2017 Canadian Cardiovascular Society Heart Failure Guideline

A Preview

Gordon Moe, MSC, MD, FRCP(C), FACC, FAHA
Dr. Gordon Moe – Presenter
Topic: CCS 2017 HF guidelines update

Relationships with commercial interests:

- Grants/Research Support: Novartis, Servier
- Speakers Bureau/Honoraria: Novartis, Servier
- Consulting Fees: Novartis, Servier, Pfizer
Disclaimer

These guidelines are not yet published; the recommendations are therefore still considered preliminary.
Objectives

1. Process of development of guideline
2. Scope of coverage of 2017 guidelines
3. Selected topics for discussion, recommendations and practical applications
Objectives

1. Process of guideline development
2. Scope of coverage
3. Selected topics and recommendations and practical applications
2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure

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Process of Development

- The primary panelists were principally responsible for the document, with input from secondary panelists and external content experts where needed.
- The constitution, roles of panels, systematic review strategy, and methods for formulating the recommendations are described on www.ccs.ca.
SPECIAL ARTICLE

Canadian Journal of Cardiology 29 (2013) 168–181

Society Guidelines

The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Acute and Chronic Heart Failure

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a Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; b St Michael’s Hospital, Toronto, Ontario, Canada;
Objectives

1. Process of development

2. Scope of coverage of the 2017 Guideline

3. Selected topics and recommendations
Scope of 2017 Heart Failure Guideline

1. Introduction
2. Definition of heart failure
3. Prognosis of risk scores
4. Prevention of heart failure and asymptomatic left ventricular (LV) dysfunction
5. Diagnosis of heart failure
6. Biomarkers/natriuretic peptides
7. Treatment

- Chronic heart failure
  - Heart failure (HF) with reduced ejection fraction (EF) (HFrEF) management
  - HF with preserved EF (HFpEF) management
  - Implantable cardiac devices
  - Advanced HF management strategies
  - Mechanical circulatory support
  - Exercise and rehabilitation
  - Important non-pharmacological and non-device options

- Cardiovascular co-morbidities
  - Atrial fibrillation
  - Coronary artery disease and revascularization
  - Right heart failure
Scope of 2017 Guideline (continued)

7. Treatment

– Non-cardiovascular co-morbidities
  • Anemia and iron deficiency
  • Diabetes
  • Cardiorenal syndrome
  • Sleep apnea

– Acute heart failure

– Special circumstances
  • Cardiomyopathies
  • Ethnicity
  • Pregnancy
  • Cardio-oncology and heart failure
  • Myocarditis
Scope of 2017 Guideline (continued)

8. Quality assurance/improvement
9. Gaps in evidence and ongoing trials
Objectives

1. Process of development
2. Scope of coverage
3. Selected topics for discussion, recommendations and practical applications for clinicians
Scope of 2017 Heart Failure Guideline

1. Introduction

2. Definition of heart failure

3. Prognosis of risk scores

4. Prevention of heart failure and asymptomatic left ventricular (LV) dysfunction

5. Diagnosis of heart failure

6. Biomarkers/natriuretic peptides
Ejection Fraction Terminology

- HF with preserved ejection fraction (HF-pEF): LVEF $\geq 50\%$;
- HF with a mid-range ejection fraction (HF-mEF): LVEF 41-49\%;
- HF with a reduced ejection fraction (HF-rEF): LVEF $\leq 40\%$.
- HF with “recovered” ejection fraction: LVEF previously $\leq 40\%$, but has increased to $>40\%$. *

Objectives

7. Treatment

– Chronic heart failure

• HFrEF management
  • HFrEF management
  • Implantable cardiac devices
  • Advanced heart failure management strategies
  • Mechanical circulatory support
  • Exercise and rehabilitation
  • Important non-pharmaceutical and non-device options

– Cardiovascular co-morbidities
  • Atrial fibrillation
  • Coronary artery disease and revascularization
  • Right heart failure

– Non-cardiovascular co-morbidities
  • Anemia and iron deficiency
  • Diabetes
  • Cardiometabolic syndrome
HFrEF: Where are we today?

