INCREASES
levels of NPs
by inhibiting their degradation by neprilysin



Vasodilation, natriuresis and diuresis

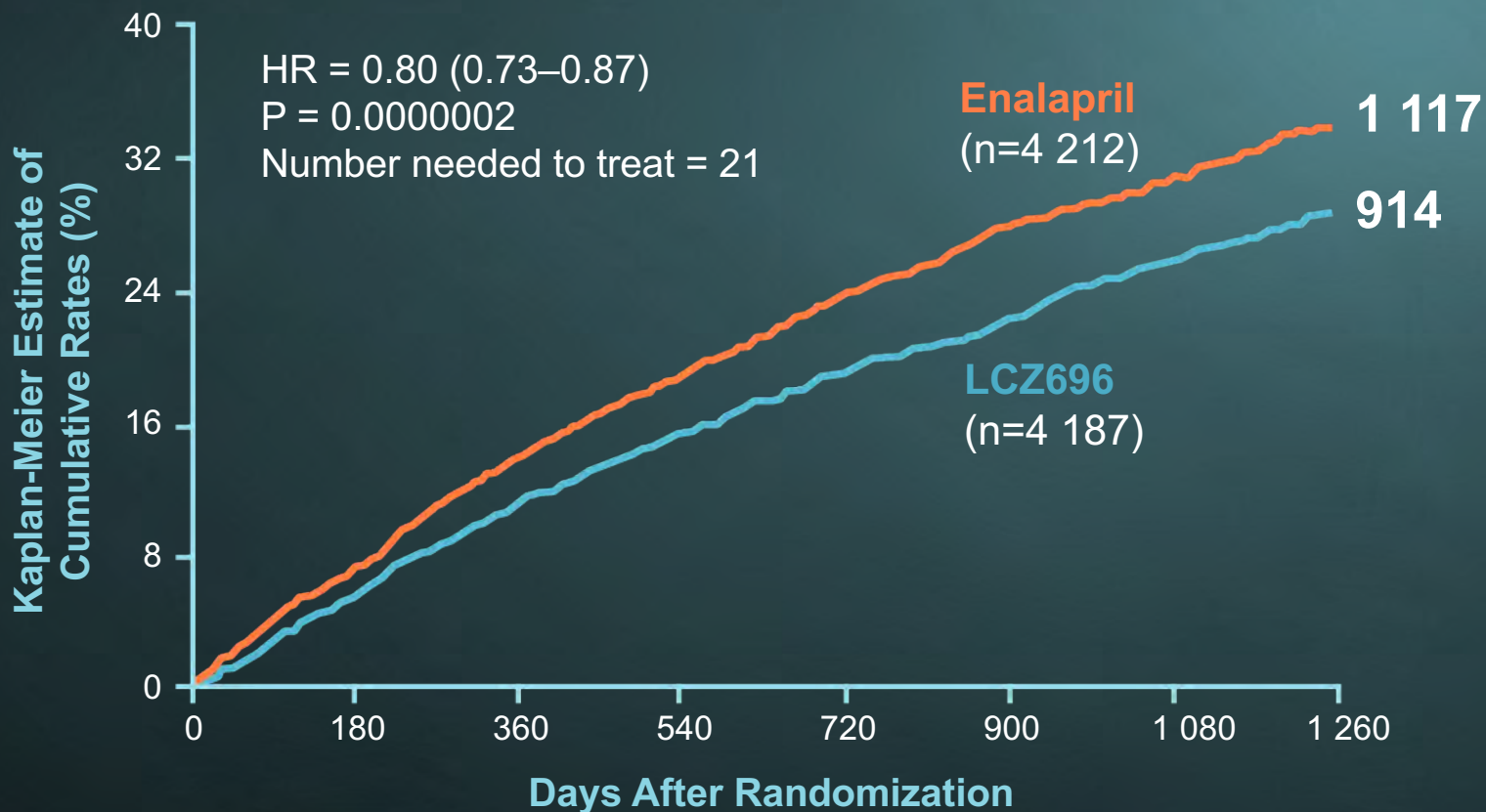


PARADIGM-HF: study design





PARADIGM-HF: cardiovascular death or HF hospitalization (primary endpoint)

