Heart Failure: Current Management Strategies

CSHP Fall Education Session- September 30th, 2017

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Objectives

1. Describe the pathophysiology & presentation of heart failure
2. Identify current management strategies for heart failure
3. Discuss heart failure treatment updates and how they may apply to practice

Patient Case

ID
- 68 year old male

CC
- Increasing SOBOE

PMHx
- HF-rEF x 5 years, NYHA II
- COPD

Physical Exam
- BP 110/60 mmHG
- HR 72 bpm
- Minimal pedal edema

Labs
-Na 138, K 4.2, SCr 86mmol/l (CrCl 61ml/min), NT-proBNP 2480 pg/ml

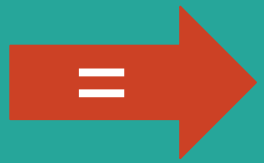
Diagnostic tests
-LVEF: 35%

Medications:
- Bisoprolol 10 mg daily
- Telmisartan 40 mg daily
- Spironolactone 25 mg daily
- Furosemide 40mg daily

What is your next step?

A. Start sacubitril/valsartan 24mg/26mg
B. Start ivabradine 7.5mg BID
C. Change spironolactone to eplerenone
D. Start hydralazine/nitrates

Congestive Heart Failure



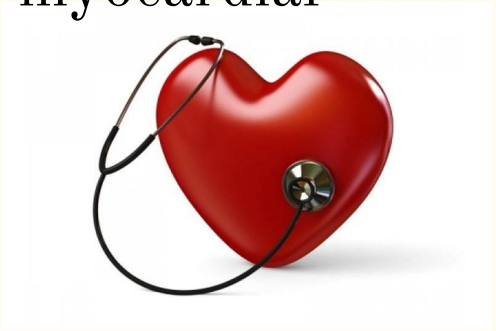
Heart Failure

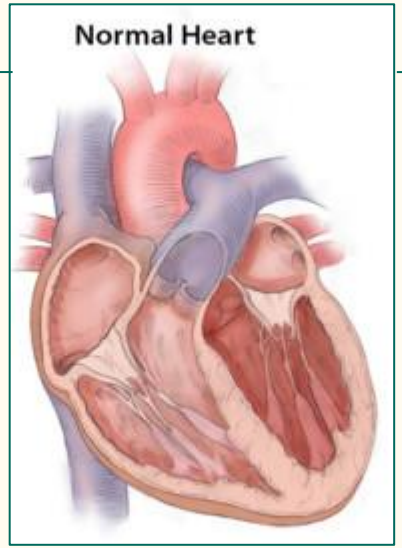
Epidemiology

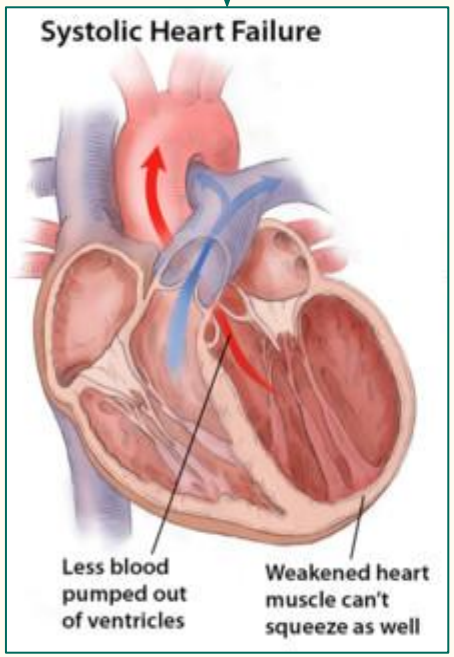
- About 600,000 Canadians living with heart failure
- 50,000 Canadians diagnosed/year
- Risk of CV death is INCREASED after HF hospitalization
- Costs to the health care system is over $2.8 million/year
- More common in men than women before age 65

Pathophysiology

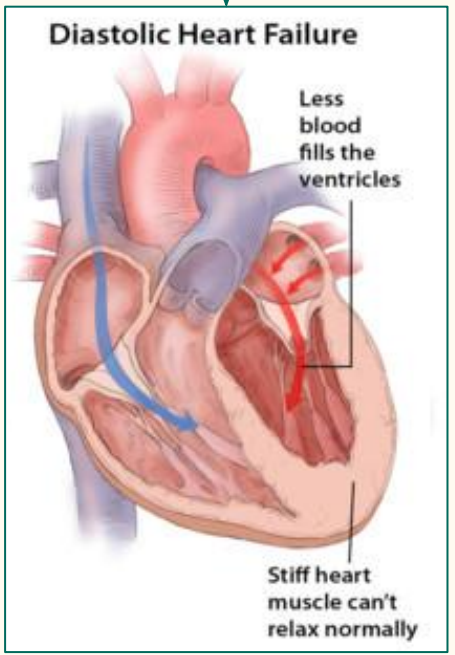
- Inability for heart to pump sufficient blood for body's metabolic needs
- ↓ **ventricular filling** (diastolic) and/or ↓ **contractility** (systolic)
- Leading causes: heart damage from previous myocardial infarction and hypertension







Reduced Ejection Fraction

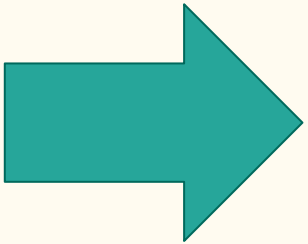


Preserved Ejection Fraction

2017 Comprehensive Update of the CCS Guidelines for the Management of Heart Failure
https://userscontent2.emaze.com

Out with the Old…

Terminology	***LVEF***
Preserved EF (HF-pEF)	**>40%**
Reduced EF (HF-rEF)	**<40%**



Terminology	***LVEF***
Preserved EF (HF-pEF)	**≥ 50%**
Mid-range EF (HF-mEF)	**41-49%**
Reduced EF (HF-rEF)	**≤40%**

Symptoms

- Primary manifestations: **dyspnea & fatigue**
- Edema
- Orthopnea
- Exercise intolerance
- Cough
- Mental status changes (confusion)

New York Heart Association (NYHA) Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue **fatigue, palpitation, dyspnea**
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. Discomfort increases with physical activity.

Diagnosis

- **Clinical history and physical exam**
  - Symptoms, functional limitation, risk factors, comorbidities, vital signs, volume status
- **Initial investigations**
  - CXR, ECG, CBC, electrolytes, renal function
- **Natriuretic peptides**
  - NT-proBNP or BNP
- **Ventricular function**
  - Echo, LVEF