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CRT, cardiac resynchronisation therapy; HF-REF, heart failure with reduced ejection fraction; H-ISDN, hydralazine/isosorbide dinitrate; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid (aldosterone) receptor antagonist; VAD, ventricular assist device

McMurray et al. Eur Heart J 2012;33:1787–1847
Angiotensin Receptor Neprilysin Inhibition (ARNI)

LCZ696, Entresto

- **Natriuretic peptides**
  - BK, ADM
  - Subs-P, VIP, CGRP

- **Angiotensin II**
  - **Neprilysin**
    - Vasodilation
    - Natriuresis
    - Diuresis
    - Inhibition of pathologic growth/fibrosis
  - **Degradation products**
  - **AT₁ Receptor**
    - Vasoconstriction
    - Sodium/water retention
    - Fibrosis/hypertrophy

- **LCZ696**
  - Sacubitril
  - Valsartan
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
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Inclusion criteria LVEF < 40%
Age 64 yr  Female 22%  NYHA class II 70%, III 24%
LVEF 0.29. SBP 122 mmHg. BNP 253 pg/ml, NT-proBNP 1613 pg/ml
eGFR 68 ml/min/1.73m², AF 37%. Prior HF hosp. 62%.
Diuretic 80%, Digitalis 30%, β-blocker 93%, MRA 56%.
ICD 15%, CRT 7%.

N=10,513  Single-blind period

Enalapril 5-10 mg bid  LCZ 100 mg bid  LCZ 200 mg bid
1-2 weeks  1-2 weeks  2 weeks

Double-blind period

LCZ696 200 mg BID (n=4187)
N = 8442 (1:1 randomization)
Enalapril 10 mg BID (n=4212)

Outcome driven (CV death): median follow-up = 27 months

Prior ACEi/ARB use were discontinued
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Primary Composite Outcome
HR: 0.80 (0.73, 0.87) \( p = 0.0000004 \)

Death from CV causes 20% risk reduction
HF hospitalization 21% risk reduction

Death from CV causes

HF hospitalization

McMurray, Packer et al NEJM 2014
2017 CCS Recommendation

Angiotensin Receptor- Neprilysin Inhibitor (ARNI)

• **Recommendation:** We recommend that an ARNI be used in place of an ACEi or ARB, in patients with HFrEF, who remain symptomatic, despite treatment with appropriate doses of GDMT, to decrease CV death, HF hospitalizations, and symptoms (Strong Recommendation, High Quality Evidence).

• **Values and preferences:** This recommendation places high value on medications proven in large trials to reduce mortality, HF re-hospitalization, and symptoms. It also considers the health economic implications of new medications.
2017 Recommendations (continued)

Practical tips:

• Drug tolerability, side effects and laboratory monitoring with use of ARNI similar to ACEi or ARB.

• The PARADIGM trial excluded patients with a serum K >5.2mmol/l, an eGFR < 30mL/min and symptomatic hypotension with a systolic blood pressure of <100 mmHg.
2017 Recommendations (continued)

Practical tips (continued):

• When switching from an ACEi to an ARNI, a washout period of at least 36 hours is required to decrease the risk of angioedema. No washout period is required for conversion between ARNI and ARBs.

• ARNI should not be used in anyone with a history of angioedema.
# Valsartan/sacubitril dosing and titration

<table>
<thead>
<tr>
<th><strong>Higher dose of RAAS inhibitor</strong></th>
<th><strong>Initial Dose</strong></th>
<th><strong>Titration</strong></th>
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<tbody>
<tr>
<td><strong>ACEI</strong></td>
<td></td>
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</tr>
<tr>
<td>Enalapril ≥10mg/d</td>
<td></td>
<td></td>
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<tr>
<td>Lisinopril ≥10mg/d</td>
<td></td>
<td></td>
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<tr>
<td>Perindopril ≥4mg/d</td>
<td></td>
<td></td>
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<tr>
<td>Ramipril ≥5 mg/d</td>
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<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan ≥16mg/d</td>
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<tr>
<td>Irbesartan ≥150 mg/d</td>
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<td></td>
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<tr>
<td>Losartan ≥50 mg/d</td>
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<tr>
<td>Olmesartan ≥10 mg/d</td>
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<td></td>
</tr>
<tr>
<td>Telmisartan ≥40 mg/d</td>
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<td></td>
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<tr>
<td>Valsartan ≥160 mg/d</td>
<td><strong>100 mg PO BID</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Lower dose of RAAS inhibitor</strong></td>
<td><strong>50 - 100mg PO BID</strong></td>
<td><strong>Over 6 weeks, increase to target 200 mg PO BID</strong></td>
</tr>
<tr>
<td>Higher risk of hypotension (eg. low baseline SBP, poor renal function)</td>
<td><strong>50mg PO BID</strong></td>
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</tr>
</tbody>
</table>

*Health Canada labeled dose of 50 mg is 24.3 mg sacubitril/25.7 mg valsartan, 100 mg BID is 48.6 mg sacubitril/51.4 mg valsartan and 200 mg is 97.2 mg sacubitril/102.8 mg valsartan.*
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.