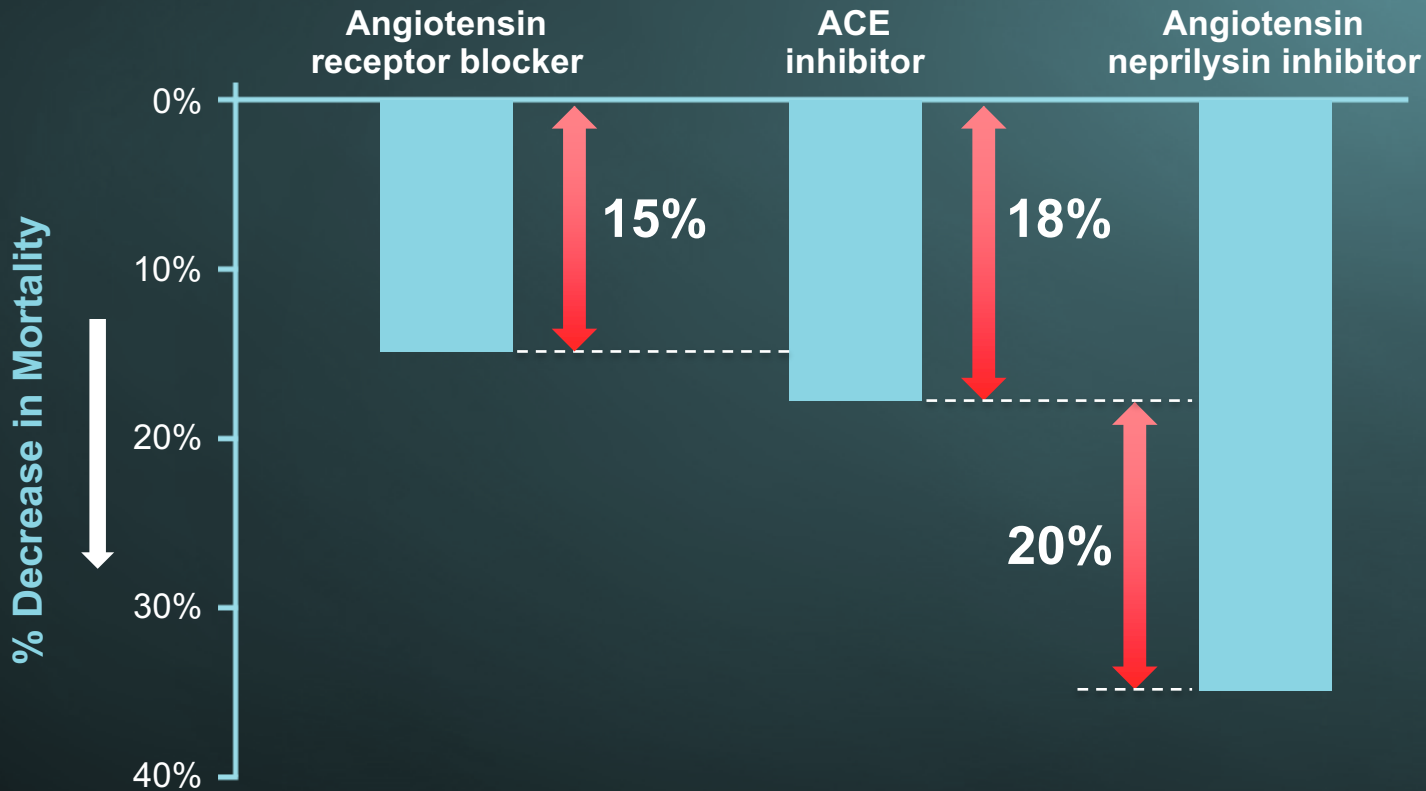


Patients at Risk

LCZ696	4 187	3 922	3 663	3 018	2 257	1 544	896	249
Enalapril	4 212	3 883	3 579	2 922	2 123	1 488	853	236

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
Novartis. Investor Presentation August 31, 2014

Angiotensin neprilysin inhibition with sacubritil/valsartan doubles 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 sacubritil/valsartan vs ACE inhibitor derived from PARADIGM-HF trial



PARADIGM-HF: adverse events

	LCZ696 (n=4 187)	Enalapril (n=4 212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	<0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	<0.001
Discontinuation for adverse event	449	516	0.02
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	---

Dosing

- Sacubutril/Valsartan 24/26 mg bid (50 bid)
- Sacubutril/Valsartan 49/51 mg bid (100 bid)
- Sacubutril/Valsartan 97/103 mg bid (200 bid)

How to Switch High Dose + Low Dose RAAS to Sacubitril-Valsartan in “Real Life”

Converting to LCZ696:¹

- **FROM ACEI:** Stop ACEI, **wait at least 36 h** after last dose (↑ risk of angioedema), then start
- **FROM ARB:** Stop ARB, no washout period necessary, start when next dose would have been due

Initial dose and titration:^{1,3,4}

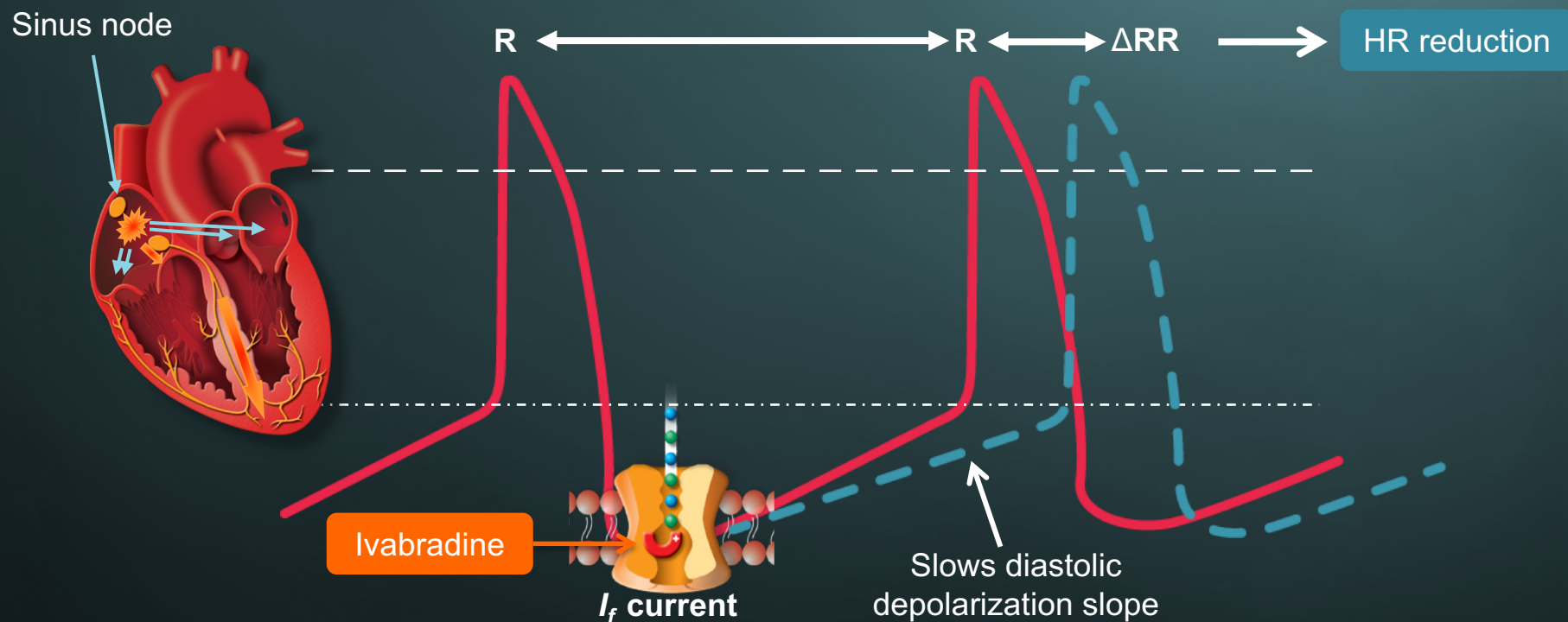
High dose RAAS inhibitor		Initial Dose	Titration
ACEI	ARB		
Enalapril ≥10mg/d lisinopril ≥10 mg/d perindopril ≥4 mg/d ramipril ≥5 mg/d	candesartan ≥16mg/d irbesartan ≥150 mg/d losartan ≥50 mg/d olmesartan ≥10 mg/d telmisartan ≥40 mg/d valsartan ≥160 mg/d	100 mg PO BID³	Increase in 3-6 weeks to target 200 mg PO BID ^{3,4}
Low dose RAAS inhibitor		*50 - 100mg PO BID^{1,4}	Over 6 weeks, increase to target 200 mg PO BID⁴
RAAS naïve			
Higher risk of hypotension (eg. low baseline SBP)			

