GUIDELINE UPDATE AT THE HF UPDATE

May 11, 2018
Toronto
Disclosures

• **Eileen O’Meara**
  – Advisory / Honoraria: Novartis, Servier, Pfizer/BMS, Bayer
  – Clinical Trials: Novartis, Amgen, Astra-Zeneca, Bayer

• **Michael McDonald**
  – Advisory / Honoraria: Novartis, Servier
  – Clinical Trials: Novartis
# Primary and Secondary Panel Members

## Primary Panel Members

<table>
<thead>
<tr>
<th>Co-Chair</th>
<th>Co-Chair</th>
<th>Liaison</th>
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<tr>
<td>Eileen O’Meara</td>
<td>Micheal McDonald</td>
<td>Phyllis Billia</td>
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<td>Howard Abrams</td>
<td>Michael Chan</td>
<td>Anique Ducharme</td>
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<td>Nadia Giannetti</td>
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<td>Justin Ezekowitz</td>
<td>Adam Grzeslo</td>
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<td>George Heckman</td>
<td>Jonathan Howlett</td>
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<td>Sheri Koshman</td>
<td>Serge Lepage</td>
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<td>Robert McKelvie</td>
<td>Gordon Moe</td>
<td>Miroslaw Rajda</td>
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<td>Elizabeth Swiggum</td>
<td>Sean Virani</td>
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<td>Shelley Zieroth</td>
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## Secondary Panel Members

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<th>Co-Chair</th>
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<tr>
<td>Abdul Al-Hesayen</td>
<td>Alain Cohen-Solal</td>
<td>Michel D’Astous</td>
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<td>Sabe De</td>
<td>Estrellita Estrella-Holder</td>
<td>Stephen Fremes</td>
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<td>Lee Green</td>
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<td>Karen Harkness</td>
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<td>Adrian Hernandez</td>
<td>Simon Kouz</td>
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<td>Frederick Masoudi</td>
<td>Heather Ross</td>
<td>André Roussin</td>
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<td>Bruce Sussex</td>
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KT Initiatives – videos, iCCS, new e-guideline website, pocket guides, integrated living document
Process Overview

- 10 years’ worth of guidelines (2006-2015)
  - > 700 recommendations, practical tips, values and preferences

- Planned comprehensive guideline update including reappraisal of evidence and re-write of all topics
  - Topic review, evidence tables generated
  - Recommendations formulated, voted on by all primary panel members
  - GRADE standards applied
  - Collaboration with relevant other guideline committees where appropriate for endorsement
  - AF, CRT, Cardio-oncology
We’re not alone

The CCS HF Guideline:

• Provides Canadian context to care delivery
• Informs policy
• Is uniquely engaged in knowledge translation activities
• Strengthens the Canadian cardiovascular community

Society of Cardiology (ESC)
Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Piotr Ponikowski, Adriaan A. Voors, Stefan D. Anker, Héctor Bueno, John G. F. Cleland, Andrew J. S. Coats, Volkmar Falk, José Ramón González-Juanatey, Veli-Pekka Harjola, Ewa A. Jankowska ...

New(er) Issues

- Classification of HF
- Emergence of biomarkers
- Prevention of HF
- New drugs for HFrEF
- Evolving indications for CIEDs
- Management of comorbidities
- Identification of evidence gaps
2017 Comprehensive Update of CCS HF Guidelines

- Definitions
- Prognosis and Risk Scores
- Prevention of HF
- Diagnosis
- Biomarkers
2017 Comprehensive Update of CCS HF Guidelines

- Treatment
  - Chronic HF
  - Advanced HF
  - Comorbidities (AF, CAD, RHF, anemia, DM, renal, sleep apnea)
  - Other (cardiomyopathies, pregnancy, ethnicity, cardio-oncology)

- Community Management

- Quality Improvement

- Evidence Gaps
Objectives for this session

- What tests should I do?
  - Develop a clear approach to the diagnosis and etiology of HF

- Which drug and which device for which patient?
  - Optimize HF therapy considering the patient's profile
  - Discuss the role of novel and emerging drug therapies

- What do I do if my patients have advanced HF?
  - Identify patients with poor prognosis and determine appropriate next steps
Which investigation for which patient?
Etiology of HF

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

HFpEF (and HFmrEF)
LVEF ≤ 40%, up to 49%

Congenital Heart Disease

Percardial Disease

Further work-up and referral as appropriate

Common etiologies

Tachycardia
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

Family history of dilated CCM

Genetic referral?

Toxic agents

Alcohol
Amphetamines
Cocaine
Steroids
Chemotherapy
Heavy metals
Radiation Rx

PPCM
Pre-eclampsia
Gestational diabetes

Inflammatory / Infectious / Immune

Myocarditis
Sarcoidosis
Infectious myocarditis
Giant cell myocarditis
Lymphocytic
Auto immune diseases

Diabetes
Thyroid disease
Renal insufficiency
Pulmonary hypertension
Cushing’s disease

Metabolic

Thiamine deficiency
Hemochromatosis
Anemia

Nutritional

Genetic or hereditary

HCM
MRV
LV noncompaction
Hemochromatosis

Appropriate blood or urine testing and/or CMR as directed by history and physical exam and other findings

Genetics referral?