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.

Study Design

Sinus rhythm, HR ≥70 bpm, LVEF ≤35%

- Ivabradine 5 mg bid
- Matching placebo, bid
- Every 4 months
- D0, D14, D28, M4
- Ivabradine 7.5/5/2.5 mg bid according to HR

Screening 7 to 30 days

3.5 years

CV mortality and HF hospitalization benefits (primary endpoint)

HR = 0.82 (0.75–0.90)  
p<0.0001

NNT: 26

2017 Recommendation

Ivabradine

• **Recommendation:** We recommend that ivabradine be considered in patients with HFrEF, 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 CV death and HF hospitalization (Strong Recommendation, Moderate Quality Evidence).

• **Values and preferences:** High value is placed on the improvement of CV death and HF hospitalizations as adjunctive therapy to standard HF treatments in a selected HF population. The health economic implications are unknown. **Differing criteria** for HR eligibility have been approved by various regulatory authorities ranging from 70 to 77 bpm with the trial entry criteria of 70 bpm (FDA HR >70 bpm; Health Canada HR > 77 bpm)
2017 Recommendations (continued)

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 blood pressure or myocardial contractility.
Is There a Role for Ivabradine in the Contemporary Management of Patients with Chronic Heart Failure in Academic and Community Heart Failure Clinics in Canada?

Sherryn Roth · Carlos Fernando · Sadia Azeem · Gordon W. Moe
## Potential Candidate for Ivabradine

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Academic (n=491)</th>
<th>Community (n=605)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt;35%</td>
<td>172 (35%)</td>
<td>184 (30%)</td>
<td>0.1045</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>279 (57%)</td>
<td>366 (61%)</td>
<td>0.2191</td>
</tr>
<tr>
<td>HR ≥ 70 bpm</td>
<td>205 (42%)</td>
<td>317 (52%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>“SHIFT”-like</td>
<td>41 (8%)</td>
<td>71 (12%)</td>
<td>0.0658</td>
</tr>
</tbody>
</table>
Objectives

1. Process of development of guideline
2. Scope of coverage
3. Selected topics, recommendations and practical applications by case illustrations
Case 1 (M.C.)

• 66 year old male
• Diagnosed HF-rEF for 13 years
• Type II diabetes, COPD, normal coronary arteries
• NYHA class I to II symptom from dyspnea
• Last LVEF 39% 2 years ago, felt not to be a candidate for 1° device
• BP 93/56 mmHg, HR 78 bpm (by auscultation)
• Minimal ankle edema, clear chest
• Holter monitor: frequent VPBs
• Na 142; K 4.5; Cr 150; eGFR 38; NT-proBNP 870
• Most recent echocardiographic LVEF 28%
Case 1 (continued)

Medications

- Candesartan 32 mg daily
- Bisoprolol 10 mg daily
- Spironolactone 25 mg daily
- ECASA 81 mg daily
- Linagliptin/Metformin 2.5/1000 mg twice daily
- Ferosemide 40 mg daily
- Started by EP on amiodarone for VPBs believed to cause symptoms..
Case 1 (continued)
Case 1 (continued)

Questions to we asked regarding next Rx

1. Ivabradine vs. sacubitril/valsartan first?

2. When to initiate therapy, before or after ICD implantation?

3. Is concomitant use of amiodarone safe?
Case 1 (continued)

- Started on ivabradine 5 mg twice daily
- Consented for ICD

- Clinic 2 weeks later, asymptomatic, BP 95/60 mmHg, HR 55 bpm, ivabradine maintained at 5 mg twice daily
- Amiodarone treatment was maintained
- ICD implanted
Case 1 (continued)

- 6 weeks later, BP 97/65 mmHg
- Creatinine 148, eGFR 39; NT-proBNP 750
- Started on sacubitril/valsartan 24.3 mg/25.7 mg twice daily
Case 1 (continued)

Reasons for what we did:

1. Sinus rhythm, HR > 77 bpm, suitable for Ivabradine
2. Low LVEF (<35%) suitable for Ivabradine and ARNI
3. Borderline BP and renal function, less suitable for ARNI, more suitable for Ivabradine
Case 2 (J.J.)