* Note: little data available using the 50 mg BID dose. PARADIGM had an option to down-titrate to 50mg BID, but no data was reported on the frequency of use.³ TITRATION used 50mg BID as the starting dose for all patients (n=429). Few were RAAS naïve n = 30.⁴



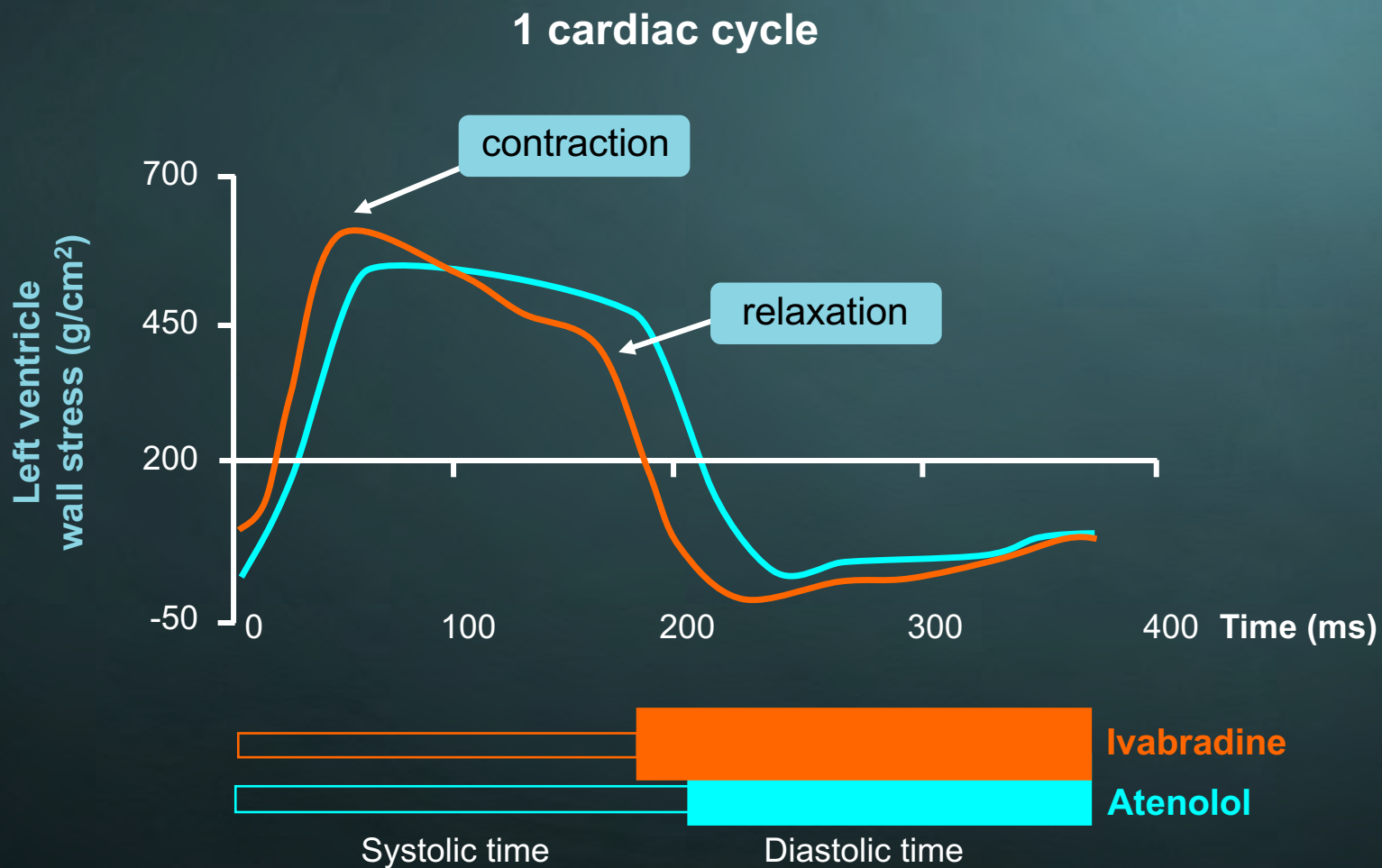
Ivabradine selectively inhibits the I_f current

I_f is the main current of diastolic depolarization that leads to the generation of a new potential action



