The sustainability of Medicare – are doctors part of the solution or part of the problem?

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Divisions of Cardiology and Clinical Epidemiology,
McGill University Health Center,
Medical Grand Rounds June 11 2013

Conflicts of Interest

I have been a paid consultant for Canadian Agency for Drugs and Technologies in Health (CADTH) and patent law firms representing generic drug companies, am also on the board of INESSS (pro bono)

Otherwise no known conflicts associated with this presentation and to,
the best of my knowledge, am equally disliked by all pharmaceutical and device companies

Genesis of this presentation

• Dec 2012, gave rounds at the Resp. Clin Epi
• In the week before that talk I looked at 4 drugs and this is a rough estimate of quasi-wasteful spending, i.e. extra spending with no or little health benefits

Drug $  
- Non generic Statins 500 – 1000MM  
- Ipilimumab 50MM  
- Dronedarone 50MM  
- Apixaban 500 -1000 MM

Perspective

- "A billion here, a billion there—pretty soon you’re talking about real money.” - Everett Dirksen US senator

Total Health Spending (%GDP) in G7 Countries

Perspective

Total Health Expenditure,
Population Growth and Aging Account for Less Than 2% of Growth in Public-Sector Health Spending

Average Annual Growth Rate, 1998 to 2008

<table>
<thead>
<tr>
<th>Year</th>
<th>Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>7.4%</td>
</tr>
<tr>
<td>2007</td>
<td>2.8%</td>
</tr>
<tr>
<td>2006</td>
<td>0.8%</td>
</tr>
<tr>
<td>2005</td>
<td>1.0%</td>
</tr>
<tr>
<td>2004</td>
<td>2.8%</td>
</tr>
<tr>
<td>2003</td>
<td>2.8%</td>
</tr>
<tr>
<td>2002</td>
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<td>2000</td>
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</tr>
<tr>
<td>1999</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

Technology: Important Supply-Side Factor for Hospital Costs

- New pharmaceuticals
- Imaging equipment (CT and MRI scanners)
- Other medical / surgical devices (Robotic) devices
- IT, Electronic health records
- Innovative procedures, applications and techniques and changes in clinical practices
- Do we get good value for these choices?

Types of Economic Analyses

<table>
<thead>
<tr>
<th>Cost-Minimization Analysis (CMA)</th>
<th>Cost-Benefit Analysis (CBA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>When the consequences of the interventions are the same, then only costs are compared. The aim is to decide the cheapest way of achieving the same outcome.</td>
<td>When both the costs and consequences of different interventions are compared in a diagram and decide if they compare directly and across programmes in similar situations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost-Effectiveness Analysis (CEA)</th>
<th>Cost-Utility Analysis (CUA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>When the consequences of different interventions may vary but can be compared in absolute terms then the consequences are compared in terms of cost per unit of consequence.</td>
<td>When interventions which we compare produce different consequences in terms of benefit (quality and quantity of life) we express them in QALYs.</td>
</tr>
</tbody>
</table>

Economic Analysis – a Simple Starting Point

- Incremental cost
- More cost
- Less cost

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Less</th>
<th>More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant</td>
<td>Reject</td>
<td>Non-dominant</td>
</tr>
<tr>
<td>Non-dominant</td>
<td>Is added effect worth $?</td>
<td></td>
</tr>
<tr>
<td>Non-dominant</td>
<td>Is reduced effect worth $ saving</td>
<td>Accept</td>
</tr>
</tbody>
</table>

Cost-utility Analysis

- Purpose: Consider both the effectiveness and cost of an intervention
- \[ CE_{2,1} = \frac{Cost_2 - Cost_1}{QALY_2 - QALY_1} \]

Cost = Cost of medical intervention + cost of illness
Effectiveness = quality-adjusted life year saved
CE = Cost-effectiveness ratio

Standard benchmark has been dialysis ≈ 50,000 $/QALY

Some difficulties

- RCTs more difficult (product modifications, “moving targets”, “learning curves”)
- Effectiveness = f (device + MD skill)
- New devices can have wider economic implications (training, health care delivery)
- Prices evolve over time
- Can QALYS be reliably measured?
- Requires constant addition of new money
- No consideration of opportunity cost
Not quite so easy

Sildenafil (Viagra) = $11,000/QALY cost-effectiveness compares favorably with that of accepted therapies for other medical conditions. (Ann Intern Med. 2000;132:933-937)

Assume disutility of 0.74 based on interview of 20 men

When their wives were interviewed disutility was 0.98 or $200,000/QALY

Statins

- Atorvastatin RCTs now >160,000 pt years
- Rosuvastatin 69,000 (35,000 pt yrs no benefit in secondary prevention compared to placebo!)
- No studies showing superiority, 3-5X more + evidence with atorvastatin

Economics

- Rosuvastatin $1.70 vs generic atorvastatin $0.56
- Sales of rosuvastatin $800MM could save > $500MM with no adverse outcomes
- Why is this drug on the MUHC drug formulary? Hospital cost is probably small (15K?) but influence on out of hospital Rx prescriptions are potentially large
- Given thin evidence base, could we not spend this money better elsewhere?
- Not only cardiologists!

Cancer de la peau: des Québécois devront être traités à Toronto! Le Soleil Oct 4 2012

Quote from lay press

“Les deux nouveaux médicaments - l'Ipilimumab et le Zelboraf - qui sont testés depuis près de trois ans, sont la seule avancée majeure pour traiter les cancers avancés de la peau. Le taux d'efficacité des médicaments est de 80 % comparativement à 10 % avec la chimiothérapie.”
Another medical journal

The NEW ENGLAND JOURNAL of MEDICINE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

- phase 3 study, to evaluate if ipilimumab +/- gp100 improves overall survival

CONCLUSIONS
Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma.