HF Management Strategies to Date

Therapies improving survival

HF with preserved EF (HF-pef) ⩾50%

- No therapies improving survival

HF with mid range EF (HF-mef) 41-49%

- No therapies improving survival

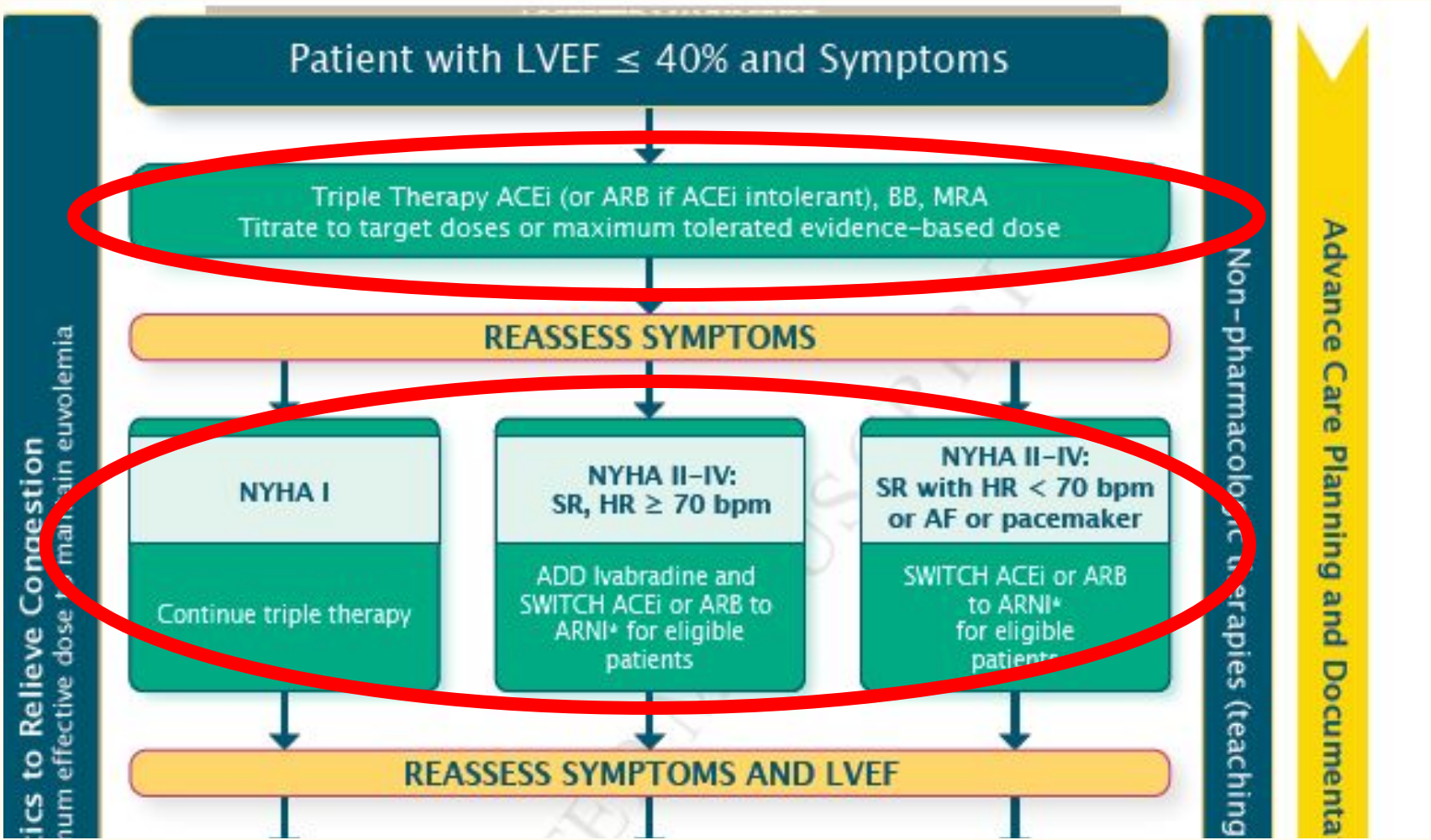
HF with reduced EF (HF-ref) ⩽40%

- Survival benefit shown with : Beta blockers, ACE inhibitors/ angiotensin receptor blockers, aldosterone antagonists, F channel inhibitors, angiotensin receptor neprilysin inhibitor

Canadian Cardiovascular Society (CCS) Guidelines

Guideline Timeline

- **2006:** Heart Failure Diagnosis and Management Guidelines
- **2007-2014:** Annual Updates
- **2015:** Heart Failure Companion: Bridging Guidelines to Your Practice
- **2017:** Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure


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
REASSESS SYMPTOMS AND LVEF
Advance Care Planning and Documenta

Angiotensin Receptor Neprilysin Inhibitor (ARNI)

Angiotensin receptor neprilysin inhibitor (ARNI)

Sacubitril (neprilysin inhibitor) + **Valsartan** (Ang II receptor blocker)

=

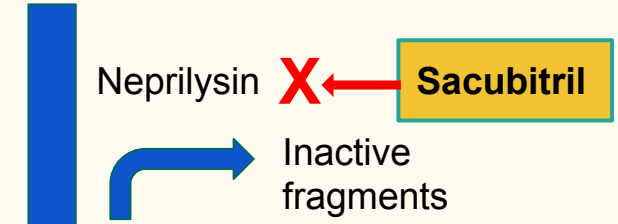
Entresto™ (sacubitril/valsartan) tablets

"LCZ696"

Sacubitril/Valsartan (Entresto)

Natriuretic Peptide System

Natriuretic peptides



Vasodilation
↓Blood pressure
↓Sympathetic tone
↓Aldosterone
↓Hypertrophy

Renin Angiotensin System

Angiotensin I

Angiotensin II

Angiotensin II Receptor

Valsartan X

Vasoconstriction
↑Blood pressure
↑Sympathetic tone
↑Aldosterone
↑Hypertrophy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

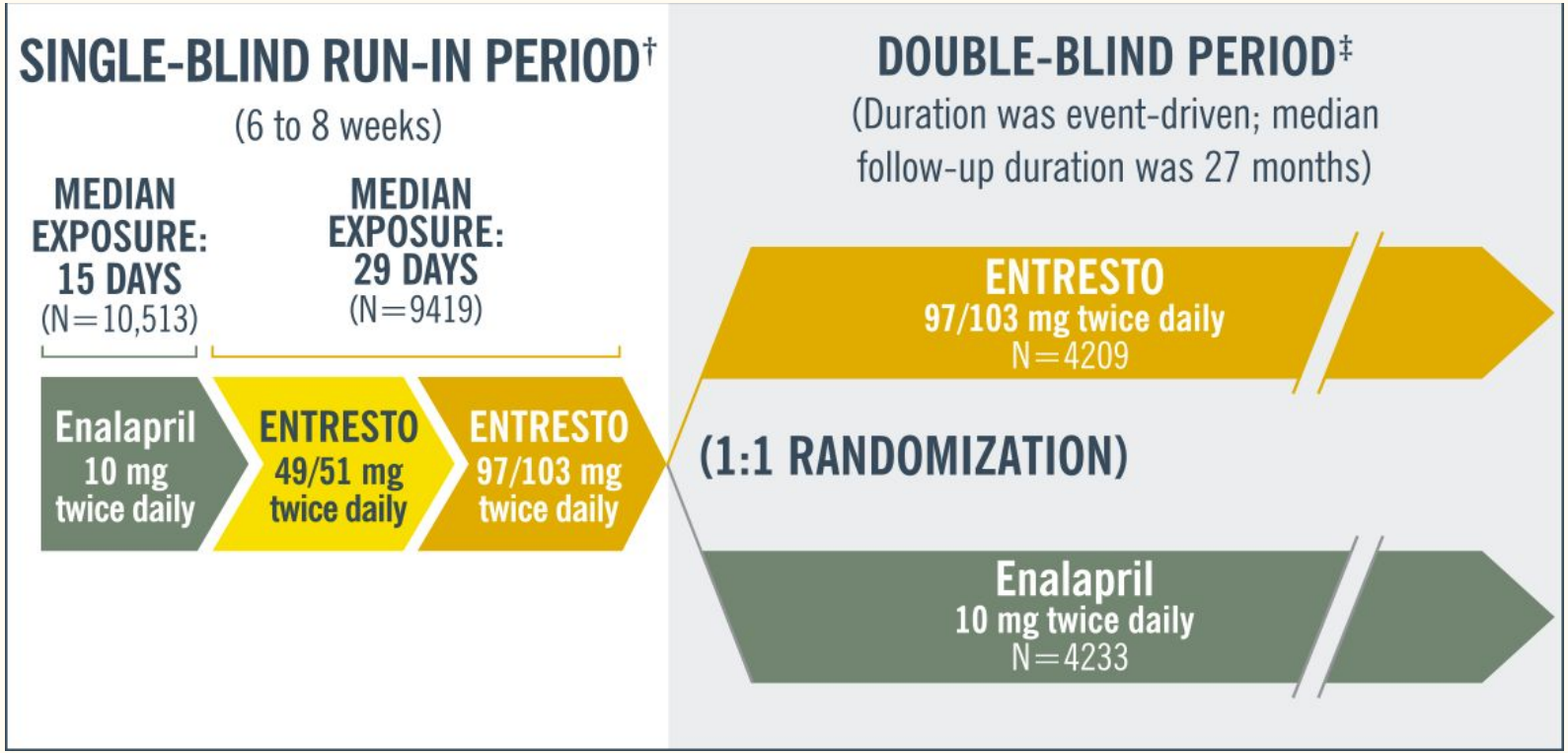
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