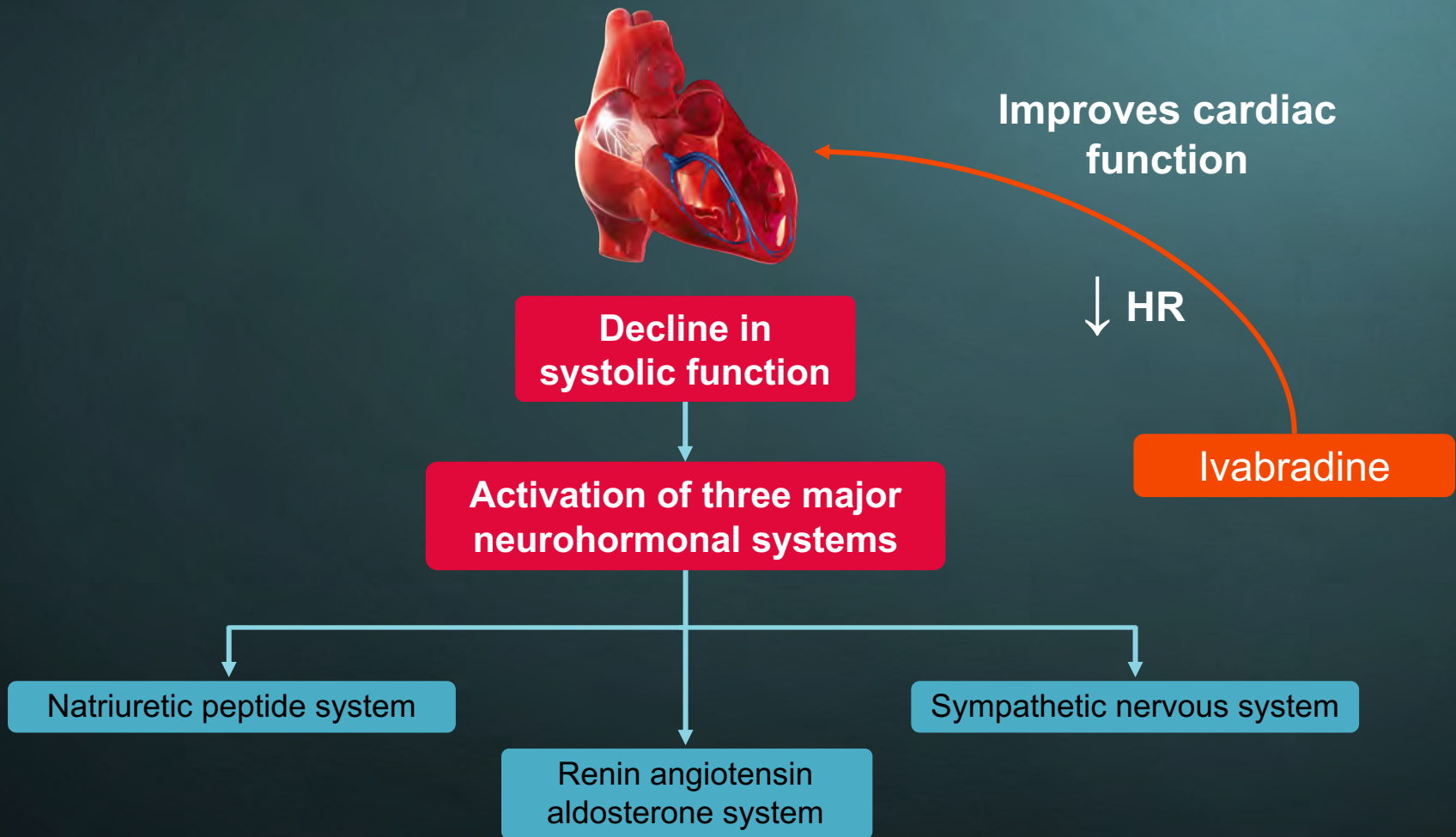


Better coronary perfusion with ivabradine

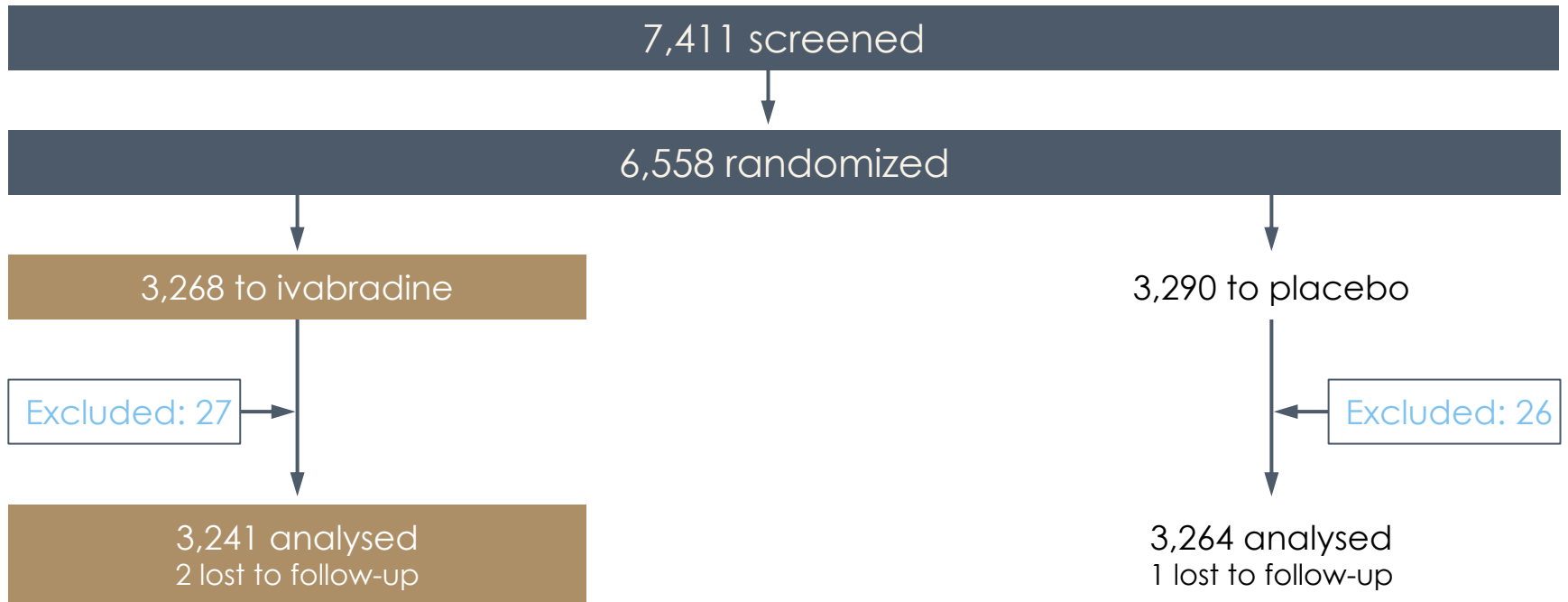




Ivabradine acts directly on cardiac function



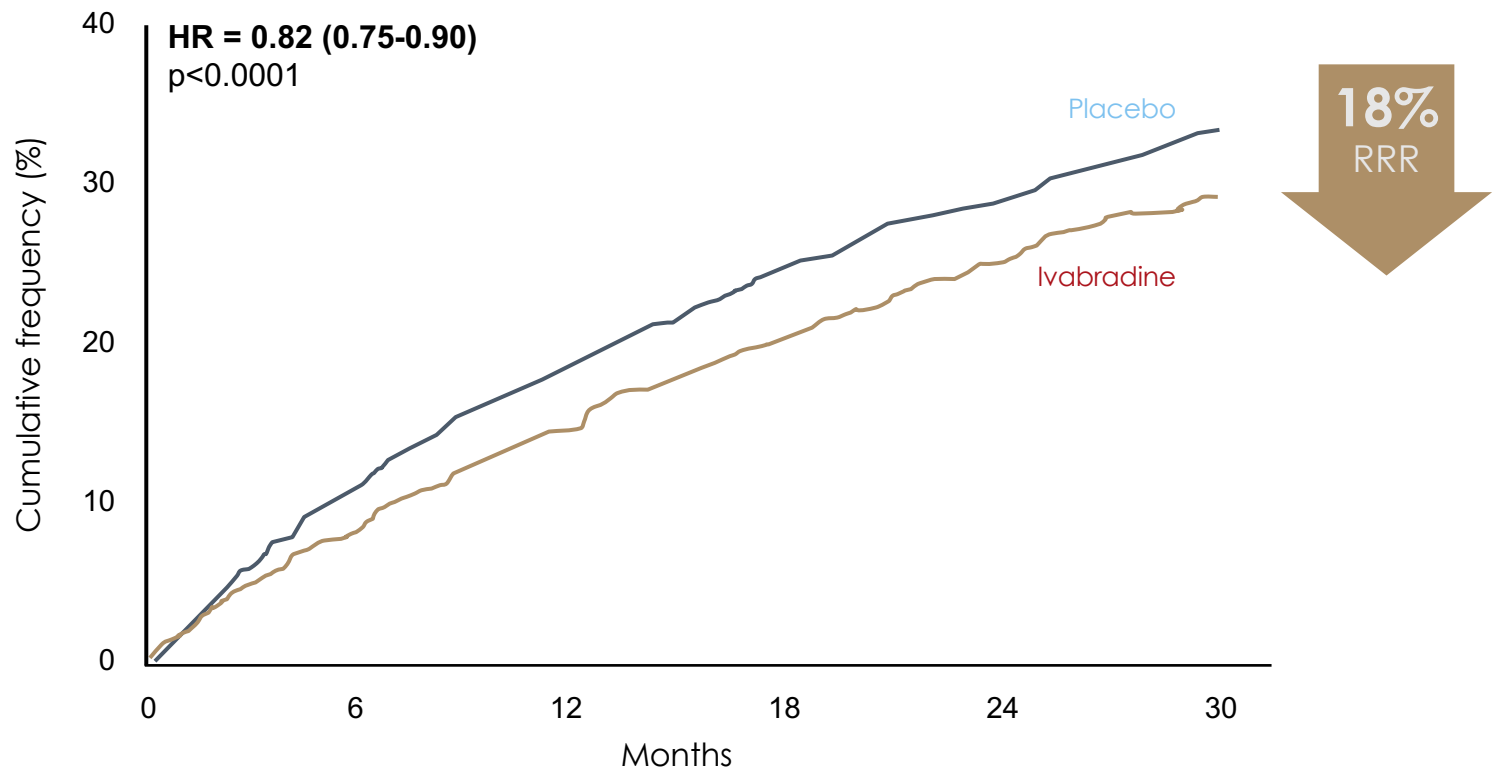
SHIFT Trial: Design And Follow Up



Median study duration: 22.9 months; maximum: 41.7 months

