POPULATION PRECISION MEDICINE AND SECONDARY PREVENTION OF HEART FAILURE

Sean A. Virani  MD, MSc, MPH, FRCPC, FCCS
Chief of Cardiology | Providence Healthcare
Physician Program Director | The Heart Centre | St. Paul’s Hospital
Associate Professor of Medicine | UBC
Past-President | Canadian Heart Failure Society
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- **Other**: None

- I will NOT discuss off-label use.
Can we resolve …

• **Precision medicine**
  • Tailoring a treatment strategy based on patient specific factors

• **Population health**
  • The health outcomes of a group of individuals, including the distribution of such outcomes within the group
Patient with LVEF ≤ 40% and Symptoms

Triple Therapy ACEi (or ARB if ACEi intolerant), BB, MRA
Titrate to target doses or maximum tolerated evidence-based dose

**REASSESS SYMPTOMS**

- **NYHA I**
  - Continue triple therapy

- **NYHA II–IV: SR, HR ≥ 70 bpm**
  - ADD Ivabradine and SWITCH ACEi or ARB to ARNI* for eligible patients

- **NYHA II–IV: SR with HR < 70 bpm or AF or pacemaker**
  - SWITCH ACEi or ARB to ARNI* for eligible patients

**REASSESS SYMPTOMS AND LVEF**

- **NYHA I or LVEF > 35%**
  - Continue present management
  - Reassess every 1–3 years or with clinical status change†

- **NYHA I–III and LVEF ≤ 35%**
  - Refer to ICD/CRT algorithm
  - Consider LVEF reassessment every 1–5 years

- **NYHA IV**
  - Consider:
    - Hydralazine/nitrates
    - Referral for advanced HF therapy (mechanical circulatory support/transplant)
    - Palliative Care referral
  - Reassess as needed according to clinical status‡

Advance Care Planning and Documentation of Goals of Care

Non-pharmacologic therapies (teaching self-care, exercise)

Diuretics to Relieve Congestion

Titrate to minimum effective dose to maintain euvolemia.
Tailoring treatment for mortality benefit
A few examples

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Clinical Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Scores</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>Natriuretic Peptides</td>
<td>Etiology</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>QRS Duration</td>
</tr>
<tr>
<td></td>
<td>Renal Function and K+</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
</tbody>
</table>

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

- 50ish year old male with ischemic cardiomyopathy, LVEF 28%
  - Status post-surgical and percutaneous revascularization
  - Complex co-morbidities including CKD
  - Persistent NYHA III symptoms with marked fatigue and postural lightheadedness

- Recent hospitalization for AHF with volume overload
  - Diuretics adjusted but the admitting team did not think there was anything additional to add/change to his baseline treatment to improve “hard outcomes”
  - Clinically euvolemic at discharge with BNP of 2100

- HF therapies
  - bisoprolol 2.5 mg po od, ramipril 2.5 mg po od, spironolactone 12.5 and furosemide 80 mg po od
  - ICD for primary prevention

- Notable patient characteristics
  - HR 75 in NSR
  - BP 90/50 with no postural drop
  - eGFR 40
  - K+ 5.4
  - QRS duration of 115ms
Q1 – Precision Medicine

• What can you do to further customize his therapies?

A. Nothing – he’s on optimally tolerated medical therapy (OTMT)
B. I would “push” his RAASi and beta-blockers to target doses and cautiously monitor his blood pressure, renal function and K+
C. I would increase his diuretic given the BNP was 2100
D. I would add ivabradine
**Recommendation 27:** We recommend preferentially using the specific drugs at target doses that have been proven to be beneficial in clinical trials as optimal medical therapy. If these doses cannot be achieved, the maximally tolerated dose is acceptable [Table 11] (Strong Recommendation, High Quality Evidence).

