Thalassemia Foundation of Canada

Cardiovascular Assessment, Complications, Prevention and Management

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Overview

• Heart Health
• Signs and Symptoms
• Iron Overload
  – Thalassemia Major
• Pulmonary Vascular Disease
  – Thalassemia Intermedia
Cardiovascular Disease and Mortality in Canada

## Heart Health

- **Cardiovascular Risk Factors**

<table>
<thead>
<tr>
<th>MODIFIABLE</th>
<th>NON-MODIFIABLE</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<tr>
<td>High cholesterol</td>
<td>Gender</td>
</tr>
<tr>
<td>Smoking</td>
<td>Age</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Family History</td>
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<tr>
<td>Physical inactivity</td>
<td></td>
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<tr>
<td>Obesity ( \rightarrow ) 30% above ideal body weight</td>
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</tbody>
</table>
Basic principles of Physical Activity

• Physical activity can be a lifesaver – literally
• Canadian Physical Activity Guidelines
  – 150 minutes of moderate- to vigorous-intensity aerobic physical activity per week, in bouts of 10 minutes or more several days of the week.
    • Moderate ➔ brisk walking or bike riding.
    • Vigorous intensity ➔ jogging or cross-country skiing
  – dramatically lowers risk of heart disease and stroke
  – prevent and control risk factors such as high blood pressure, high cholesterol, type 2 diabetes, osteoporosis, certain types of cancer and obesity.
• Adding more activity to your daily life may also reduce stress levels, increase energy, improve sleep and digestion.
• Benefits may begin within the first week of regular activity. For example, your blood pressure may start to come down, and you could start to feel more energetic and relaxed. After three months, you may experience better health, improved posture and balance, stronger muscles and bones, more confidence and a more positive outlook on life.

Heart and Stroke Foundation of Canada
Physical Activity

RECOMMENDATIONS
Canadians

• Adults should accumulate a minimum of 30 minutes per day of physical activity on most days of the week. This can be accomplished by:
  • Using active modes of transportation such as cycling and walking to get to and from work as well as for other short trips around town
  • Identifying community-based resources and programs to help people become more physically active.

Heart and Stroke Foundation of Canada
Anemia

↑ cardiac dimensions
↑ stroke volume
↑ Heart Rate
↓ BP
↓ Vascular Resistance

Diabetes

Coronary artery disease

Kremastinos et al, *Circ Heart Fail. 2010;3:451-458*
Heart Failure

• The inability of the heart to pump enough to meet the needs of the body
Symptoms of Heart Failure

- Shortness of breath
- Chronic lack of energy
- Cough w/ frothy sputum
- Swelling of feet & legs
- Difficulty sleeping at night due to breathing problems
- Swollen or tender abdomen w/ loss of appetite
- Increased urination at night
- Confusion and/or impaired memory
A Key Indicator for Diagnosing Heart Failure

Ejection Fraction (EF)

- Ejection Fraction (EF) is the percentage of blood that is pumped out of your heart during each beat.
Four Classes of Heart Failure

Class I: Mild
Class II: Mild
Class III: Moderate
Class IV: Severe
Symptoms

Class I
No symptoms
Can perform ordinary activities without any limitations

Class II
Mild symptoms
Occasional swelling
Somewhat limited in ability to exercise or do other strenuous activities
No symptoms at rest

Class III
Noticeable limitations in ability to exercise or participate in mildly strenuous activities
Comfortable only at rest

Class IV
Unable to do any physical activity without discomfort
Symptoms at rest
Iron Overload
Cardiac Involvement

• Once the heart begins to accumulate iron, it can do so rapidly
• Cardiac iron can also accumulate even in the presence of negative liver iron balance or at extremely low liver iron concentrations (<5 mg/g dry weight).
• Cardiac iron balance appears to depend upon the hours per week of chelation coverage more than the grams per week of drug administered.
• This observation probably accounts for the critical dependence of chelation compliance on survival

Noetzli et al, Blood 2008; Brittenham et al, NEJM 1994
Monitoring - MRI

• Cardiac T2*:  
  – preclinical recognition of myocardial iron  
  – stratifies prospective cardiac risk  
  – tracks response to modifications in iron chelation therapy

• MRI assessment of cardiac function - highly accurate and reproducible assessment of ventricular function

Wood and Noetzli, Annals of New York Aca Sci 2010
Pathologic myocardial iron overload occurs when iron binding capacity is saturated and labile free iron species begin to circulate.

