Managing Cardiovascular Disease: Impact On The Workplace

Jafna L. Cox, BA, MD, FRCPC, FACC

Heart and Stroke Foundation of Nova Scotia Endowed Chair in Cardiovascular Outcomes Research
Professor of Medicine and of Community Health and Epidemiology, Dalhousie University
Relevant Disclosures – JL Cox

- Has sat on regional advisory boards hosted by Sanofi
- Has met with Medical Science Liaisons from both Amgen and Sanofi
Objectives

- To review the current and predicted future burden of cardiovascular disease (CVD)
- To review the potential benefits in terms of holding back the tide with current therapeutic options
- To review the challenges that continue to be faced despite the availability of effective management approaches and treatments
- To look briefly at what might be game-changing therapies, which are likely to come to market in the very near future
The Global Epidemiologic Transition

- The world has experienced an epidemiologic transition
  - Leading causes of death have shifted from infectious disease and acute illness to chronic disease and degenerative illness
  - Currently, 63% of all deaths worldwide stem from such non-communicable diseases
    - The chief drivers are cardiovascular diseases, cancers, chronic respiratory diseases, diabetes and mental health

What This Epidemiologic Transition Portends

- Chronic diseases are estimated to account for a cumulative output loss of US$ 47 trillion over the next two decades
  - Put in perspective, this equals 75% of global GDP in 2010 (which was US$ 63 trillion)
  - CVD and mental health conditions are the dominant contributors to this global economic burden

International CHD Mortality Trends: Three Decades Of Continuous Success

Trends Among Men, 1968-2003


CHD = coronary heart disease
The Global Burden Of CVD: Current Status And Future Concerns

- Despite major improvements since the 1960s, CVD remains the greatest health threat worldwide\(^1\)
  - Claims a life every 38 seconds in the US\(^2\)
    - Every 7 minutes, a Canadian dies of heart disease or stroke\(^3\)

- Recent data suggest that CVD rates are no longer falling but have leveled, and may even be increasing in those 35-54 years-of-age
  - Claims more lives globally than cancer, chronic lower respiratory disease and accidents combined\(^4\)

- The WHO projects that over the next 10 years in Canada\(^5\):
  - Over 2 million people will die from a chronic disease
  - Deaths from chronic diseases will increase by 15% and many of these will be as a result of CVD

---

Current Trends In Canada: Number and Deaths Due to CVD*, by Year, 1950-2004

## Costs Of Cardiovascular Disease In Canada

<table>
<thead>
<tr>
<th>Component</th>
<th>Males</th>
<th>Females</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital care</td>
<td>$2,338.0</td>
<td>$1,823.8</td>
<td>$4,161.8</td>
</tr>
<tr>
<td>Drugs</td>
<td>$836.0</td>
<td>$903.2</td>
<td>$1,772.8</td>
</tr>
<tr>
<td>Physician care</td>
<td>$432.3</td>
<td>$389.2</td>
<td>$822.3</td>
</tr>
<tr>
<td>Mortality (as the cost of premature death)</td>
<td>$5,280.1</td>
<td>$2,970.0</td>
<td>$8,250.0</td>
</tr>
<tr>
<td>Long-term disability</td>
<td>$1,976.3</td>
<td>$1,175.2</td>
<td>$3,151.5</td>
</tr>
<tr>
<td>Short-term disability</td>
<td>$176.3</td>
<td>$77.0</td>
<td>$253.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Component</th>
<th>0-14 years</th>
<th>15-34 years</th>
<th>35-64 years</th>
<th>65+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital care</td>
<td>$47.5</td>
<td>$97.9</td>
<td>$1,278.0</td>
<td>$2,730.3</td>
</tr>
<tr>
<td>Drugs</td>
<td>$10.6</td>
<td>$46.0</td>
<td>$735.3</td>
<td>$963.3</td>
</tr>
<tr>
<td>Physician care</td>
<td>$7.2</td>
<td>$31.8</td>
<td>$323.5</td>
<td>$459.8</td>
</tr>
<tr>
<td>Mortality (as the cost of premature death)</td>
<td>$36.5</td>
<td>$215.5</td>
<td>$3,891.2</td>
<td>$4,106.8</td>
</tr>
<tr>
<td>Long-term disability</td>
<td>Data N/A</td>
<td>$208.8</td>
<td>$1,664.6</td>
<td>$1,061.3</td>
</tr>
<tr>
<td>Short-term disability</td>
<td>Data N/A</td>
<td>$44.6</td>
<td>$166.1</td>
<td>$42.7</td>
</tr>
</tbody>
</table>