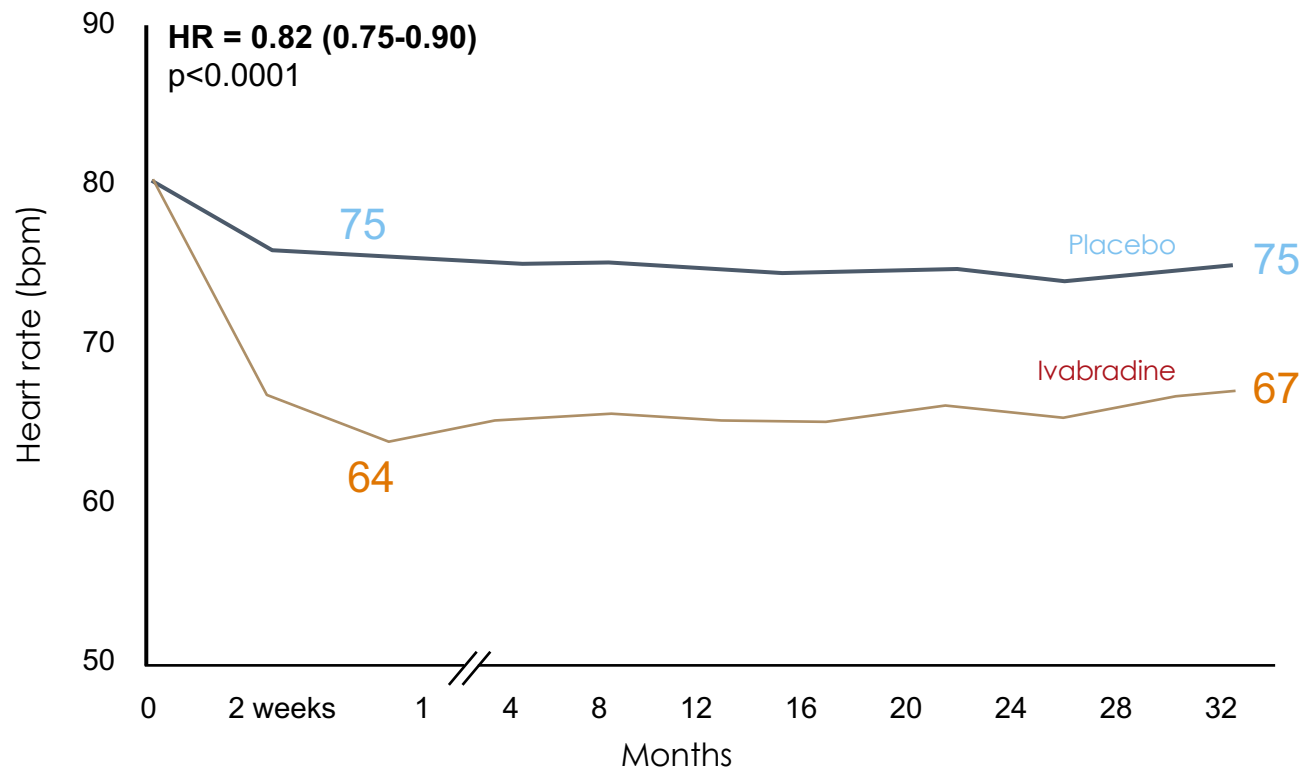
- Swedberg K, *et al.* SHIFT Investigators. *Lancet.* 2010;376(9744):875-85.

SHIFT Trial: Primary Endpoint CV Death Or Hospital Admission For Worsening CHF



• Swedberg K, et al. SHIFT Investigators. Lancet. 2010;376(9744):875-85.