<table>
<thead>
<tr>
<th>T2*</th>
<th>EJECTION FRACTION – LV and RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>6-8</td>
</tr>
<tr>
<td>50%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Kirk et al, Circ 2009; Alpendurada et al, Eur Heart J 2010
# Therapeutic Trials With Cardiovascular End Points in Thalassemia Over the Last Decade

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Design</th>
<th>Study Population</th>
<th>Regimen</th>
<th>End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kremastinos et al</td>
<td>Prospective</td>
<td>52 TM pts with recent HF diagnosis</td>
<td>Regular transfusions and DFO plus standard HF therapy</td>
<td>Survival at 5 years</td>
<td>Enhanced survival (48%)</td>
</tr>
<tr>
<td>Anderson et al</td>
<td>Cross sectional</td>
<td>45 TM pts</td>
<td>DFO vs DFP</td>
<td>Cardiac iron (T2*) and LVEF (CMR)</td>
<td>DFP group: better T2* (34 vs 11 ms) and LVEF (70% vs 63%)</td>
</tr>
<tr>
<td>Piga et al</td>
<td>Retrospective</td>
<td>129 TM pts</td>
<td>DFO vs DFP</td>
<td>Heart disease (new or worsened) at 4 years or later</td>
<td>DFP: lower occurrence of heart disease (4% vs 21%)</td>
</tr>
<tr>
<td>Galia et al</td>
<td>Randomized</td>
<td>72 TM pts</td>
<td>DFO vs DFP</td>
<td>Cardiac iron (CMR, HSIR) at 1 year</td>
<td>No difference in HSIR</td>
</tr>
<tr>
<td>Aessopos et al</td>
<td>Cross sectional</td>
<td>131 TM pts 74 Ti pts</td>
<td>Regular transfusions and DFO (TM)—no regular therapy (Ti)</td>
<td>Clinical assessment and echocardiography</td>
<td>Clinical HF: 4% in TM, 3% in Ti. Low LVEF: only in TM (8%). Sign. PHT: only in Ti (23%)</td>
</tr>
<tr>
<td>Pennell et al</td>
<td>Randomized</td>
<td>61 TM pts on DFO</td>
<td>DFO vs DFP</td>
<td>Cardiac iron (T2*) and LVEF (CMR) at 1 year</td>
<td>DFP: greater improvement in T2* and LVEF</td>
</tr>
<tr>
<td>Pepe et al</td>
<td>Cross sectional</td>
<td>36 TM pts</td>
<td>DFO vs DFP</td>
<td>Cardiac iron (CMR, T2*)</td>
<td>DFP: better outcome (T2*, 35 vs 27 ms)</td>
</tr>
<tr>
<td>Christoforidis et al</td>
<td>Prospective</td>
<td>50 TM pts (children or young adults)</td>
<td>DFO+DFP vs DFO</td>
<td>Cardiac and liver iron (CMR, T2*)</td>
<td>DFP+DFO: ↓ myocardial iron; DFO: ↑ liver iron</td>
</tr>
<tr>
<td>Tanner et al</td>
<td>Randomized and placebo controlled</td>
<td>65 TM pts with mild to moderate cardiac iron (T2* 8 to 20 ms) on DFO</td>
<td>DFO+DFP vs DFO</td>
<td>Cardiac iron (T2*), FMD and LVEF (CMR) at 1 year</td>
<td>DFP+DFO: greater improvement in T2*, FMD and LVEF</td>
</tr>
<tr>
<td>Tanner et al</td>
<td>Prospective</td>
<td>15 TM pts with severe cardiac iron (T2* &lt;8 ms) on DFO</td>
<td>DFO+DFP</td>
<td>Cardiac iron (T2*) and LVEF (CMR)</td>
<td>Improved T2* and LVEF</td>
</tr>
<tr>
<td>Maggio et al</td>
<td>Randomized</td>
<td>265 TM pts</td>
<td>DFO vs DFP vs sequential DFO+DFP vs DFO+DFP</td>
<td>Survival</td>
<td>DFO monotherapy: worse survival</td>
</tr>
<tr>
<td>Berdoukas et al</td>
<td>Prospective</td>
<td>232 TM pts</td>
<td>DFO vs DFP vs DFO vs DFX</td>
<td>Annual change in cardiac and liver iron (T2*)</td>
<td>DFO+DFP: ↓ both cardiac and liver iron; DFP: ↓ only cardiac iron; DFO: ↓ only liver iron</td>
</tr>
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## Cardiovascular Evaluation, Monitoring and Treatment Plan of Thalassemia Patients