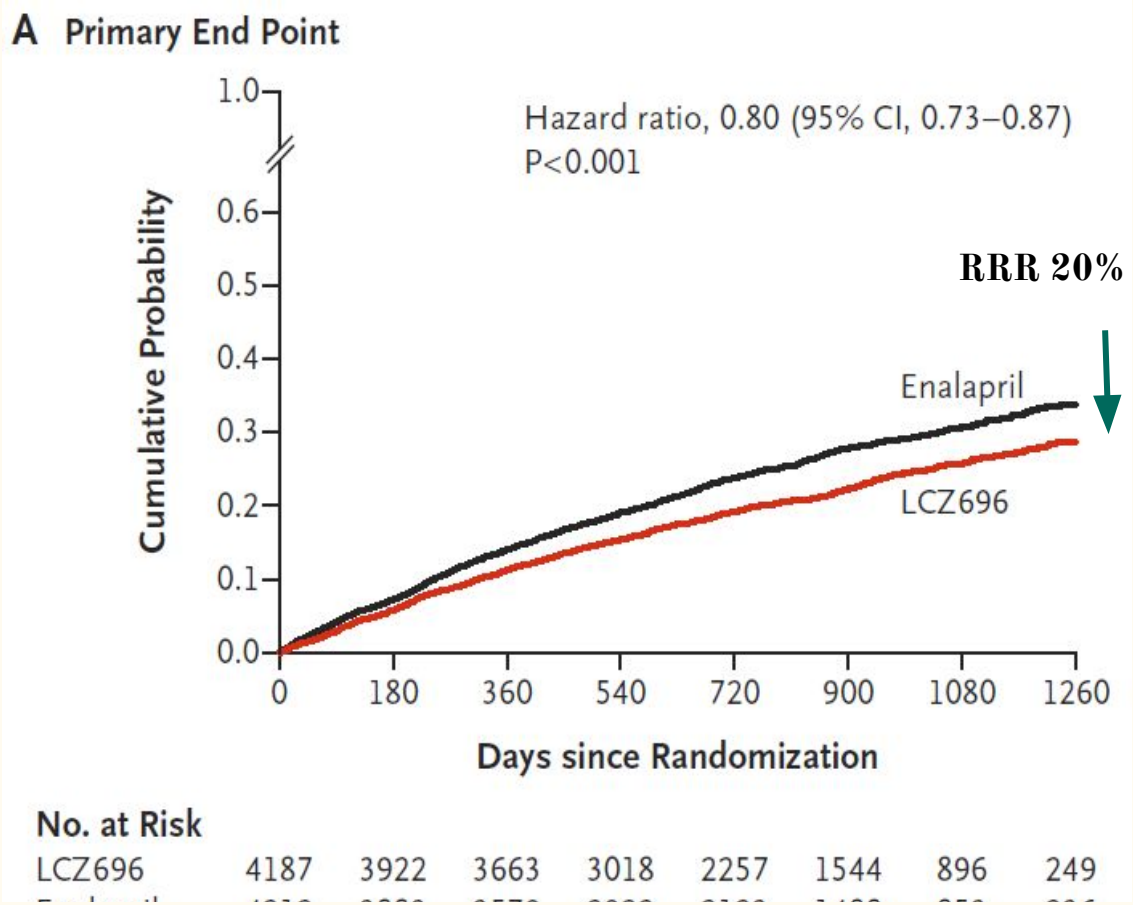
PARADIGM-HF

P	Patients with HF NYHA class II-IV with EF ≤40%
I	LCZ696 200 mg twice daily (Sacubitril 97mg/ Valsartan 103 mg twice daily)
C	Enalapril 10 mg twice daily
O	Composite of death from cardiovascular causes or hospitalization for heart failure

PARADIGM-HF


SINGLE-BLIND RUN-IN PERIOD†
(6 to 8 weeks)
MEDIAN EXPOSURE: 15 DAYS (N=10,513)
MEDIAN EXPOSURE: 29 DAYS (N=9419)
Enalapril 10 mg twice daily
ENTRESTO 49/51 mg twice daily
ENTRESTO 97/103 mg twice daily
DOUBLE-BLIND PERIOD‡
(Duration was event-driven; median follow-up duration was 27 months)
(1:1 RANDOMIZATION)
ENTRESTO 97/103 mg twice daily N=4209
Enalapril 10 mg twice daily N=4233

Primary outcome: CV mortality or first hospitalization for HF



Entresto vs enalapril:
21.8% vs 26.5%,
p<0.001

ARR: 4.7%
NNT: 21

PARADIGM-HF: Outcomes

Efficacy

- 3.2% ARR in CV death : NNT 31
- 3% ARR in first hospitalization : NNT 33
- 2.3% ARR in death from any cause: NNT 44