Hereditary / familial

Obtain further history as needed?
Scenario 1: 56 y.o. male with new onset HF

- M 56, admitted mid-April 2018 to referring center for severe global HF evolving for 1-2 months, NYHA III on transfer (April 25)
- Improving symptoms of OTP, PND with IV diuretics
- Hemodynamics stable, O2 2L/min with 95% saturation
- No chest pain
- Type II diabetes and hyperlipidemia
- No HTN
- Notion of LVEF at 40% in 2016
- S/P stent in Cx-marginal in 2014
Scenario 1: 56 y.o. male with new onset HF

- What else would you like to know on history?
- Family history?
- Alcohol consumption?
- Drug consumption?
- Viral symptoms?
- Meds?

IV Lasix 80mg tid
Ramipril 2.5mg bid
Spironolactone 25mg qd
B-blocker withdrawn on admission at ref. center
Scenario 1: 56 y.o. male with new onset HF

- ECG: SR 86 bpm, non specific repolarization abnormalities
- Normal kidney function (creatinine 65 umol/L, eGFR > 60)
- Glucose 7-8 mmol/L
- Hs-TnT 41-44 ng/L
- Hb 115, WBC, Platelets N
- TSH 9.85 mU/L
- Serum iron 3.7 umol/L, transferrin saturation 7%
- Ferritin 132 ug/L
- Albumine 24 g/L
Scenario 1: 56 y.o. male with new onset HF

- **Echocardiogram shows:**
  - LV 68mm/
  - LVEF 10%
  - Cardiac index 1.8L/min/m2 (no inotropes)
  - Moderate RV dysfunction
  - PAPs 48mmHg
  - LA: mild dilatation
  - Mild MR, TR ¾
  - CVP estimated 20mmHg
Scenario 1:
What is the likely cause of his heart failure with LVEF 10%?

1. Ischemic

2. Ischemic with some other cause likely

3. Non ischemic
Etiology of HF

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

- **HFrEF (and HFmrEF)**
  - LVEF ≤ 40%, up to 49%
  - Common etiologies
    - Tachyarrhythmia
    - Valve disease
    - Known or risk factors for CAD
      - CAD work-up
    - LVH
      - Hx of HTN?*

- **HFP EF**
  - LVEF ≥ 50%
  - Congenital Heart Disease
  - Pericardial Disease
  - Further work-up and referral as appropriate

- **Significant CAD (Ischemic)**
- **No Significant CAD**
- **Probable hypertensive HF / hypertensive cardiomyopathy**
Evaluating for Coronary Disease

**Angina or angina-equivalent symptoms?**

**YES**
- Is the patient a suitable risk for surgical revascularization?
  - **YES**
    - Coronary angiography
  - **NO**
    - Noninvasive rest and stress imaging according to local preference

**NO**
- Is the patient a suitable risk for surgical revascularization?
  - **YES**
    - Either a) noninvasive rest and stress imaging according to local preferences or b) directly to coronary angiography
  - **NO**
    - Is patient potential candidate for PCI?
      - **YES**
        - Noninvasive rest and stress imaging according to local preferences
      - **NO**
        - Medical therapy
Investigation

Recommendation

We recommend the choice of investigations should first be guided by careful history and physical examination and when clinical evidence suggests a possible cause and the planned test(s) result would be reasonably expected to lead to a change in clinical care (Strong Recommendation, Low Quality Evidence).
Coronary Angiogram shows…
Angiogram report

• Left main intermediary lesion
  • 40-50%

• LAD & Cx
  • Mid LAD 50-70% (at D2)
  • Mid Cx 50-70%
  • M2 70-90% in previous DES

• RCA
  • Proximal RCA 50-70%
Differential Diagnosis?

• More likely
  • Coronary disease/ischemic cardiomyopathy

• Less likely
  • Infectious/post infectious cardiomyopathy
  • Myocarditis
  • Systemic illness related
  • Infiltrative/storage disease
  • Endocrinopathy
  • Familial/genetic
Other etiology considerations

- Family history of dilated CMF
  - Toxic agents
    - Alcohol
    - Amphetamines
    - Cocaine
    - Steroids
    - Chemotherapy
    - Heavy metals
    - Radiation Rx
  - Pregnancy history
    - PPCM
    - Pre-eclampsia
    - Gestational diabetes
  - Inflammatory / Infectious / Immune
    - Myocarditis
    - Sarcoïdosis
    - Infectious
    - Hypereosinophilia
    - Giant cell
    - Lymphocytic
    - Auto-immune diseases
  - Metabolic
    - Diabetes
    - Thyroid disease
    - Adrenal insufficiency
    - Pheochromocytoma
    - Cushing's disease
  - Nutritional
    - Thiamine deficiency
    - Selenium deficiency
    - Marfan syndrome
    - Obesity
  - Infiltrative diseases
    - Amyloidosis
    - Glycogen storage disease
    - Fabry disease
  - Genetic or hereditary
    - HCM
    - ARVC
    - LV noncompaction
    - Hemochromatosis

- Genetics referral
- Hereditary / familial
- Obtain further history as needed

- Appropriate blood or urine testing and/or CMR as directed by history and physical exam and other findings
- Genetics referral

LESS COMMON
So... New onset HF. LVEF seems disproportionally low in relation to observed coronary lesions...