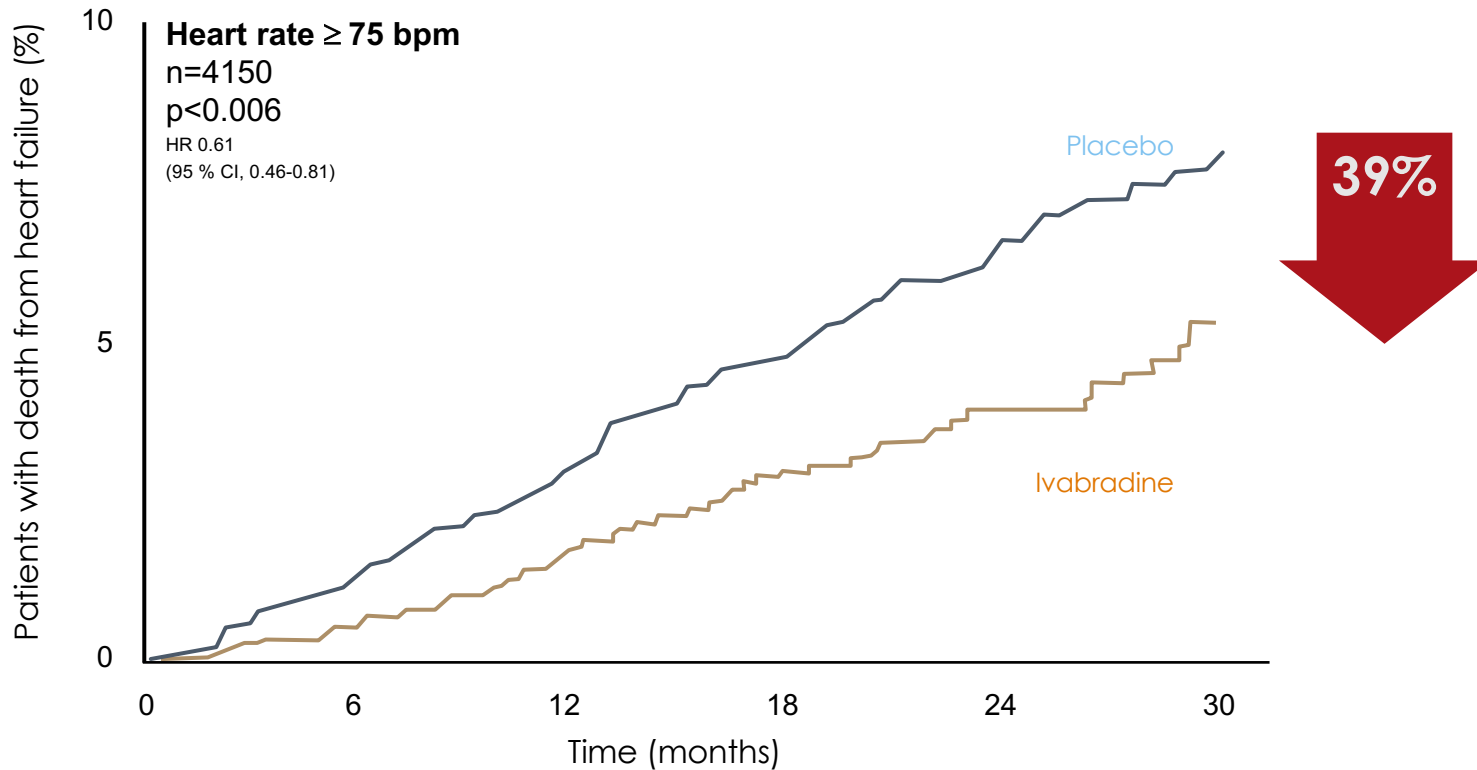
SHIFT Trial: Mean Heart Rate Reduction



**Mean
ivabradine dose:**
6.4 mg bid
at 1 month
6.5 mg bid
at 1 year

• Böhm M, et al. *Lancet*. 2010 ;376(9744):886-894.

SHIFT Trial: Ivabradine Reduces The Risk Of Death For Heart Failure



- Böhm M *et al.* *Clin Res Cardiol.* 2012;102(1):11-22.
- Ivabradine or placebo is given on top of guideline-recommended therapy including ACE inhibitor, β -blocker, mineralocorticoid receptor antagonist

Heart Rate Reduction

- Beta blockers (BB) are first line
 - Often residual heart rate is high or there is another intolerance
 - For those in NSR with HR > 70, up to 13% of HF population
- Ivabradine on top of BB will improve:
 - Morbidity if HR > 70 bpm
 - Mortality if HR > 75 bpm

Effects of Ivabradine on Primary and Secondary Endpoints in the SHIFT Study

	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (25%)	937 (29%)	0.82 (0.75-0.90)	<0.0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0.90 (0.80-1.02)	0.092
Cardiovascular mortality	449 (14%)	491 (15%)	0.91 (0.80-1.03)	0.128
Death from heart failure	113 (3%)	151 (5%)	0.74 (0.58-0.94)	0.014
Other endpoints				
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0.74 (0.66-0.83)	<0.0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0.85 (0.78-0.92)	0.0002
Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.				

- Ivabradine resulted in 18% reduction in the primary end point
- Effect mainly driven by reduction in hospital admissions for worsening HF (26%) and deaths due to HF (26%)

2017 Recommendation: Ivabradine

Recommendation

We recommend that ivabradine be considered in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT with a resting HR > 70 BPM, in sinus rhythm and a prior HF hospitalization within 12 months, for the prevention of cardiovascular death and HF hospitalization (Strong Recommendation, Moderate Quality Evidence).

Practical tips:

- Every effort should be made to achieve target or maximally tolerated doses of beta-blockers prior to initiation of ivabradine
- Ivabradine has no effect on BP or myocardial contractility

Comparison: Ivabradine vs Sacubitril-Valsartan

- **Ivabradine**

- **Add on therapy**

- Little evidence for de novo HF
 - Need BB titrated first
- Indicated for those in NSR and HR >70 bpm
- Limited by bradycardia, fatigue
- Not affected by BP, creatinine
- Other side effects less common
- One titration (5, 7.5 bid) at 2 week interval