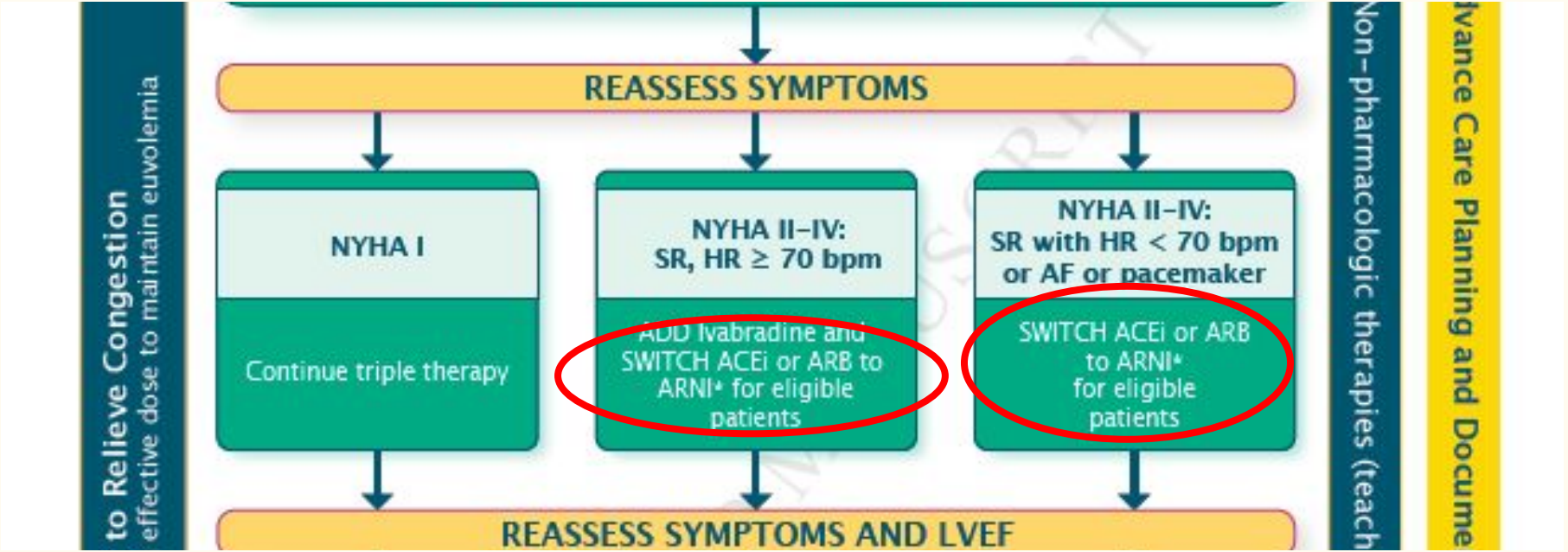
All statistically significant

PARADIGM-HF: Outcomes

Safety

- Less likely to be discontinued due to adverse event (10.7% vs 12.3%, p=0.03)
- Less likely to cause cough (11.3% vs 14.3%), hyperkalemia (4.3% vs 5.6%) or renal impairment (3.3% vs 4.5%, all $p<0.05$)
- More likely to cause symptomatic hypotension
  - Mean SBP at 8 months 3.2 mmHg lower in Entresto group

When do we use it?



When do we use it?

CCS Guidelines:

- an ARNI should be used **in place of an ACEi or ARB, in patients with HFrEF NYHA Class II to IV, who remain symptomatic despite treatment with maximum tolerated doses of ACEI/ARB + BB + MRA**

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Checklist

☑ Ejection fraction $<40\%$

☑ NYHA Class II or III

☑BP $\geq$ 100 mm Hg

☑ eGFR $\geq$ 30 ml/min

☑ Potassium $<$ 5.2 mmol/L

☑ ACEi/ARB, BB, MRA at max tolerated dose

Entresto (LCZ696)- Supplied

Low dose	Moderate dose	High (target) dose
24mg/26mg Sacubitril/Valsartan aka 50mg	**49mg/51mg** Sacubitril/Valsartan aka 100mg	**97mg/103mg** Sacubitril/Valsartan aka 200mg

103mg of valsartan in Entresto = **160mg of valsartan in Diovan**

Entresto (LCZ696)- Dosing

<table>
<tr><th colspan="2">Baseline</th><th>Initial Dose</th><th>Titration</th></tr>
<tr><td colspan="2">Higher dose of RAAS inhibitor</td><td rowspan="3">49/51mg BID</td><td rowspan="3">Increase to target 97/103mg BID over 2-4 weeks</td></tr>
<tr><td>ACEI</td><td>ARB</td></tr>
<tr><td>Enalapril ≥10mg/d
lisinopril ≥10mg/d
perindopril ≥4mg/d
ramipril ≥5 mg/d</td><td>candesartan ≥16mg/d
irbesartan ≥150 mg/d
losartan ≥50 mg/d
olmesartan ≥10 mg/d
telmisartan ≥40 mg/d
valsartan ≥160 mg/d</td></tr>
<tr><td colspan="2">Lower dose of RAAS inhibitor, higher risk of hypotension (low BP, > 75yrs poor renal function), or moderate hepatic impairment</td><td>24/26mg BID</td><td>Increase to target 97/103mg over 6 weeks</td></tr>
</table>

Entresto (LCZ696)

Switching:

From ACEI → 

↑ Risk of angioedema

Stop ACEI 36 hours prior to first dose of Entresto

From ARB → ✓

Initiate Entresto at the time the next dose is due

Safety & Precautions

- **Contraindications:** hx of angioedema
- **Adverse effects:** hypotension, hyperkalemia, dizziness, renal impairment, angioedema, may increase statin levels, alzheimers?
- **Monitor:** K+, SCr, BP 1 week after initiation, after each dose increase and with each practitioner visit

Safety & Precautions

- **Drug interactions:**
    - ACE/ARB, aliskiren (RAAS), potassium sparing diuretics, trimethoprim, K supplements (↑ K), NSAIDs (↑ SCr), lithium (lithium toxicity), statins? (statin toxicity)

Safety & Precautions

- **Elevates BNP** levels- use NT pro BNP
- **Should not** be initiated in patients with acutely decompensated heart failure, or clinically-relevant ischemic events, such as acute myocardial or cerebral infarction

Coverage

- **Entresto cards**
  - Covers cost of prescription

Welcome to the Entresto™ Advantage Patient Support Program

To help you get started on Entresto™, Novartis is pleased to provide you with the Entresto™ Advantage Patient Support Program that provides financial assistance towards your Entresto™ therapy. This program will supplement your coverage up to the total cost of your Entresto™ prescription.

Present Your Card
Present your Entresto™ Advantage Patient Support card and prescription to your pharmacist.

Keep Your Card
Bring your card to all future pharmacy visits. Expiration of the Entresto™ Advantage Patient Support Program will be at manufacturer's discretion.