- PET-Rubidium/Persantine: Fix deficit in basal inferolateral and anterolateral was with good viability indices, as well as for the rest of the myocardium. LVEF ≈ 20%
- No deficit induced by persantine but the diffuse myocardial flow reduction could reflect balanced ischemia
- However, there was no transient dilatation of LV
- Nuclear med consultant agreed that a CMR might help us R/O other concomitant etiology.
Scenario 1:

- CMR shows: Severe biventricular systolic dysfunction with hypokinesis more marked in lateral and inferolateral walls where LGE is seen on at least 50% of the thickness at basal and mid-wall ➔ Suggests ischemic CMP with fibrosis in the Cx territory.

- Cardiac dysfunction indeed out of proportion in comparison to the degree of fibrosis (consider other cause combined with CAD?)
Scenario 1: 56 y.o. male with likely ischemic CMP
What do you do next?

- A) Surgery consult and schedule for CABG
- B) Colonoscopy
- C) Scan of thorax-abdomen-pelvis and brain
- D) Consult VAD-transplant team in view of high risk revascularization
- E) A and D
- F) All of the above
Scenario 1: 56 y.o. male with likely ischemic CMP
What do you do next?

- RV catheter after patient loss 75 pounds of water!!!
- PAP 36/15 (mean 23) mmHg
- CVP 9 mmHg
- Mean wedge 18 mmHg
- Cardiac index 2.01 L/min/m²
- RVSWI 23-9 x 2010/72 =392
HF Etiology: M. McDonald
Which investigation for which patient?
Scenario 2: 70 F, newly diagnosed with HFrEF (LVEF 35%)

- NYHA III (moderate-severe) symptoms
- PMHx: HTN, DM2
- Meds: Amlodipine 7.5mg/d, metformin 1g bid
- Labs: creat 122, lytes normal
- ECG: Sinus rhythm, left bundle branch block
- Coronary angio: normal looking coronaries

- For optimization of medication for HFrEF: “is she appropriate for one of those new fancy drugs?”
• Initial Rx:
  • furosemide 40 mg/d,
  • ramipril 2.5 mg bid
  • carvedilol 6.25mg bid
  • amlodipine stopped, metformin continued

• Over next 3 months
  • No hospitalizations, but still NYHA II; describes satisfactory quality of life
  • Meds: ramipril 5 mg bid, carvedilol 12.5mg bid, metformin 1g bid
  • BP 114/72, HR 72, appears euvolemic on exam;
  • BNP 299 pg/mL
What is your next move?

A. Add mineralocorticoid antagonist

B. Substitute ramipril for sacubitril-valsartan

C. Add low dose digoxin

D. Refer for prophylactic ICD if LVEF < 35%

E. Nothing; this patient feels well, is tolerating meds, and is happy with her physician
**Triple Therapy**

**ACEi/ARB + beta blocker + MRA**

**EMPHASIS HF**

- 2700+ patients, NYHA II
- Eplerenone vs Placebo;
- Median f/u 21mo
- Mortality in placebo group = 15.5%
- 25% reduction in mortality
- Baseline ACEi/ARB and beta blocker in 94% and 87%

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**Graph**

Hazard ratio, 0.76 (95% CI, 0.62–0.93)

P=0.008

Death from Any Cause (%)

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Placebo</th>
<th>Eplerenone</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>22.5</td>
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**No. at Risk**

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<tr>
<th></th>
<th>Placebo</th>
<th>Eplerenone</th>
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<tr>
<td>0</td>
<td>1373</td>
<td>1364</td>
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<tr>
<td>1</td>
<td>947</td>
<td>972</td>
</tr>
<tr>
<td>2</td>
<td>587</td>
<td>625</td>
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<tr>
<td>3</td>
<td>242</td>
<td>269</td>
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Zannad et al NEJM 2011
Triple Therapy for HFrEF

ACE INHIBITOR

+ 

B-BLOCKER

(max tolerated dose)

MRA

(max tolerated dose)
Next Follow Up: 3 months later

- Feels ‘ok;’ but fatigues easily
  - No hospitalizations
  - Persistent NYHA II sx

- Meds:
  1. Ramipril 5 mg bid
  2. Carvedilol 12.5 mg bid
  3. Spironolactone 25 mg/d
  4. Metformin 1 g bid

- BP 108/70, HR 78; JVP 3 cm

- BNP 185, CBC normal, creat 104, k 4.3
And now what?