# Cardiovascular Disease Prevention: Population Attributable Risk And Economic Impact

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No previous history of MI or stroke (candidates for primary prevention)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequately controlled risk factors</td>
<td>Reference</td>
<td>32%</td>
<td>Reference</td>
<td>Not estimated</td>
</tr>
<tr>
<td>1 inadequately controlled risk factor</td>
<td>1.04 (0.7-1.5)</td>
<td>44%</td>
<td>Not significant</td>
<td>Not estimated</td>
</tr>
<tr>
<td>≥2 inadequately controlled risk factors</td>
<td>2.0 (1.4-2.8)</td>
<td>17%</td>
<td>14%</td>
<td>13.2</td>
</tr>
<tr>
<td><strong>Previous history of MI or stroke (candidates for secondary prevention)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequately controlled risk factors</td>
<td>2.6 (1.3-5.1)</td>
<td>2%</td>
<td>4%</td>
<td>3.3</td>
</tr>
<tr>
<td>1 inadequately controlled risk factor</td>
<td>4.2 (2.9-6.3)</td>
<td>2%</td>
<td>7%</td>
<td>6.2</td>
</tr>
<tr>
<td>≥2 inadequately controlled risk factors</td>
<td>5.7 (3.9-8.3)</td>
<td>2%</td>
<td>8%</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Qureshi et al., *Stroke* 2004; 35: 2346-2350
The State Of The Union: 
The Impact of Traditional Cardiovascular Risk Factors in Canada

- Smoking
  - Shortens life 13-15 years
  - Contributes to >37,000 deaths a year; 11,000 (29%) are heart disease and stroke-related
  - If current rates continue, about 1 million Canadians will die over the next 20 years as a direct result of smoking and second-hand smoke

- Obesity
  - Number of overweight/obese North Americans has increased rapidly over the past 30+ years
  - The percentage of overweight children and adolescents has risen dramatically since 1970
    - 26% of Canadian children 2-17 years of age are overweight or obese
  - If trends persist, overweight/obesity may become the leading cause of death

The State Of The Union: The Impact of Traditional Cardiovascular Risk Factors in Canada

**Diabetes**
- Globally, around 3.2 million deaths every year are attributable to the complications of diabetes
  - Represents six deaths every minute
- Overall, direct health care costs of diabetes range from 2.5% to 15% of annual health care budgets
- If current trends continue, 1 in 3 people born in 2000 will develop DM in their lifetime

**Hypertension**
- From 1991-2001, age-adjusted mortality due to HTN rose 36.4% and the number of deaths by 53%
- Every 20mmHg increase in sBP results in a 2-fold increase in coronary artery disease
- NS has highest prevalence of hypertension (20.4%) in persons ≥ 12 years in Canada (16.4%)
Hyperlipidemia

- Worldwide, high cholesterol levels are responsible for about 4.4 million deaths annually
  - Elevated lipid levels are estimated to account for
    - 56% of global Ischemic heart disease
    - 18% of global strokes
- Affects 45% of men and 43% of women in Canada, with 10 million people above target levels
- Overall, every 1% reduction in total cholesterol translates into a 2% decrease in coronary events
- A 1 mmol/L lowering in total cholesterol in those 40 to 89 years of age results in 33% fewer cardiac deaths
- Since 1990, the decline in CAD incidence has stalled despite marked increases in lipid-lowering drug use
  - Suggests that treating just those at highest-risk alone will not shift the population curve

Canadian Food Groups
Canadian Fitness Craze
Metabolic Syndrome
Evolution in the Understanding of CVD

Traditional CVD Perspective

Global CV Risk Perspective

Multiple Independent Risk Factors

Vascular Disease is an Interplay of Risk Factors

Effect Of Multiple Risk Factors On CHD Mortality: More Than The Sum Of Their Parts

LDL Lowering And Reduction In CVD Events: A Clear And Fundamental Relationship

- Results of a meta-analysis of data from 90,056 participants in 14 randomized statin trials
  - 5-year incidence of major CV events falls about 20% per mmol/L drop in LDL, irrespective of starting cholesterol level, gender, age, or pre-existing disease

Baigent et al., Lancet 2005; 366: 1267
Prior Treatment Paradigm:
Fixed Treatment Targets

Why stop here?