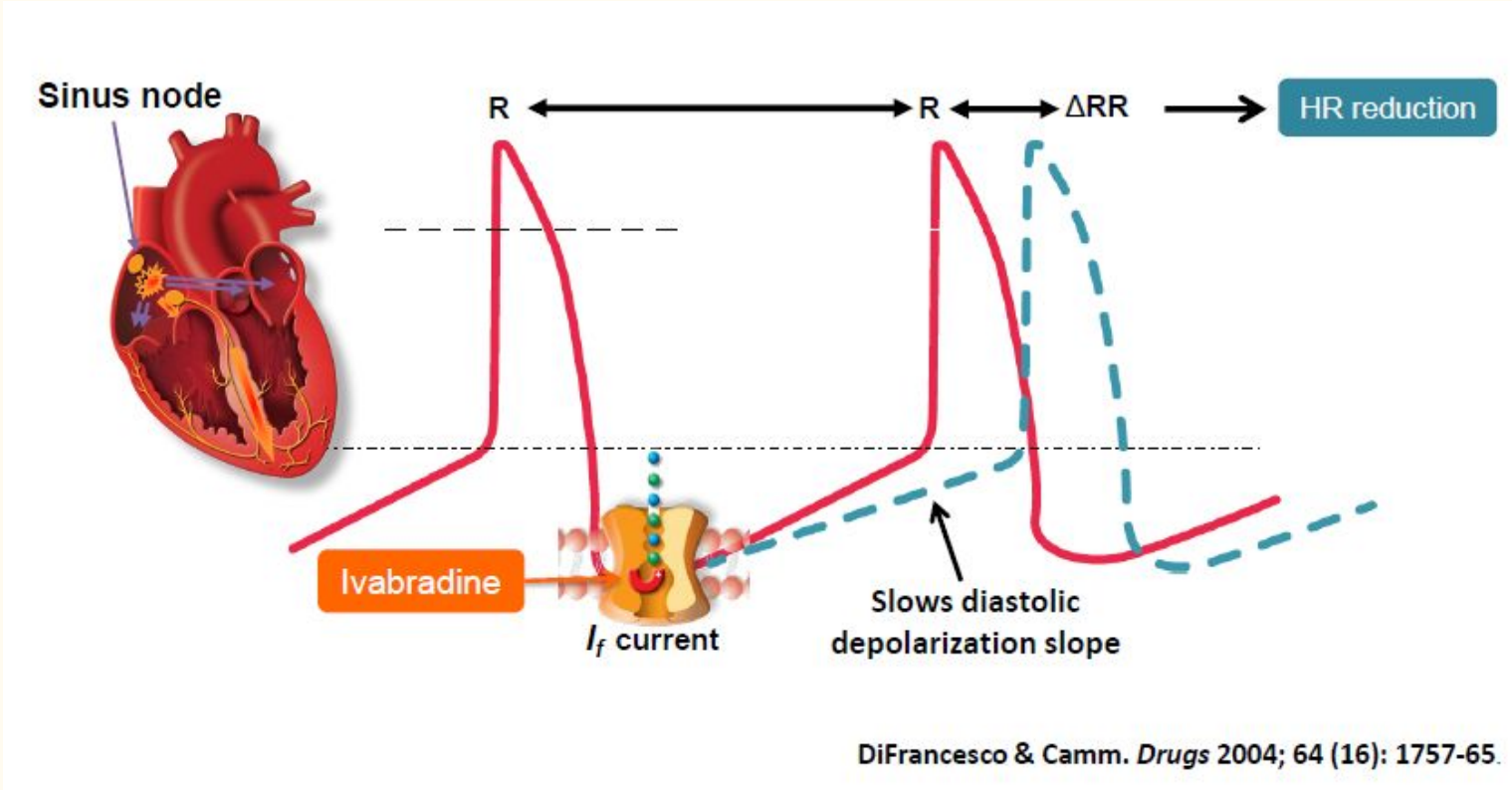
Please Remember to Keep Your Card

Coverage

- **Recently added to NB formulary : Special Authorization**
- NYHA class II or III HF who meet the following criteria:
  - LVEF $< 40\%$.
  - NYHA class II to III symptoms despite at least four weeks of treatment with a stable dose of ACEI or ARB and BB and AA
  - BNP $\geq$150 pg/mL or NT-proBNP $\geq$600 pg/mL.

F-Channel Inhibitors

Ivabradine (Lancora™)



Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

Lancet 2010; 376: 875–85
Published Online
August 29, 2010
DOI:10.1016/S0140-6736(10)61198-1

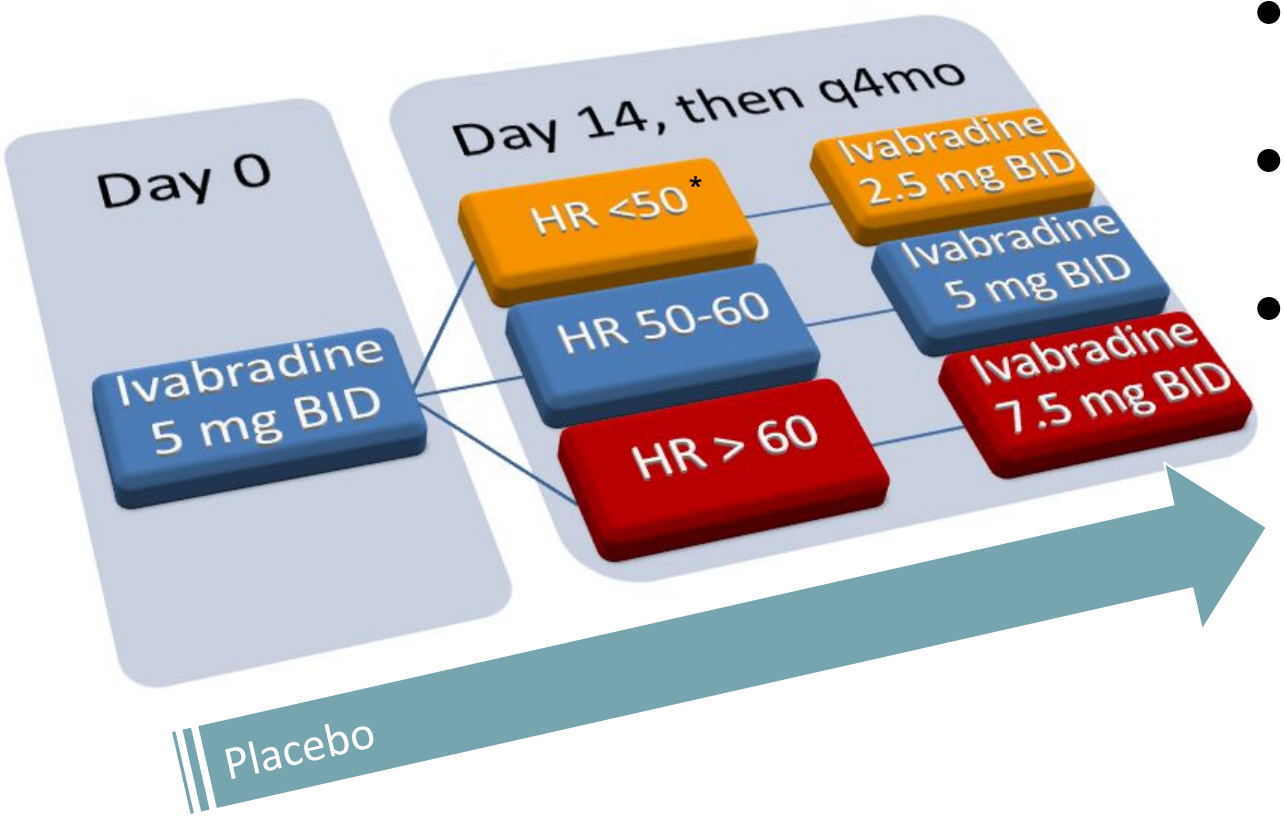
Summary

Background Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

SHIFT 2010

P	Adults in sinus rhythm, with resting HR ≥70 bpm, LVEF ≤ 35%, stable symptomatic chronic HF (NYHA II-IV) for ≥ 4 wk, HF hospitalization within 12 mo, and on guideline-directed therapy (ACE/ARB, BB, **+/-** aldosterone antagonist)
I	**Ivabradine 5 mg BID/ 7.5 mg BID/ 2.5 mg BID**
C	Placebo
O	CV death or HF hospitalization