A. Substitute ramipril for sacubitril-valsartan

B. Add low dose digoxin

C. Refer for prophylactic ICD if LVEF < 35%

D. Nothing; this patient feels well, is tolerating meds, and is happy with her physician
PARADIGM-HF: Primary endpoint (CV death or HF hospitalization)

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Enalapril (n=4212)

Sac-Val (n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Patients at Risk

LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236

Patient started on valsartan/sacubitril

- 48.6mg / 51.4mg bid
  - titrated to target dose (97.2mg/ 102.8mg bid) a few weeks later
  - BP 100/60, HR 78bpm, renal function, lytes all stable

- Returns to see you in 3 months
  - NYHA II symptoms
What is your next move?

A. Add ivabradine 5 mg bid

B. Reassess LVEF

C. Refer for ICD or CRT device
Newer Therapies for HFrEF: Ivabradine

Ivabradine selectively inhibits the If current the sinus node.

- 90% B blockers
- 91% Ace or ARB
- 60% Aldactone

Ivabradine reduces the slow diastolic depolarisation phase.
### Effects of Ivabradine on Primary and Secondary Endpoints in the SHIFT Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine group (n=3241)</th>
<th>Placebo group (n=3264)</th>
<th>HR (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
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<tr>
<td>Cardiovascular death or hospital admission for worsening heart failure</td>
<td>793 (25%)</td>
<td>937 (29%)</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
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<td><strong>Mortality endpoints</strong></td>
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<td>All-cause mortality</td>
<td>503 (16%)</td>
<td>552 (17%)</td>
<td>0.90 (0.80-1.02)</td>
<td>0.092</td>
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<tr>
<td>Cardiovascular mortality</td>
<td>449 (14%)</td>
<td>491 (15%)</td>
<td>0.91 (0.80-1.03)</td>
<td>0.128</td>
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<tr>
<td>Death from heart failure</td>
<td>113 (3%)</td>
<td>151 (5%)</td>
<td>0.74 (0.58-0.94)</td>
<td>0.014</td>
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<td><strong>Other endpoints</strong></td>
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<tr>
<td>Hospital admission for worsening heart failure</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Any cardiovascular hospital admission</td>
<td>977 (30%)</td>
<td>1122 (34%)</td>
<td>0.85 (0.78-0.92)</td>
<td>0.0002</td>
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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%)

Therapeutic Approach to Patients With HFrEF

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

Advance Care Planning and Documentation of Goals of Care
CCS Guideline Recommendation Rationale
Repeat Echo After Titration of Triple Therapy

~25% of patients with initial LVEF <40% (HFrEF) may increase to >40% over 1 year f/u
So what about devices if EF remains low: Is now the time I should….

A) Refer for implantable cardioverter defibrillator (ICD)?

B) Refer for cardiac resynchronization therapy (CRT)?
ICD Reduces Mortality in Spectrum of HF Patients: Amiodarone No Better than Placebo (SCD-HeFT)

- 2500 patients, LVEF ≤35%
- Ischemic and non-ischemic
- Randomized to ICD vs amiodarone vs placebo
- Follow-up ~45 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at Risk</th>
<th>Months of Follow-up</th>
<th>Hazard Ratio (97.5% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Amiodarone vs. placebo</td>
<td>845 772 715 484 280 97</td>
<td></td>
<td>1.06 (0.86–1.30)</td>
<td>0.53</td>
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<tr>
<td>ICD therapy vs. placebo</td>
<td>847 797 724 505 304 89</td>
<td></td>
<td>0.77 (0.62–0.96)</td>
<td>0.007</td>
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<tr>
<td>Placebo</td>
<td>829 778 733 501 304 103</td>
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ICDs in non-ischemic cardiomyopathy: Contemporary confusion?

**DANISH Trial**
- 1116 patients with non-ischemic CMP, LVEF ≤35%
- 1:1 randomized to ICD vs no ICD
- Median f/u 68 months, Median age 64 yrs
  - No difference in overall mortality
  - Significant reduction in incidence of SCD
  - Interaction seen with patients <68yrs vs >68 yrs of age
  - Very low rates of sudden death overall (8% in control group over study duration)
  - Excellent background therapy ~60% received CRT
  - Importance of individualizing device decisions!