<table>
<thead>
<tr>
<th>Patient Profile</th>
<th>Basic Evaluation†‡</th>
<th>CMR—T2*</th>
<th>General/Hematologic Measures</th>
<th>Cardiological Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic pts with no evidence of heart disease or myocardial iron load</td>
<td>First at puberty</td>
<td>First at late teens or early 20s Every 12 months thereafter</td>
<td>Pretransfusional Hb at 9 to 10.5 g/dL Regular iron chelation Management of other causes of heart failure§§ Life style modifications (smoking, lack of exercise, and excess alcohol)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic pts with increased cardiac iron load but normal cardiac function</td>
<td>Every 6 to 12 months</td>
<td>Every 12 months</td>
<td>Pretransfusional Hb at 9 to 10.5 g/dL Intensification of iron chelation¶</td>
<td>Slow transfusion with diuretics Specific cardiac medications#</td>
</tr>
<tr>
<td>Asymptomatic pts with evidence of heart disease</td>
<td>Every 3 to 6 months</td>
<td>At diagnosis of heart disease Every 6 to 12 months thereafter</td>
<td>Pretransfusional Hb at 10 to 11 g/dL Intensification of iron chelation¶</td>
<td>Slow transfusion with diuretics Specific cardiac medications#</td>
</tr>
<tr>
<td>Symptomatic heart disease</td>
<td>Weekly to every 1 to 4 months, depending on clinical course</td>
<td>At symptoms onset Every 6 to 12 months thereafter</td>
<td>Pretransfusional Hb at 10 to 11 g/dL Intensification of iron chelation¶</td>
<td>Slow transfusion with diuretics Specific cardiac medications#</td>
</tr>
</tbody>
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Pulmonary Hypertension

- Pulmonary hypertension is abnormally high blood pressure in the arteries of the lungs
- It makes the right side of the heart need to work harder than normal
- We routinely look for it on echocardiograms
- Right ventricular systolic pressure
  - Estimate of the pressures in the lungs
Pulmonary Hypertension Symptoms

• Shortness of breath or light-headedness during activity is often the first symptom
• Fast heart rate (palpitations) may be present.
• Over time, symptoms occur with lighter activity or even while at rest.
Pulmonary Hypertension

• Diagnosis – by catheterization
  – Directly measure the pressures in the lungs
  – Treatment

• Medications that lower the lung pressures
Cardiomyopathy in β-thalassemia

Thalassemia major

- Dilated left ventricular cardiomyopathy
  - Iron overload
    - Immuno-inflammatory factors
    - Increased frequency of CMR
    - Increased chelation
    - Institution of HF medications

- Restrictive left ventricular filling
  - Iron overload
  - Increased frequency of CMR
  - Increased chelation
  - Medications to remove XS fluid
Heart&Stroke eTools for a healthier you

These easy-to-use eTools can help you lead a healthier life. You’ll be able to set and achieve goals to manage your blood pressure or achieve a healthy weight and keep track of important details such as medications and appointments. Sign up for any or all of the eTools, depending on your needs.

My Heart&Stroke Risk Assessment™
You can determine your risk for heart disease and stroke by answering these confidential questions.
Take the Assessment now »

My Blood Pressure Action Plan™
You can use this interactive tool to track your blood pressure readings, set goals and receive appointment and medication reminders.
Already registered? Sign in »

My Health eSupport™
You’ll receive regular emails to support and encourage you to achieve a healthier life.
Sign up now »

My Healthy Weight Action Plan™
You can achieve and maintain a healthy weight with this 12-week program developed by experts.
Already registered? Sign in »