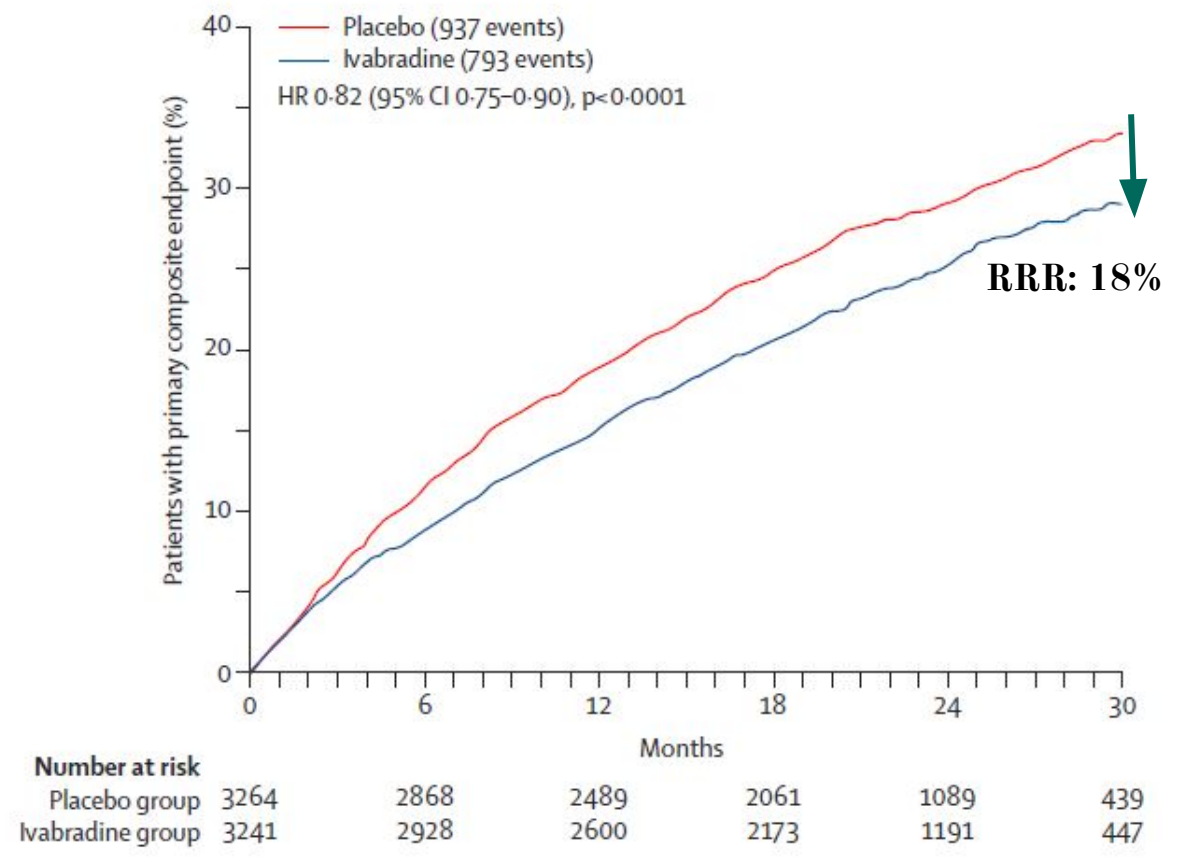
SHIFT Study Design



- Blinding & random allocation
- Median follow up 22.9 mo
- Assessed **resting** heart rate at 2 weeks, then every 4 months, which guided dose adjustments.

*HR in bpm

Primary Outcome: CV mortality or HF hospitalization



Ivabradine vs placebo:
24.5% vs 28.7%, $p<0.0001$

ARR: 5%
NNT: 20

Results

2º endpoints (ivabradine vs placebo)

- 1 % ARR in **CV mortality**: NNT 100
- 5% ARR in **Hospital Admission for HF:** NNT 20
- 2 % ARR in **Death from HF**: NNT 50
- 4% ARR in **All-cause hospital admissions:** NNT 25

Statistically significant

*HR was 8 bpm lower in ivabradine group at end of study

Subgroup Analysis

Patients receiving $\geq 50\%$ target beta blocker dose (56% in each group)

- **Primary endpoint and secondary mortality endpoints:** not significantly reduced
- **HF hospital admissions:** significantly reduced by 19%

SHIFT

Adverse Events

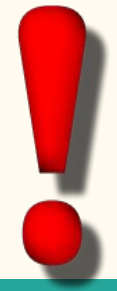
- Symptomatic bradycardia (5%)
- Asymptomatic bradycardia (6%)
- Atrial Fibrillation (9%)*
- Visual changes (3%)

Fewer all serious adverse events found in study group

*not statistically significant

Ivabradine(Lancora) Safety & Precautions

- **Contraindications:** acute HF, BP <90/50, resting HR <60 bpm, hepatic impairment, pacemaker, prolonged QT
- **Adverse effects:** bradycardia, AFib, visual changes, vertigo, heart block, ventricular tachycardia*, hypotension*, venticular fibrillation*, torsades de pointes*
- **Drug interactions:** strong and moderate CYP3A4 inhibitors, CYP3A4 inducers, QTc prolonging agents, K^+ depleting diuretics, amiodarone, simvastatin



**Post-Market/Case Reports (<1%)*

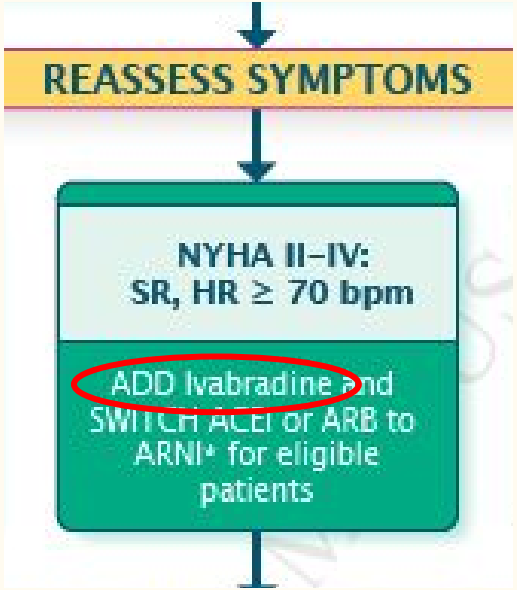
Safety & Precautions, cont'd

- No safety data for CrCl $<$15mL/min
- Pregnancy and breastfeedings risks cannot be ruled out
- Limited data in patients with cardiac devices (ICD or CRT). Caution and close cardiac monitoring is recommended.

When do we use it?

CCS Guidelines:

- Ivabradine should be considered in patients with HFrEF who:
  - Are symptomatic despite treatment with appropriate doses of ACEi + BB + MRA
  - Have a resting HR > 70 bpm,
  - Are in sinus rhythm
  - Had a prior HF hospitalization within 12 months



Administration & Dosing

- BID with meals
- Initiate at 5 mg BID. Titrate to target dose of 7.5 mg BID (max dose) as long as tolerated, and not to a specific HR
- Start ivabradine at the lowest dose in patients > 75years of age (e.g. 2.5mg po BID).
- Discontinuation of treatment should be considered if despite use of the highest dose (7.5 mg BID) **for several months**, there has been **no clear decrease** in the patient's resting heart rate.

Ivabradine(Lancora) Coverage

- Currently not covered by NBPDP
- Cost per day is approximately $2.50

Patient Case

ID
- 68 year old male

CC
- Increasing SOBOE

PMHx
- HF-rEF x 5 years, NYHA II
- COPD

Physical Exam
- BP 110/60 mmHG
- HR 72 bpm
- Minimal pedal edema

Labs
-Na 138, K 4.2, SCr 86mmol/l (CrCl 61ml/min), NT-proBNP 2480 pg/ml

Diagnostic tests
-LVEF: 35%

Medications:
- Bisoprolol 10 mg daily
- Telmisartan 80 mg daily
- Spironolactone 25 mg daily
- Furosemide 40mg daily

What is your next step?

A. Start sacubitril/valsartan 24mg/26mg
B. Start ivabradine 7.5mg BID
C. Change spironolactone to eplerenone
D. Start hydralazine/nitrates

Option

A. Start low dose Entresto

- BP >100
- K < 5.2
- eGFR > 30ml/min
- on stable doses on ARB, BB and MRA

Summary : Entresto and Ivabradine

Both medications should only be considered after standard triple therapy has been completed with ACEi + BB + MRB