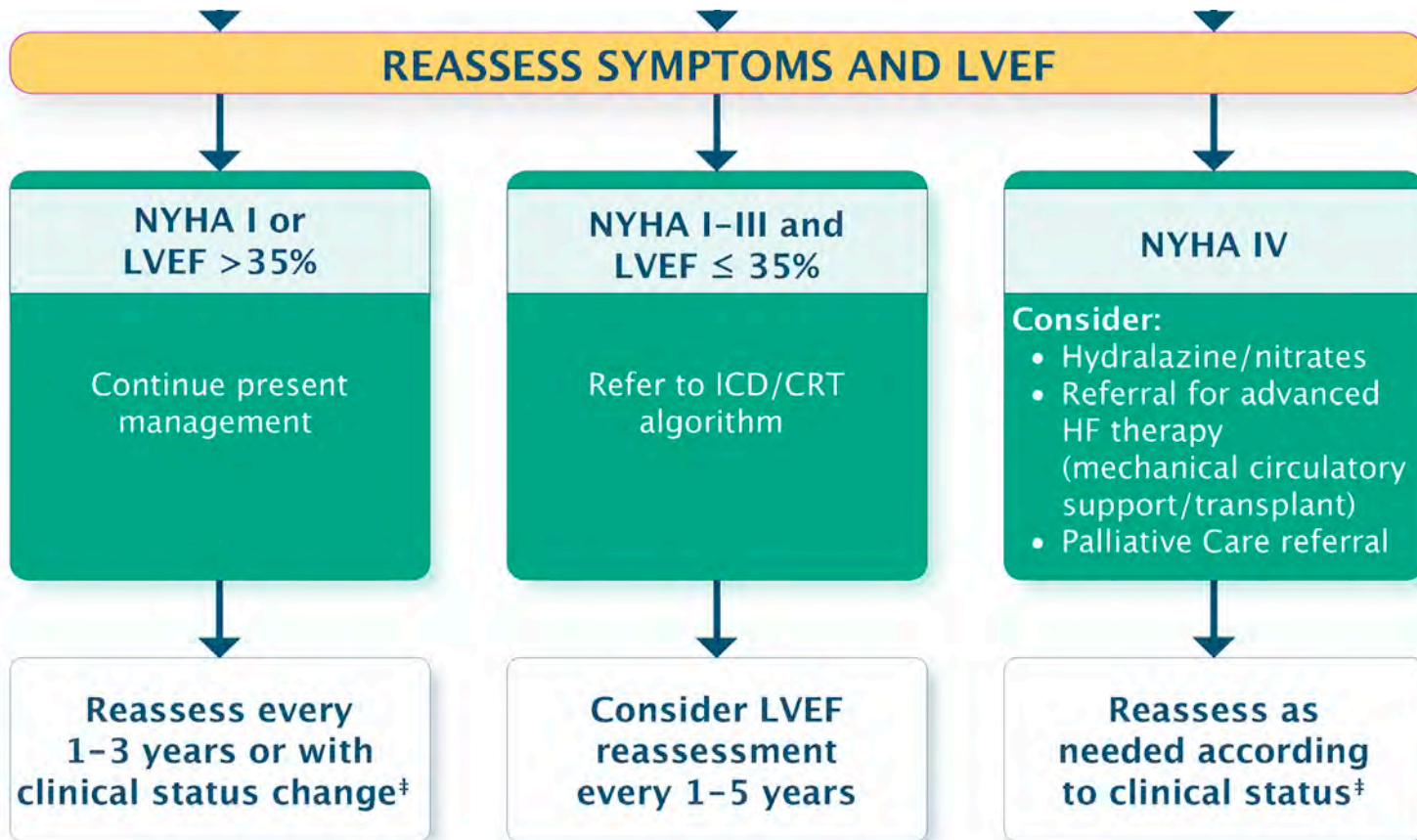
- **Sacubitril-Valsartan**

- **Replacement for ACE/ARB**

- Little evidence for de novo HF
 - Needs ACE/ARB first (for now)
- Indicated for those on ACE/ARB
- Limited by hypotension, creatinine, potassium
- Not affected by HR
- Other side effects not common
- Two titrations (50, 100, 200 bid) for 6-12 weeks

Therapeutic Approach to Patients With HFrEF

Diuretics to
Titrate to minimum effective dose



Teaching self care, exercise)

Implementation of Goals of Care

Prevention vs. Treatment of HF

Therapies that ONLY prevent HF:

- Statins
- BP control, eg CCBs, thiazides
- SGLT2 inhibitors
- Antiplatelets?
- Weight loss?
- Primary prevention?

Therapies that ONLY treat established HF:

- ARNi
- Ivabradine
- CRT/ICD
- MRA

Therapies that BOTH treat and prevent HF:

- ACEi/ARB
- Beta blockers
- Exercise

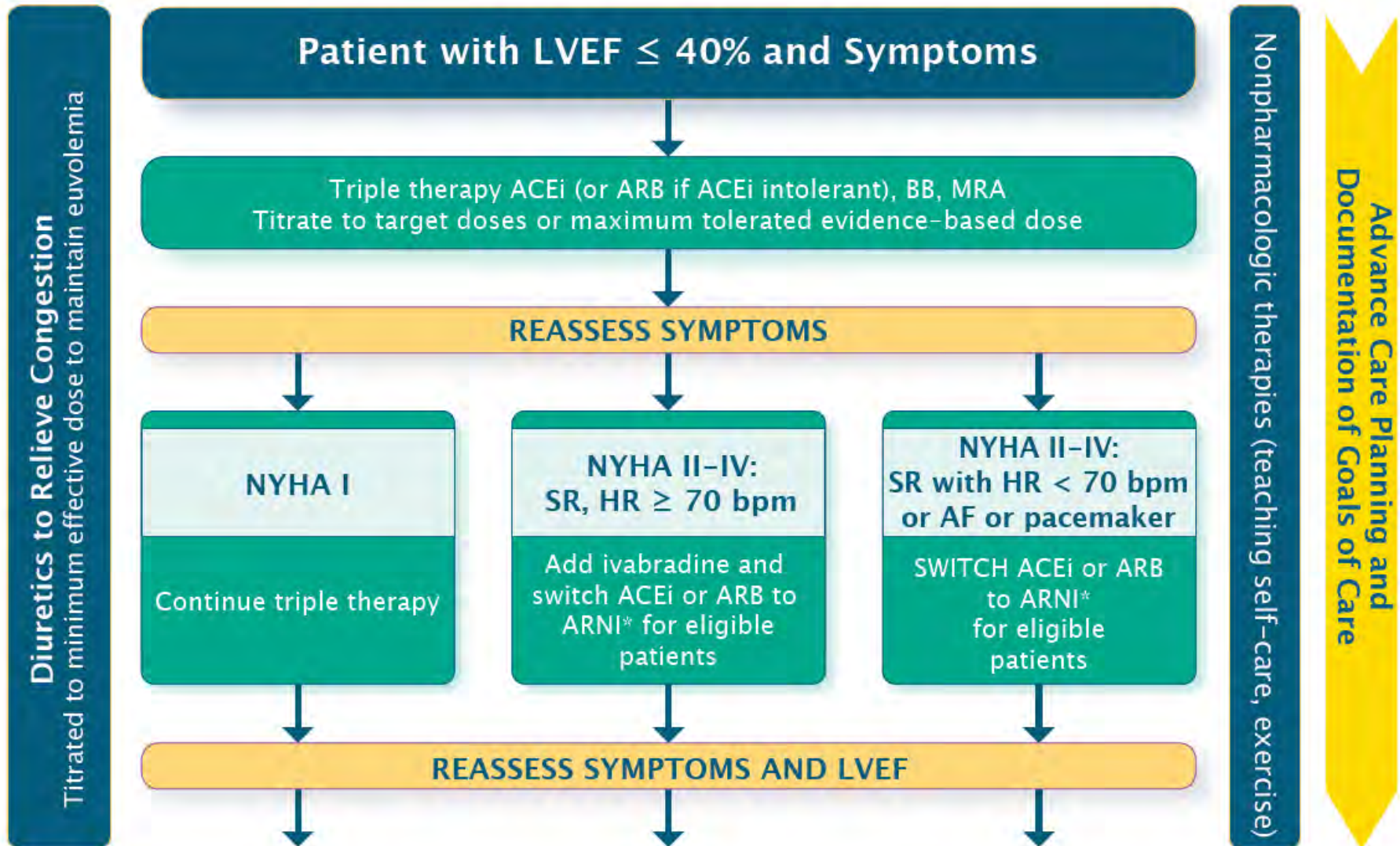
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, Calcium channel blockers; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; SGLT2, sodium-glucose co-transporter 2