ICD

We recommend consideration of primary ICD in patients with:

Ischemic cardiomyopathy, NYHA II-III symptoms, LVEF $\leq 35\%$ at least 1 month post MI and at least 3 months post revascularization (for ischemic cardiomyopathy)

Nonischemic cardiomyopathy, NYHA II-III symptoms, LVEF $\leq 35\%$ at least 3 months following optimization of guideline directed medical therapy

*(Strong Recommendation, High Quality Evidence)*
Cardiac Resynchronization (+/− ICD) Improves Survival: The COMPANION Trial

- 1520 patients, NYHA III/IV, EF <35%, QRS >120 msec
- Randomized (1:2:2) to medical therapy alone, CRT-P, or CRT-D
- HR for mortality 0.76 with CRT-P, 0.64 reduction with CRT-D at ~15mo

We recommend CRT for patients in sinus rhythm with NYHA II-IV symptoms despite optimal medical therapy, LVEF ≤35%, and QRS duration ≥130 ms with LBBB

*(Strong Recommendation, High Quality Evidence)*

We suggest CRT may be considered for patients in sinus rhythm with NYHA II-IV symptoms, despite optimal medical therapy, LVEF ≤35%, and QRS duration ≥150 ms with non-LBBB

*(Weak Recommendation, Low Quality Evidence)*
But this patient also has diabetes: what about the SGLT inhibitors?

• Which scenario would apply to people with Type II DM in your practice?

A. Recommend SGLTi to prevent the occurrence of HF
B. Recommend SGLTi to treat HF of all types
C. Recommend SGLTi to treat HFrEF only
Framingham Heart Study:
high rate of heart failure in Patients with Diabetes
over 30 years of follow-up

Risk of CVD events by age and sex

Ages 35-64

Risk Ratio

Total CVD    CHD    Cardiac Failure    Intermittent Claudication    Stroke

Men  Women

\( p < 0.001 \) for all values.

Evidence for benefit of SGLT2i’s on HF risk in patients with diabetes: EMPA-REG OUTCOME Trial

- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD (10.1% had HF at baseline)
  - BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)

Study medication was given in addition to standard of care. The trial was to continue until ≥691 patients experienced an adjudicated primary outcome event.

CVD, cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; MDRD, Modification of Diet in Renal Disease; SGLT2i, Sodium-glucose co-transporter-2 inhibitor

EMPARG-REG Outcome:
significant reduction in 3-point mACE and CV death

EMPA (Empagliflozin) is associated with a significant reduction in 3-point major adverse cardiac event (MACE) and cardiovascular (CV) death compared to placebo. The primary outcome was 3-point MACE, which includes non-fatal myocardial infarction (MI), non-fatal stroke, and CV death. Empagliflozin was found to be statistically significant for the primary outcome with a hazard ratio (HR) of 0.86 (95% CI: 0.74–0.99) and a p-value of 0.0382. Other outcomes such as CV death, non-fatal MI, and non-fatal stroke also showed a trend in favor of empagliflozin, although not all were statistically significant.

**Patients with event/analysed**

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<td><strong>Primary outcome:</strong></td>
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<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86 (0.74–0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62 (0.49–0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87 (0.70–1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24 (0.92–1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

*Primary outcome.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction

Heart failure hospitalization or CV death
EMPA-REG Outcome

HR 0.66
(95% CI 0.55, 0.79)
p<0.0001

10% of pts with history of HF at baseline

No. of patients
Empagliflozin
Placebo
4687 4614 4523 4427 3988 2950 2487 1634 395
2333 2271 2226 2173 1932 1424 1202 775 168

Months
0 6 12 18 24 30 36 42 48

Patients with event (%)
0 5 10 15

Placebo
Empagliflozin

European Journal of Heart Failure
Volume 19, Issue 1, pages 43-53, 21 SEP 2016 DOI: 10.1002/ejhf.633
CANagliflozin cardioVascular Assessment Study (CANVAS) in patients with diabetes:

**TRIAL DESIGN**

- **2-week placebo run-in**
  - Randomization (R)
  - Canagliflozin 300 mg
  - Canagliflozin 100 mg
  - Placebo

- **Key inclusion criteria:**
  - A1c ≥7.0% to ≤10.5%
  - eGFR ≥30 mL/min/1.73 m²
  - Age ≥30 years and history of prior CV event OR age ≥50 years with ≥2 CV risk factors (DM duration ≥10 yrs, SBP >140 on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL <1 mmol/L)
  - ~14% of patients had HF at baseline

---

A1c, glycated hemoglobin; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; R, randomization; SBP, systolic blood pressure