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

Ezekowitz et al. Can J Cardiol 33(11):1342-1433
The higher the HR …
the higher the risk of CV mortality and HF hospitalization

<table>
<thead>
<tr>
<th>HR at baseline (bpm)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 - &lt; 72</td>
<td>1.00</td>
</tr>
<tr>
<td>72 - &lt; 75</td>
<td>1.15</td>
</tr>
<tr>
<td>75 - &lt; 80</td>
<td>1.33</td>
</tr>
<tr>
<td>80 - &lt; 87</td>
<td>1.80</td>
</tr>
<tr>
<td>≥ 87</td>
<td>2.34</td>
</tr>
</tbody>
</table>

Risk increases by:
3% per 1-bpm increase in HR
16% per 5-bpm increase in HR

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

<table>
<thead>
<tr>
<th>Heart rate at discharge (bpm)</th>
<th>40-60</th>
<th>61-70</th>
<th>71-80</th>
<th>81-90</th>
<th>&gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>14.6%</td>
<td>23.9%</td>
<td>28.9%</td>
<td>18.7%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Hazard ratio for 30-day mortality</td>
<td>1.06</td>
<td>Referent</td>
<td>1.21</td>
<td>1.70</td>
<td>1.88</td>
</tr>
<tr>
<td>p-value</td>
<td>0.720</td>
<td>Referent</td>
<td>0.185</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Prespecified Endpoints</th>
<th>$\geq 70$ bpm</th>
<th>$\geq 77$ bpm</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Primary endpoint</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or hospital admission for worsening HF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mortality endpoints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
</tr>
<tr>
<td>Death from HF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Other endpoints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospital admission</td>
</tr>
<tr>
<td>Any CV hospital admission</td>
</tr>
<tr>
<td>Hospital admission for worsening of HF</td>
</tr>
</tbody>
</table>

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

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

High-Risk Heart Failure with Reduced EF
LVEF ≤ 40 within 12 months
HF event (hospitalization, ED visit, outpatient IV diuretics) within prior 12 mos
NT-proBNP > 2000 pg/mL within prior 30 days

Usual Care
N=550

Biomarker-Guided
NT-proBNP < 1000 pg/mL
N=550

Follow up: 2 wks, 6 wks, 3 months, then Q3 month for 12–24 mos

Additional 2-week follow-up after changes in therapy

Primary endpoint: Time to CV death or first HF hospitalization
Secondary endpoints:
• All-cause mortality
• Total days alive and out of hospital during follow-up
• CV mortality or CV hospitalization
• Safety
• Health-related quality of life
• Resource utilization, costs, cost effectiveness
GUIDE-IT: Primary Endpoint
Time to CV death or HF Hospitalization

HR (CI) = 0.983 (0.791, 1.222)
P value = 0.875

Duration of follow-up: Median (25th, 75th)
Biomarker-guided: 15 (7, 24)
Usual care: 15 (7, 24)
Case: Patient Johan Hulete– Part II

• You initiate ivabradine at the first post-discharge visit
  • Before you can up-titrate the dose or follow-up with the patient, he presents to hospital with AHF
  • Apparently, he was unable to afford his medications

• In hospital, he is diuresed and discharged home
  • There are no changes to his HF therapies

• After his second admission, he is referred to the HF Clinic at discharge
  • Follow-up appointment within 2 weeks per CCS Companion Recommendations

• Discharge Summary
  • “Hopefully the HF Clinic can help ensure a seamless transition to the community … and the patient would benefit from the multidisciplinary team approach”
Q2 – Population Health

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

A. Nurse
B. Physician and nurse
C. Physician, nurse and nurse practitioner
D. Physician, nurse, nurse practitioner and pharmacist
E. Physician, nurse, nurse practitioner, pharmacist and dietician
F. Depends on the size of the community and available services
**Recommendation 175:** We recommend that specialized outpatient HF clinics or disease management programs provide access to an interprofessional team ideally including a physician, a nurse, and a pharmacist with experience and expertise in HF (Strong Recommendation, High Quality Evidence).

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

Ezekowitz et al. Can J Cardiol 33(11):1342-1433
Define each level of HF care by provider type and the core competencies associated with each role (i.e. level of training, scope of practice).

Describe the key services and resources (human and structural) that must be in place at each level of care as well as the tools necessary to support optimal patient care at each stage (e.g. care plans/protocols, educational resources, quality assurance strategies).

Describe how and what should travel with patients between levels (hubs) of care to provide seamless transitional care and to optimize the patient and provider experience of care.
Precision Public Health:
Precision medicine and population health

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

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