Adapted from Howlett JG et al. Can J Cardiol 2016; 32:296-310

Back to case

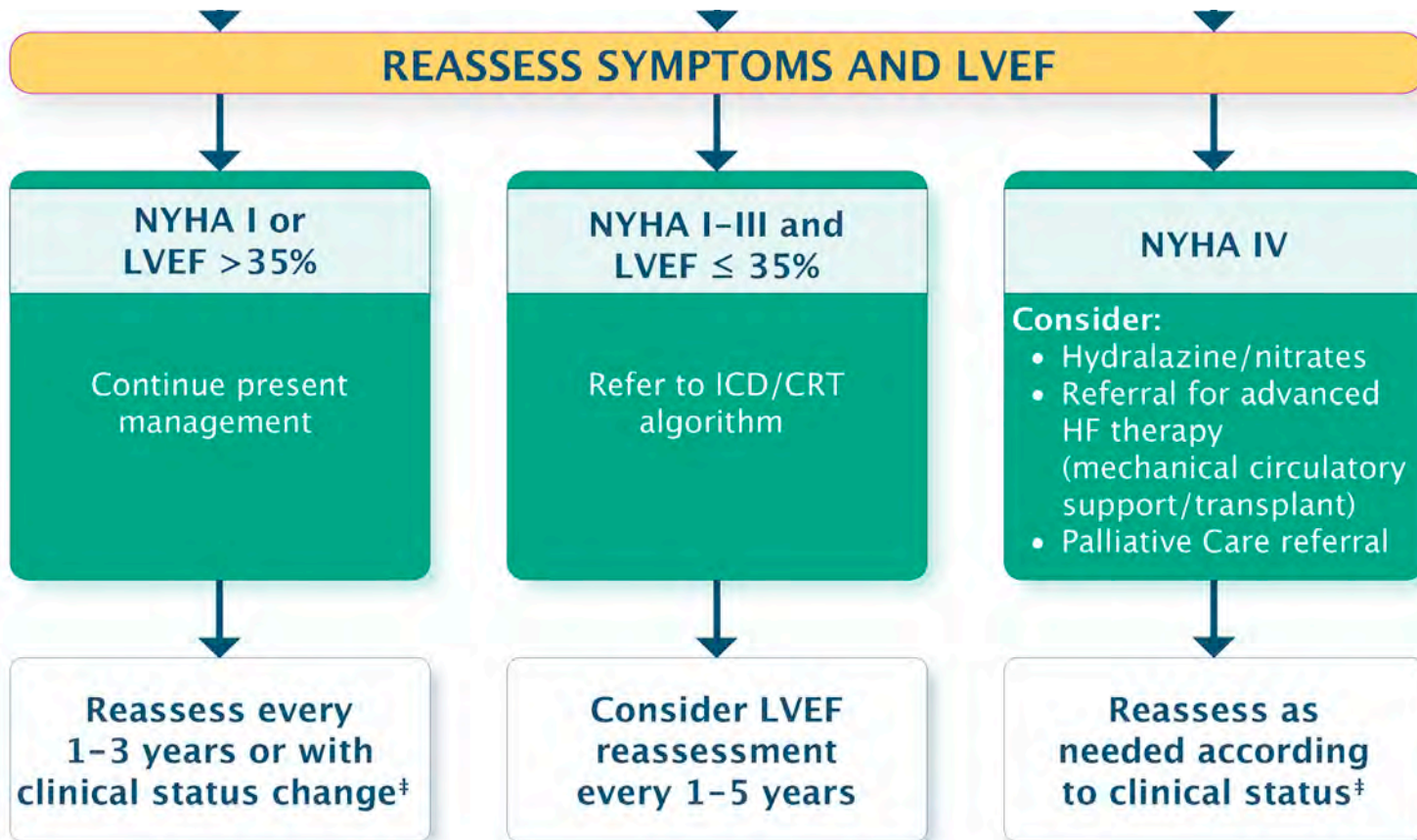
- Started on beta-blocker, ACE-I and MRA and able to achieve target dosing over 3 months
- Still complains of SOB at FC 2 workload
- What now?
 - Stop ACE-I and start Sacubitril/Valsartan if SBP and potassium <5.2
 - Add Ivabradine if HR still > 70
 - Reassess EF – consider ICD/CRT

Therapeutic Approach to Patients With HFrEF



Therapeutic Approach to Patients With HFrEF

Diuretics to
Titrate to minimum effective dose



Teaching self care, exercise)

Implementation of Goals of Care

Conclusions

- Heart Failure is common chronic disease with a long term guarded prognosis
- Current treatments include the use of a multidisciplinary team working to use non-pharmacologic and pharmacologic treatment with best care involving a shared model of care between specialists and primary care physicians

Conclusions

- Using evidence based dosing for heart failure drugs will help to improve outcomes
- Newer therapies are available with Sacubitril/Valsartan and Ivabradine

Thank you