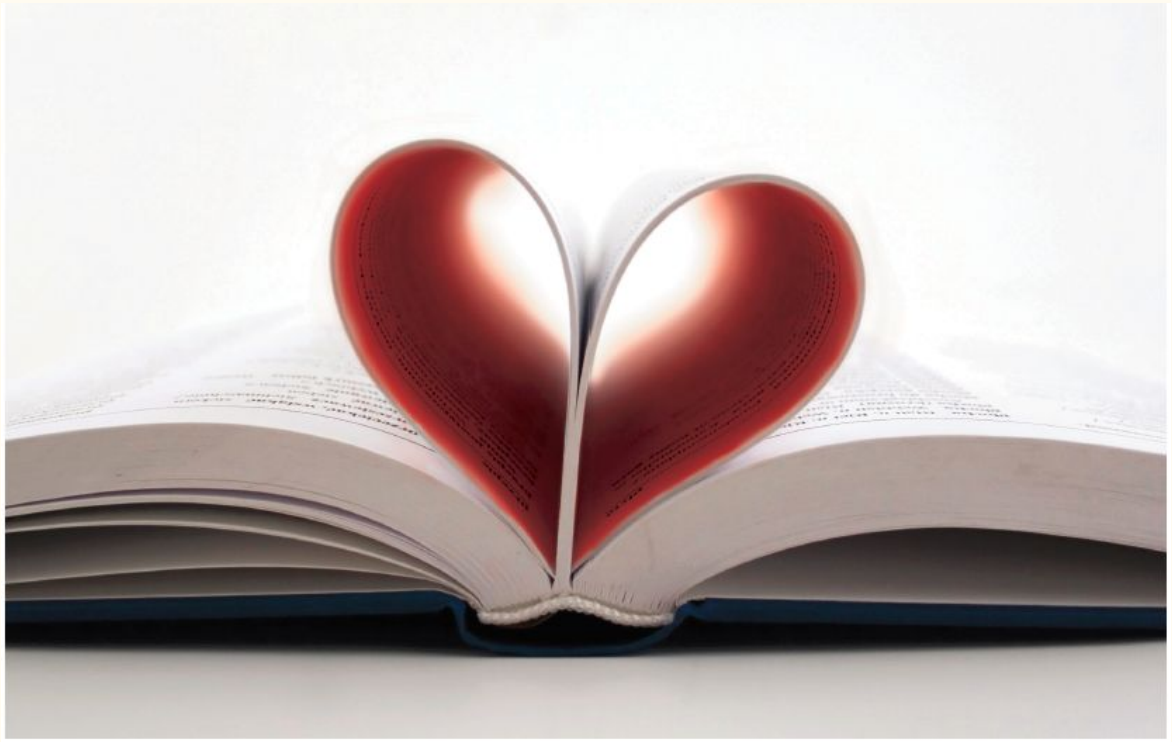
Entresto

- **Limited by BP and hyperkalemia**
  - BP $\geq$ 100 mmHg
  - K+ $<$ 5.2
- Reduced CV death, hospitalization for HF and all cause mortality

Ivabradine

- **Limited by HR**
  - CCS: $>$ 70 bpm
- Reduced death from HF, hospitalization for HF, and all cause-hospitalization

Thank You



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- Truven Health 2017: Micromedex.[Accessed September 2017]

LANCORA™ dosing recommendations

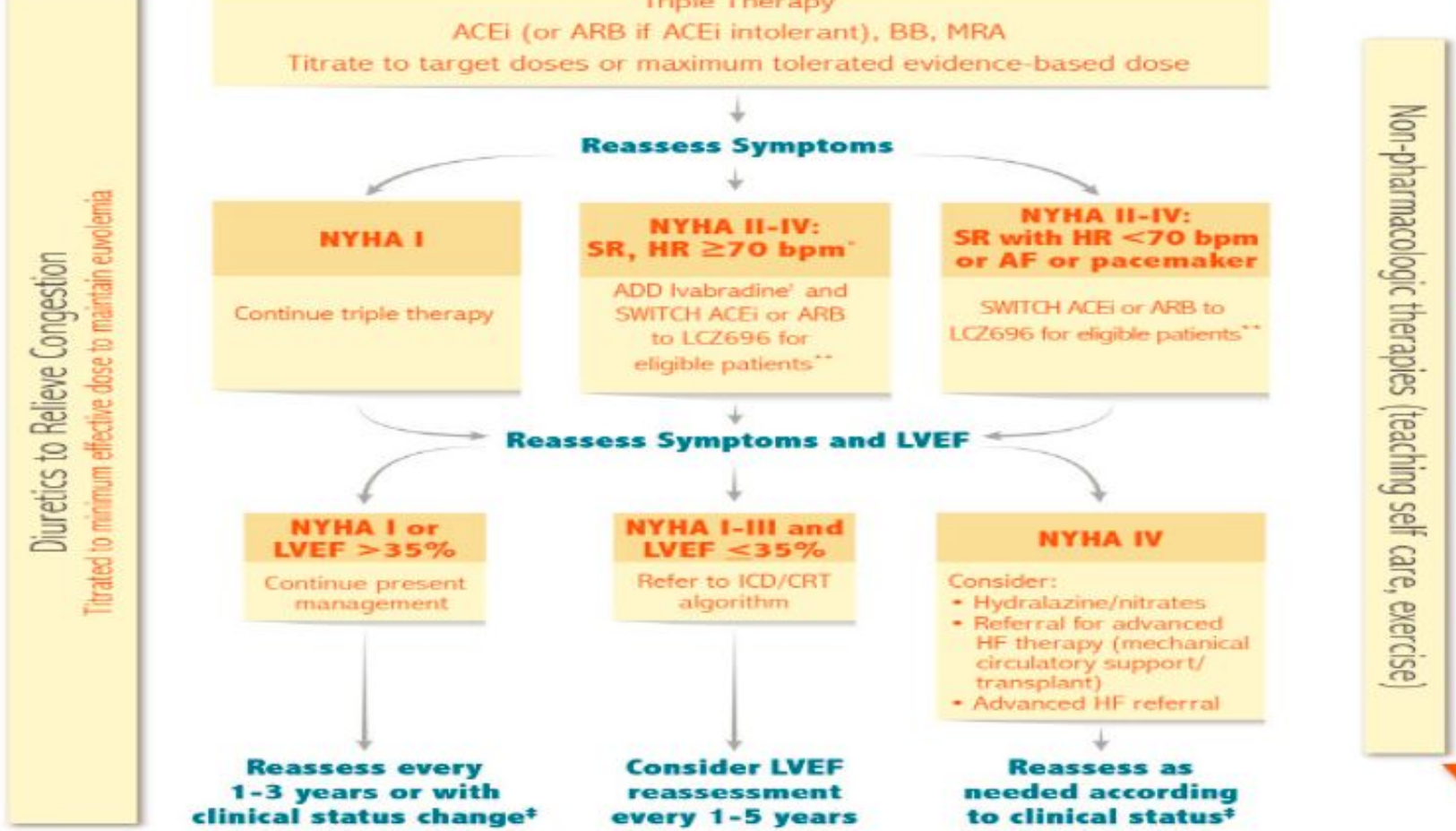
Recommended dose & dosage adjustment

Initiation and titration		Titration schedule designed for ease of use	
Recommended starting dose: **5 mg BID**	**After 2 weeks:** Review dose and, depending on heart rate, **adjust according to the following information:**	Persistently at or above 60 bpm	Increase dose to the next higher dose (Maximum dose 7.5 mg BID)
		Persistently between 50 bpm and 60 bpm	Maintain dose
		Persistently below 50 bpm or symptoms related to bradycardia*	Decrease dose to the next lower dose (Minimum dose 2.5 mg† BID)