Prior treatment target

CV Risk

Risk Factors
Current Treatment Paradigm: Lower Treatment Targets

Risk is a continuous variable

Treat to lowest possible levels
## CCS Dyslipidemia Guidelines Update 2012: Lowering The Threshold

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Initiate therapy if</th>
<th>Primary target LDL C</th>
<th>Alternate target</th>
</tr>
</thead>
</table>
| **High** | Consider treatment in all (Strong, High) | ≤ 2 mmol/L or ≥ 50% decrease in LDL-C (Strong, High) | ➢ Apo B ≤ 0.8 g/L  
➢ Non HDL-C ≤ 2.6 mmol/L (Strong, High) |
| FRS ≥ 20% | | | |
| **Intermediate** | LDL-C ≥ 3.5 mmol/L (Strong, Moderate)  
➢ For LDL-C < 3.5 consider if: Apo B ≥ 1.2 g/L or Non-HDL-C ≥ 4.3 mmol/L (Strong, Moderate) | ≤ 2 mmol/L or ≥ 50% decrease in LDL-C (Strong, Moderate) | ➢ Apo B ≤ 0.8 mg/L  
➢ Non HDL-C ≤ 2.6 mmol/L (Strong, Moderate) |
| FRS 10%-19% | | | |
| **Low** | LDL-C ≥ 5.0 mmol/L  
➢ Familial hypercholesterolemia (Strong, Moderate) | ≥ 50% reduction in LDL-C (Strong, Moderate) | |
Poor Adherence: An Important Risk Factor Threatening Overall CV Management
The Magnitude Of The Nonadherence Problem

- WHO suggests only 50% of patients with chronic illness take therapies as prescribed; up to 30% of prescriptions in the US are never filled.¹,²
  - Within 1 year, ~50% of patients stop their drugs
    - Especially lipid-lowering and antihypertensive agents
  - A further ~35% discontinue treatment by 2 years³,⁴
  - Due to improper use, 30% - 50% of prescriptions fail to produce the desired therapeutic results

- Nonadherence to medication is associated with greater morbidity and mortality in chronic diseases.⁵,⁶
  - It is estimated that an additional $170 billion annually in the US is spent as a consequence of nonadherence.⁷

---

³ National Council on Patient Information and Education, 1997;
⁵ Ho PM, e et al, Arch Intern Med. 2006; 166:1836-1841;
⁶ Sokol MC et al., Arch Intern Med. 2006; 166:1836-1841;
⁷ Caro JJ et al, CMAJ. 1999; 160: 31-37
Achieving Lower Targets: A Challenge Despite The Availability Of Effective Therapy

- GUIDE (Guidelines Based on Undertaking for Improvement in Dyslipidemia Related Events) program
  - Multicentre observational cohort of 2577 Canadian patients with persistent hypercholesterolemia
  - Achieved over 90% adherence with guideline recommendations for statin therapy, higher than in many other reports
  - But, only 41% of the cohort attained LDL-C <2.0 mmol/L despite a comprehensive treatment regimen with statins and ezetimibe

- Several reasons proposed for the failure to achieve targets, including patient adherence issues and resistance to therapy

Teoh et al. *Am J Cardiol* 2009;104(6):798-804
All curves are based on a Cox proportional hazards model adjusted for covariates. The median follow-up was 494 days for acute coronary syndrome, 430 days for coronary artery disease, 235 days for primary prevention, and 303 days for overall Jackevicius CA, et al. JAMA. 2002;288(4):462-467. doi:10.1001/jama.288.4.462
The Need For Other Approaches: A More Targeted Therapy With Potential For Better Adherence

- Traditional treatments are often less targeted in terms of their effect and take more of a “one size fits all” approach.
- Biological treatments hold out the promise of acting more focally to address the severely afflicted or treatment resistant patient.
- Depending on their mode of administration, they have the potential to improve adherence as well.
Biologic Therapy In Inflammatory Bowel Disease: Effective In Patients Resistant To Conventional Treatment

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Natalizumab</th>
<th>Placebo</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Gordon et al. (45)</td>
<td>11</td>
<td>18</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Ghosh et al. (44)</td>
<td>118</td>
<td>185</td>
<td>46</td>
<td>63</td>
</tr>
<tr>
<td>Sandborn et al. (42) ENACT-1</td>
<td>457</td>
<td>724</td>
<td>126</td>
<td>181</td>
</tr>
<tr>
<td>Sands et al. (36)</td>
<td>33</td>
<td>52</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Targan et al. (35) ENCORE</td>
<td>191</td>
<td>259</td>
<td>210</td>
<td>250</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1,238</strong></td>
<td><strong>533</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>M-H, random, 95% CI</strong></td>
</tr>
<tr>
<td></td>
<td><strong>810</strong></td>
<td><strong>412</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.88 (0.83, 0.94)</strong></td>
</tr>
</tbody>
</table>