- 85 years old male
- Diagnosed HF-rEF for $\approx 5$ years
- CABG in 1996, PCI in 2010
- *Paroxysmal* atrial fibrillation, *rare* episodes
- NYHA class II symptom from dyspnea and fatigue
- Recent LVEF 35% MUGA
- $2^\circ$ ICD in 2010 for VT

- BP 145/67 mmHg, HR 72 bpm average (by auscultation)
- Mild ankle edema, chest was clear

- Na 140; K 4.3; Creatinine 120; eGFR 46; NT-proBNP 2390
Case 2 (continued)

Medications

- Bisoprolol 5 mg daily
- Eplerenone 25 mg daily
- Apixaban 5 mg twice daily
- Telmisartan 40 mg daily
- Furosemide 20 mg daily
- Rosuvastatin 40 mg daily
Case 2 (Continued)
Case 2 (continued)

Questions we asked regarding next Rx

1. Ivabradine vs. switching to sacubitril/valsartan?

2. When to initiate therapy, before or after CRT, or is he a candidate for CRT?
Case 2 (continued)

• Telmisartan switched to sacubitril/valsartan 49/51 mg twice daily
• Felt not a candidate for CRT because of borderline QRS (130 msec)

• See in clinic 3 weeks later, remained asymptomatic, BP 110/58 mmHg, HR 72 bpm; K 4.4, creatinine 135, eGFR 40, NT-proBNP 1890
• Sacubitril/valsartan increased to 98/102 mg twice daily
Case 2 (continued)

Reasons for what we did:

1. Relatively preserved kidney function and high BP (candidate for ARNI).
2. History of paroxysmal atrial fibrillation (not a candidate for Ivabradine)
3. 40% < LVEF > 35% (candidate for ARNI)
Objectives

8. Quality assurance/improvement

9. Gaps in evidence and ongoing trials
Gaps in Evidence

The panel identified several gaps in evidence that, when filled, will further aid in the diagnosis, prognosis, treatment or organization of care for patients with HF. These are not exhaustive and many research avenues should be pursued by the research community.

- What is the effect of utilizing a validated risk score in clinical practice?
- **Which therapies should be targeted for patients who present with HF-mrEF or HF-pEF, and which biomarkers should guide these choices?**
- What is the role of sacubitril/valsartan and other new therapies in *de novo* patients with HF?
Gaps in Evidence (continued)

• What are the implications of withdrawing therapy with limited or no efficacy in the current era of other therapies e.g. digoxin, statins, multivitamins?
• Which of the diabetes-related therapies should be used in patients with or without diabetes and HF?
• What role does dietary micro or macronutrients have on clinical outcomes for patients with HF?
• What is the role of anti-platelet agents (e.g. aspirin) or oral anti-coagulants in patients with sinus rhythm and HFrEF?
• Does genetic variability play a role in response to current therapy, and can this be personalized?
Gaps in Evidence (continued)

- Should all patients with HFrEF without a known etiology undergo genetic testing?
- What is the role of destination therapy LVADs in the context of changing medical and device therapy?
- Should patients with a non-ischemic etiology of HF receive CRT alone rather than CRT-D?
- What is the role of bromocriptine, other HF-related therapies, and genetic testing in patients with PPCM?
• What is the role of existing and novel therapies in patients with severe renal dysfunction?

• Are there subgroup populations who would benefit from ultrafiltration?
Closing Remarks

1. 2017 CCS HF guideline is the most comprehensive guideline document to date.

2. Values and preferences as well as practical tips provide guidance to practicing clinicians.

3. Gaps in evidence remain, but they provide opportunities for ongoing and future research.
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards

Quality of evidence

– **High** (further research very unlikely to change confidence in the estimate of effect)
– **Moderate** (further research likely to have an important impact on confidence in the estimate of effect and may change the estimate)
– **Low** (further research very likely to have an important impact on confidence in the estimate of effect and likely to change the estimate)
– **Very Low** (estimate of the effect very uncertain).

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards

Grades of Recommendations

- **“Strong”** (desirable effects clearly outweigh undesirable effects or clearly do not),
- **“Weak”** (the desirable effects probably outweigh the undesirable effects).
- **“Conditional”** recommendations are used in instances where significant uncertainty remains for a variety of reasons or Health Canada approval of a drug or a device is not obtained.

Values and Preferences

Outline other considerations that weigh into a decision including resource use, equity, feasibility, and acceptability, cost and patient preferences.
Gaps in Evidence

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Gaps in Evidence (continued)

• What is the role of existing and novel therapies in patients with severe renal dysfunction?

• Are there subgroup populations who would benefit from ultrafiltration?
**LANCORA™ dosing recommendations**

**Recommended dose & dosage adjustment**

**Initiation and titration**

**Recommended starting dose:**
- 5 mg BID

**After 2 weeks:**
- Review dose and, depending on heart rate, **adjust according to the following information:**

**Titration schedule designed for ease of use**

- **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.