**CANVAS:**

significant reduction in HF hospitalization but not cv death

---

**Hospitalization for Heart Failure**

- **HR 0.67 (95% CI, 0.52–0.87)**
- **Placebo**
- **Canagliflozin**

**CV Death Component of Primary Outcome**

- **HR 0.87 (95% CI, 0.72–1.06)**
- **Placebo**
- **Canagliflozin**

---

**Table:**

<table>
<thead>
<tr>
<th>Years since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4347</td>
<td>5795</td>
</tr>
<tr>
<td>1</td>
<td>4198</td>
<td>5653</td>
</tr>
<tr>
<td>2</td>
<td>3011</td>
<td>4437</td>
</tr>
<tr>
<td>3</td>
<td>1274</td>
<td>2643</td>
</tr>
<tr>
<td>4</td>
<td>1236</td>
<td>2572</td>
</tr>
<tr>
<td>5</td>
<td>1180</td>
<td>2498</td>
</tr>
<tr>
<td>6</td>
<td>829</td>
<td>1782</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>Years since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>4279</td>
<td>5723</td>
</tr>
<tr>
<td>8</td>
<td>3119</td>
<td>4576</td>
</tr>
<tr>
<td>10</td>
<td>1356</td>
<td>2761</td>
</tr>
<tr>
<td>12</td>
<td>132</td>
<td>2710</td>
</tr>
<tr>
<td>14</td>
<td>1292</td>
<td>2651</td>
</tr>
<tr>
<td>16</td>
<td>924</td>
<td>1904</td>
</tr>
</tbody>
</table>

Intent-to-treat analysis.

CI, confidence interval; CV, cardiovascular; HF, heart failure

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>We recommend that diabetes should be treated according to the Canadian Diabetes Association’s national guidelines to achieve optimal control of blood glucose levels <em>(Strong Recommendation, Moderate Quality Evidence).</em></td>
</tr>
<tr>
<td>We suggest that the use of empagliflozin, a SGLT-2 inhibitor, be considered for patients with type 2 diabetes and established cardiovascular disease for the prevention of HF-related outcomes <em>(Weak Recommendation, Low Quality Evidence).</em></td>
</tr>
</tbody>
</table>
Treatment of Diabetes in People with Heart Failure

2018 Clinical Practice Guidelines

Chapter 28
Kim A. Connelly MBBS PhD,
Richard E. Gilbert MBBS PhD,
Peter Liu MD FRCPC FACC
Key Changes

• New information on
  • The use of DPP4 inhibitor and GLP1 receptor agonists in people with type 2 diabetes and heart failure
  • Role of SGLT2 inhibitor in patients with established CVD to reduce heart failure hospitalization
  • Role of sacubitril/valsartan in patients with heart failure with reduced ejection fraction (HFrEF)

CVD, cardiovascular disease
Diabetes in Heart Failure Checklist

- Treat heart failure in people with diabetes the SAME as you would a person without diabetes
- METFORMIN recommended if eGFR >30 mL/min/1.73 m²
- If eGFR <60 mL/min, use Renin Angiotensin Aldosterone system or sacubitril/valsartan blockade carefully
- Do NOT use thiazolidinediones
- Avoid saxagliptin in patients with heart failure and diabetes
Diabetes → Increased Risk of Heart Failure Independent of Ischemia

- Diabetic cardiomyopathy
- 2 to 4-fold increase incidence of heart failure in diabetes
- Asymptomatic abnormalities of ventricular systolic and diastolic function, independent of ischemic heart disease or systemic hypertension
- Independent risk factors for heart failure
  - Elevated A1C
  - Albuminuria

*Underlying ischemic heart disease should be ruled out.*
# Hospitalization for Heart Failure: DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXAMINE</strong>¹</td>
<td>106/2701 (3.9%)</td>
<td>89/2679 (3.3%)</td>
<td>1.19</td>
<td>0.90, 1.58</td>
<td>0.220</td>
</tr>
<tr>
<td>(alogliptin vs. placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAVOR-TIMI 53</strong>²</td>
<td>289/8280 (3.5%)</td>
<td>228/8212 (2.8%)</td>
<td>1.27</td>
<td>1.07, 1.51</td>
<td>0.007</td>
</tr>
<tr>
<td>(saxagliptin vs. placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TECOS</strong>³</td>
<td>228/7332 (3.1%)</td>
<td>229/7339 (3.1%)</td>
<td>1.00</td>
<td>0.83, 1.20</td>
<td>0.983</td>
</tr>
<tr>
<td>(sitagliptin vs. placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval


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Recommendation 1

1. Individuals with diabetes and heart failure should receive the same heart failure therapies as those identified in the evidence-based *Canadian Cardiovascular Society Heart Failure* recommendations (http://www.onlinecjc.ca/article/S0828-282X(12)01379-7/pdf)
Recommendation 2

2. Unless contraindicated, metformin may be used in people with type 2 diabetes and heart failure [Grade C, Level 3]. Metformin should be temporarily withheld if renal function acutely worsens, and should be discontinued if renal function significantly and chronically worsens [Grade D, Consensus]
3. For people with NYHA class I-IV, exposure to TZDs should be avoided [Grade A, Level 1]

4. Beta blockers should be prescribed when indicated for heart failure with reduced ejection fraction, as they provide similar benefits in people with or without diabetes [Grade B, Level 2]
5. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73 m$^2$, an SGLT2 inhibitor with demonstrated heart failure hospitalization reduction may be added to reduce the risk of heart failure hospitalization [Grade B, Level 2 for empagliflozin; Grade C, Level 2 for canagliflozin]