Total events: 810, Placebo 412

Heterogeneity: $\chi^2 = 2.11$, d.f. = 4 ($P = 0.72$); $I^2 = 0$

Test for overall effect: $Z = 3.88$ ($P = 0.0001$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Infliximab</th>
<th>Placebo</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Sands et al. (56)</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Probert et al. (57)</td>
<td>17</td>
<td>23</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Rutgeerts et al. (59) ACT 2</td>
<td>94</td>
<td>241</td>
<td>85</td>
<td>123</td>
</tr>
<tr>
<td>Rutgeerts et al. (59) ACT 1</td>
<td>96</td>
<td>243</td>
<td>80</td>
<td>121</td>
</tr>
<tr>
<td>Janner et al. (58)</td>
<td>18</td>
<td>24</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>539</strong></td>
<td><strong>288</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>M-H, random, 95% CI</strong></td>
</tr>
<tr>
<td></td>
<td><strong>231</strong></td>
<td><strong>201</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.72 (0.57, 0.91)</strong></td>
</tr>
</tbody>
</table>

Total events: 231, Placebo 201

Heterogeneity: $\chi^2 = 13.53$, d.f. = 4 ($P = 0.009$); $I^2 = 70$

Test for overall effect: $Z = 2.74$ ($P = 0.006$)

---

Advantages Of Long-Acting Biologicals: The Example Of Reduced Absenteeism With BioAdvance

Absentism in patients with Crohn's disease (n=206)

- Number of work days missed
  - >5 days
  - 2 - 5 days
  - 1 day
  - half day
  - 0 days

Before BioAdvance vs. After BioAdvance

*BioAdvance Patient Survey 2012, data on file Janssen Canada*
Advantages Of Long-Acting Biologicals: The Example Of Reduced Disability With BioAdvance

Number of patients with Ulcerative Colitis reported being on disability (n=75)

Before BioAdvance
- Yes: 31%
- No: 69%

After BioAdvance
- Yes: 3%
- No: 97%

*BioAdvance Patient Survey 2012, data on file Janssen Canada*
Alirocumab/Evolocumab: Fully Human Monoclonal Antibody Targeting PCSK9

- PCSK9 (*Proprotein convertase subtilisin/kexin of type 9*)
  - A protein made by the liver to control LDL-receptors
  - Works to increase LDL-receptors (LDLR) on the liver
  - Promotes degradation of LDL-cholesterol (LDL-C)
  - Allows more cholesterol to be removed from the blood
  - Can work in combination with statins to control cholesterol
Alirocumab/Evolocumab: Efficacy Of The First-to-Market PCSK9 Inhibitors

**LDL Cholesterol Reduction**

- Standard therapy
- Evolocumab

**CV Event Reduction**

Rate of major CV events (death from CHD, nonfatal MI, ischemic stroke or unstable angina requiring hospitalization)

- Standard therapy: 3.3%
- Alirocumab: 1.7%

Alirocumab
LDL-C Reductions and Goal Achievement

**COMBO I**
All patients on background of maximally tolerated statin ± other lipid lowering therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean (SE) % change from baseline to Week 24</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-48.2% (3.3)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>-50.7% (3.2)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C
All patients on background of maximally-tolerated statin

**COMBO II**

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean (SE) % change from baseline to Week 24</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-50.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>-61.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Long term (HeFH or high risk patients on background of maximally tolerated statin)

FH I (HeFH patients on background of maximally tolerated statin)

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent change from baseline to Week 24 in LDL-C</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-48.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>43.4% with dose increase†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

*Intent-to-treat (ITT) Analysis  †75 mg Q2W increased to 150 mg Q2W at Week 12 if LDL-C levels at Week 8 were ≥1.81 mmol/L [70 mg/dL].
Evolocumab (PCSK9i mAb): Phase III LDL-C Lowering Summary

The percentage change in levels of lipoprotein(a) and triglycerides was analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (SE) is shown.
Who May Need PCSK9 Inhibitors?

71 Million Americans have high cholesterol

11 Million Americans uncontrolled on cholesterol therapy may be targeted

1-2 Million Potential Targeted PCSK9 inhibitor population in U.S.

- Statin intolerant
- Genetic disorder (FH)
- Uncontrolled on statins

Sources:
An Effective Approach To Improving Adherence: The Patient Adherence Program

- Patient assistance programs (PAP)
  - Established for biologic disease modifying therapies to improve patient knowledge and compliance and provide follow-up

- The experience of Enliven®, a Canadian PAP for etanercept
  - 14,335 Canadians with rheumatoid arthritis enrolled 2000-2007
  - Adherence rate at one year for etanercept therapy was 82%

- Apart from the PAP, a drug needing to be taken only once or twice a month should potentially improve compliance and adherence

Some Closing Remarks

- Despite some major gains, the CVD burden continues to grow
- The extent to which it will increase depends on how well the risks for CVD are prevented or controlled
- Hyperlipidemia is especially frustrating to manage as it is a “silent killer”; and while we do have effective treatments for it, these are too often not enough
- New therapeutic approaches will soon be available
- But how well these treatments will live up to their promise and for whom they will be prescribed remains to be determined

Stay tuned...