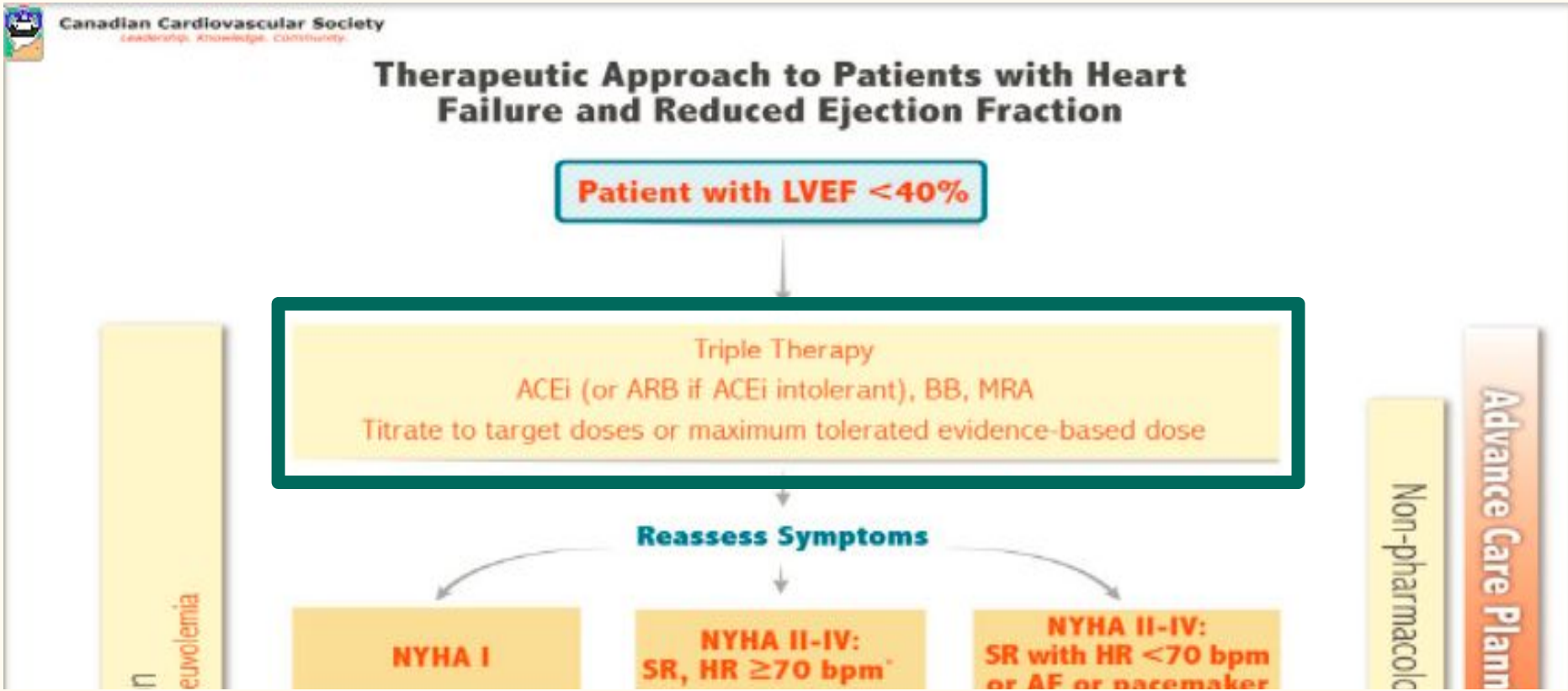
*Such as dizziness, fatigue or hypotension
†Half of the 5-mg tablet

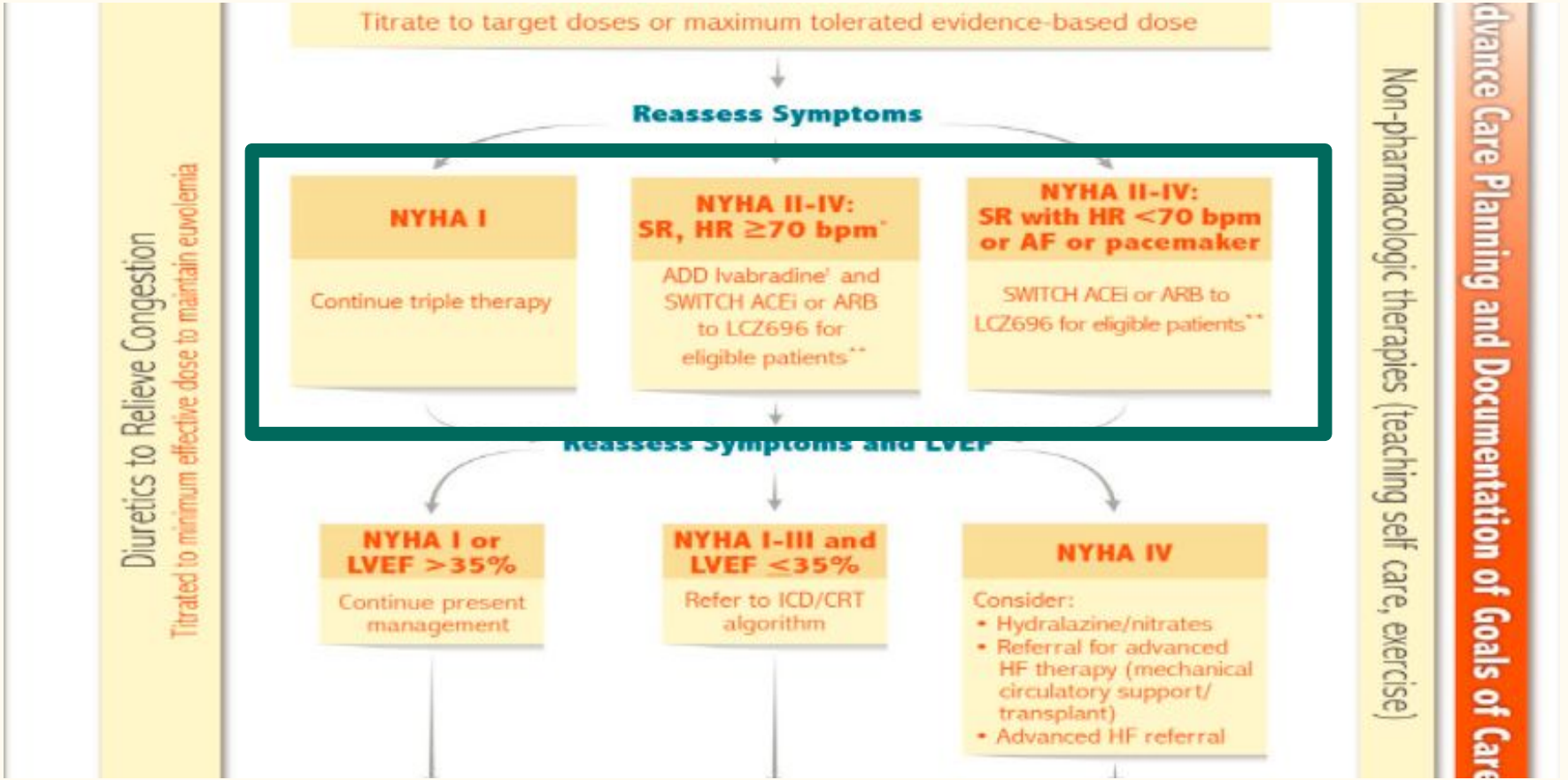
- Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening **during meals.**
- Treatment must be **discontinued** if heart rates **below 50 bpm or symptoms of bradycardia** persist. No rebound effect was observed after abrupt withdrawal of ivabradine.

Lancora (ivabradine) product monograph; Dec .2016.



*Pending Health Canada approval
†Ivabradine may be added when available in Canada
**LCZ696, when available in Canada, will replace ACEi or ARB in patients with elevated NP or recent hospitalization (BNP >150pg/ml or NT-pro-BNP >600 pg/ml)
‡Refer to Table 4


Canadian Cardiovascular Society
Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction
Patient with LVEF <40%
Triple Therapy
ACEi (or ARB if ACEi intolerant), BB, MRA
Titrate to target doses or maximum tolerated evidence-based dose
Reassess Symptoms
NYHA I
NYHA II-IV:
SR, HR ≥70 bpm
NYHA II-IV:
SR with HR <70 bpm
Non-pharmacolo
Advance Care Plann


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 LCZ696 for eligible patients**
NYHA II-IV: SR with HR <70 bpm or AF or pacemaker
SWITCH ACEi or ARB to LCZ696 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)
• Advanced HF referral
Diuretics to Relieve Congestion
Titrated to minimum effective dose to maintain euvolemia
Non-pharmacologic therapies (teaching self care, exercise)
dvance Care Planning and Documentation of Goals of Care