CVD, cardiovascular disease
Recommendation 6

6. In people with diabetes and heart failure with an eGFR <60 mL/min/1.73 m$^2$ and/or if combined RAAS blockade is employed:

- Starting doses of ACE inhibitors or ARBs should be halved [Grade D, Consensus]
- Serum electrolytes and creatinine, BP and body weight, as well as heart failure symptoms and signs, should be monitored within 7-10 days of any initiation or titration of therapy [Grade D, Consensus]
- Dose-up titration should be more gradual (with monitoring of BP, serum potassium and creatinine) [Grade D, Consensus]

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; RAAS, renin angiotension aldosterone system
Advanced HF
Scenario 3:
68 M, non-ischemic CMP admitted for acute HF

- 5 visits to ED in 4 months, 3 admissions
- On max tolerated sac-val, bisoprolol (doses recently reduced), spironolactone + lasix, digoxin
- LVEF 20%, Severe functional MR, ICD in situ
- Comorbidities
  - A fib, CKD (creat 150s); severe depression; Crohn’s disease

- On presentation:
  - HR 70bpm irreg, SBP 86 mmHg, edematous
  - Labs: Hb 100g/L, creat 188, Na 130, K+ 5.0
Your estimate of this patient’s 1 year mortality would be:

A. 1-10%
B. 10-20%
C. 30-40%
D. >80%
# 2017 Guidelines: Prognostic risk scores

## Risk Scores

<table>
<thead>
<tr>
<th>Score Name</th>
<th>Population</th>
<th>Endpoint</th>
<th>Other Considerations</th>
<th>Access</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle Heart Failure Model</td>
<td>HFrEF</td>
<td>Mortality risk at 1, 2 and 5 years with or without intervention. Mean life expectancy.</td>
<td>Restricted to clinical trial patients with 'severe' HF; Lab data entry non-SI units; More than 20 variables to enter.</td>
<td><a href="http://Dept.s.washington.edu/shfm/"> Dept of Washington.edu/shfm/</a></td>
<td>Age, gender, NYHA class, weight, EF, SBP, diuretic dose, Na, K, Hgb, cholesterol, uric acid, BNP, aldosterone, use of statins, QRS&gt;120msec, use of beta-blocker/ACEi/ARB blocker/allopurinol/statins, QRS&gt;120msec, use of beta-blockers.</td>
</tr>
<tr>
<td>MAGGIC Risk Score</td>
<td>HFrEF and HFrEF</td>
<td>Mortality risk at 1 and 3 years</td>
<td>Cohorts from many sites; missing data in the overall analysis.</td>
<td><a href="http://www.heartfailurerisk.org">www.heartfailurerisk.org</a></td>
<td>Age, gender, NYHA class, diabetes, COPD, timing of diagnosis, EF, smoking, SBP, creatinine, BMI, use of beta-blocker/ACEi/ARB blocker/allopurinol/statins, QRS&gt;120msec, use of beta-blockers.</td>
</tr>
<tr>
<td>3C-HF</td>
<td>HFrEF and HFrEF</td>
<td>Mortality risk at 1 year</td>
<td>Patients from centres with experience with HF management; mostly Caucasian patients; Lab data entry in non-SI units.</td>
<td><a href="http://www.3chf.org/site/home.php">http://www.3chf.org/site/home.php</a></td>
<td>Age, NYHA class, AF, valvular heart disease, EF, anemia, diabetes, hypertension, creatinine, use of ACEi/ARB or beta-blockers.</td>
</tr>
<tr>
<td>BCN- Bio-HF</td>
<td>HFrEF and HFrEF</td>
<td>Mortality risk at 1, 2 and 3 years</td>
<td>Limited to patients with chronic HF treated in HF unit in a tertiary hospital. Lab data entry in US units. Use of biomarkers improves accuracy but is optional.</td>
<td><a href="http://www.BCNBioHFcalculator.cat">www.BCNBioHFcalculator.cat</a></td>
<td>Age, gender, NYHA class, Na, eGFR, Hgb, EF, diuretic dose, use of statins, beta-blockers or ACEi/ARB blocker/allopurinol/statins, hs-cTnT, ST2, Nt-pro-BNP.</td>
</tr>
<tr>
<td>EFFECT</td>
<td>Hospitalized HFrEF and HFrEF</td>
<td>30-day and 1-year mortality</td>
<td>Limited to hospitalized patients</td>
<td><a href="http://www.ccort.ca/Research/CHFRiskModels.aspx"> http://www.ccort.ca/Research/CHFRiskModels.aspx</a></td>
<td>Age, respiratory rate, SBP, BUN, Na, CVD, dementia, COPD, cirrhosis, cancer, Hgb</td>
</tr>
<tr>
<td>EHMRG</td>
<td>HFrEF and HFrEF; patients presenting to the ED</td>
<td>7-day mortality</td>
<td>Limited to patients presenting to the ER and only short-term mortality; missing current clinically important variables</td>
<td><a href="https://ehmrg.ices.on.ca"> https://ehmrg.ices.on.ca</a></td>
<td>Age, arrival by ambulance, triage SBP, triage HR, triage O2 sat, potassium, creatinine, active cancer, metolazone, troponin. Optional: BNP, serum sodium, serum urea, NT-proBNP at discharge and change in NT-proBNP.</td>
</tr>
<tr>
<td>ELAN</td>
<td>Hospitalized HFrEF and HFrEF</td>
<td>180-day mortality</td>
<td>Limited to hospitalized patients</td>
<td><a href="http://ELAN.org"> ELAN.org</a></td>
<td>NT-proBNP at discharge, NT-proBNP at discharge and change in NT-proBNP.</td>
</tr>
<tr>
<td>ADHERE</td>
<td>HFrEF and HFrEF</td>
<td>In-hospital mortality</td>
<td>Limited to hospitalized patients</td>
<td><a href="http://www.adhere.org"> http://www.adhere.org</a></td>
<td>BUN, creatinine, SBP</td>
</tr>
<tr>
<td>LACE</td>
<td>Hospitalized patients</td>
<td>30-day mortality or readmission</td>
<td>Limited to hospitalized patients</td>
<td><a href="http://LACE.org"> LACE.org</a></td>
<td>Length of stay, acute admission, comorbidity index, # of ED visits in last 6 months</td>
</tr>
</tbody>
</table>

### What is the prognosis?

**Multiple risk scores exist to assess prognosis in HF. Key factors:**
- Age
- New York Heart Association class
- Renal function
- Sodium
- Ejection fraction
- Systolic blood pressure
- ACEi or ARB/BB
- Biomarkers
Prognostic Risk Scores

• This patient has a poor overall prognosis
  • 1 year mortality estimated at between 30-60%

• Risk Scores:
  • May be useful adjunct to facilitate timing of referral
  • Avoid relying on single, or opinion-based prognostic factors
  • Help plan approach to care, including goals, wishes, expectations
Advanced Heart Failure – Broad Definition

• Patients have significant cardiac dysfunction plus
  • marked symptoms of dyspnea, fatigue
  • end-organ hypo-perfusion at rest
  • symptoms with minimal exertion despite maximal medical therapy

• Refractory symptoms requiring specialized interventions to manage symptoms or prolong life

*No one diagnostic criteria for ‘Advanced HF’*
What’s the next step?

A. Refer for upgrading ICD to CRT-D

B. Refer for mitra-clip procedure

C. Refer for long term LVAD or transplantation

D. Discharge to hospice care on milrinone
Clinical Criteria for Heart Transplantation or LVAD

- LVEF typically < 25%
- Unacceptable symptoms despite maximum medical or device therapy
- Recurrent HF hospitalization within 6 months
- Measured peak VO$_2$ < 14 ml/kg/min
- Recurrent ventricular arrhythmias
- Progressive cardiorenal syndrome
- Cardiac cachexia
- Intolerance of oral HF medications
Commercially available long-term LVADs in 2018

Heatmate II  
Heatmate III  
HeartWare HVAD
Improvements in LVAD therapy over time

2009: Axial continuous flow pumps improve survival vs. 1st gen pulsatile flow pump for “destination therapy”

2018: Current centrifugal flow pumps (HM 3) superior to axial-flow pump (HM 2) with respect to stroke/thrombotic complications
Contraindications for:

**LVAD**
- Major comorbidities
  - Severe COPD, CKD, PAD, liver disease
  - Severe frailty
- Severe psychosocial disability
- Active infection
- Poor non-cardiac survival
- RV dysfunction

**Transplant**
- Major comorbidities
  - Severe COPD, CKD, PAD, liver disease
  - Severe frailty
- Severe psychosocial disability
- Active infection
- Poor non-cardiac survival
- Irreversible pulmonary hypertension
Back to our case:

• Patient became inotrope dependent in CCU

• Not well suited for transplantation

• Offered LVAD as ‘destination therapy'
  • Did not wish to pursue this after much consideration

• Mitra clip discussed – “too little, too late”

• Patient wished to pursue active palliation
25,000 - 50,000
Advanced HF

200 transplants
200 VADs

25,000 - 50,000
Advanced HF

600,000 with
HF diagnosis

200 transplants
200 VADs

25,000 - 50,000
Advanced HF

600,000 with
HF diagnosis

VAD, Transplant
CRT pacemaker, experimental interventions
ICD
Sacubitril-Valsartan, Ivabradine
ACEi/ARB, Beta blocker
MRA
Lifestyle intervention
Risk factor control

Chronic Disease Management
Managing fluid overload

Palliative Care
Summary

• Evolving standard of care for HFrEF

• Investigation and treatment decisions can be individualized depending on clinical scenario

• Risk assessment can be facilitated by validated risk scores; recognition of high risk patients should trigger evaluation for advanced therapies
  • VAD, transplant, palliation