Some interesting quotes - Academic integrity

- "Draft prepared by six of the academic authors in collaboration with the sponsor and a professional medical writer paid by the sponsor."
- "All the authors signed a confidentiality disclosure agreement with the sponsor."
- "Data were collected by the sponsors and analyzed in collaboration with the senior academic authors."

Survival

Median survival 10 vs 6.4 months
24 months 22% vs. 14%
HR 0.68, p<0.001

Disease free progression

Median progression free survival identical

What was the primary outcome?

- The original primary end point was the best overall response rate at 24 months (i.e., the proportion of patients with a partial or complete response).
- Primary end point amended to overall survival (January 15, 2009) on the basis of “data from phase 2 studies suggest that there is a long-term survival effect”
- But and the referenced phase 2 study actually had no comparator group to suggest better survival

Phase 2 Data
Clinical doubts

• Randomization from Sept 2004 and completed on July 25, 2008, with 676 pts but planned sample size 750 so why stopped early and why was the primary outcomes changed?
• Was the data looked at prematurely?
• Grade 3 or 4 immune-related adverse events was 10-15% vs. 3.0%, resolution about 6 weeks or 50% of median extra survival time
• Le Soleil news report inaccurate but successful in pressuring government

The elephant in the room

• The drug costs $92 800 (10% of population would receive it twice, $184K)
• Sponsor assumes 1 yr extra survival and gets ICER of $98K, using 10 year horizon
• Is this reasonable?

Survival

HR 0.68, p<0.001

The elephant in the room

• The drug costs $92 800 (10% of population would receive it twice, $184K)
• Sponsor assumes 1 yr extra survival and gets ICER of $98K, using 10 year horizon
• Is this reasonable?
• Reality mean additional survival < 3-4 months
• No good estimates QoL
• ICER $300K, 0% probability < 100K
• Quebec budget impact likely 21MM over 3 years
• Other places where we could get better value?
Back to cardiology - ATHENA 2009

**Results**

- Approved FDA July 2009 based on 24% reduction of primary endpoint
- Secondary outcome CV mortality reduction RR 0.71 (0.51–0.98) p= 0.03
- Was this compelling evidence (risk benefits analysis) for approval?

**Canadian 2010 guidelines**

- Better than active amiodarone?
  - DIONYSIS (published June 2010) compared both the efficacy and safety of amiodarone and dronedarone in 504 persistent AF patients.
  - Premature study drug discontinuation due to drug intolerance occurred more frequently with dronedarone (75.1% versus 58.8%, HR 1.59 95% CI 1.28–1.98; P < 0.0001).
  - Deaths occurred in 2 of 249 dronedarone patients and 5 of 255 amiodarone patients.

- Was placebo an appropriate comparator?
  - While other drugs have not been shown to reduce recurrent AF hospitalizations, an outcome not been previously measured, they have been shown to reduce recurrent AF
  - ATHENA primary benefit uniquely driven by fewer AF hospitalizations (7.3%)
  - Is it not reasonable to think that if other drugs reduce recurrent AF episodes, it is likely they will reduce hospitalizations due to recurrent AF?

**Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dronedarone (N=2156)</th>
<th>Placebo (N=2327)</th>
<th>Hazard Ratio for Dronedarone (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome — no. (%)</td>
<td>734 (33.9)</td>
<td>917 (39.4)</td>
<td>0.76 (0.69–0.86)</td>
</tr>
<tr>
<td>First hospitalization due to cardiovascular events — no. (%)</td>
<td>675 (30.9)</td>
<td>859 (36.9)</td>
<td>0.74 (0.67–0.82)</td>
</tr>
<tr>
<td>First hospitalization — no. (%)</td>
<td>336 (14.4)</td>
<td>530 (21.8)</td>
<td>0.63 (0.55–0.72)</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>116 (5.4)</td>
<td>139 (6.0)</td>
<td>0.84 (0.66–1.08)</td>
</tr>
</tbody>
</table>

- Approved FDA July 2009 based on 24% reduction of primary endpoint
- Secondary outcome CV mortality reduction RR 0.71 (0.51–0.98) p= 0.03
- Was this compelling evidence (risk benefits analysis) for approval?
Primary - Stroke, Embolism, or CV Death

Is the drug really safe?

- Previously ANDROMEDA showed increased mortality in CHF patients (25 (8.1%) vs 12 (3.8%), HR 2.13; 95% CI 1.07 to 4.25)
- Other small trials (ERATO, EURIDIS and ADONIS) also showed increased deaths (9 in the 913 dronedarone patients vs.3 in 498 placebo patients.)

How to combine studies?

- Spectrum from assuming complete independence (don’t combine) to homogeneity (assuming identical studies with no between study variation)
- Choice of homogeneity or independence too limited for practical decisions (cf need to make informative inferences with absent or limited data).

Hierarchical modeling

- Possible compromise between these 2 extremes involves hierarchical modeling (may follow Bayesian or frequentist paradigm)
- This involves a more flexible assumption termed exchangeability, which may be regarded as a compromise between assuming independence and assuming identicality of the treatment effects from different sources

Hierarchical modeling

- With a hierarchical model, information from all of the exchangeable groups is shared to some extent (borrowed);
- The amount of borrowing is flexible and results in the partial pooling of data.
- The effect of borrowing is shrinkage as estimates are pulled toward one another with a narrowing of their intervals
- Shrinkage may introduce bias, more than offset by a reduction in variance, and total accuracy increases.
The totality of the evidence

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Deaths Total</th>
<th>Deaths</th>
<th>Patients Total</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exam, 2007</td>
<td>1 80 88</td>
<td>4.90</td>
<td>3.58 (0.60, 7.95)</td>
<td></td>
</tr>
<tr>
<td>Knockhersen, 2008</td>
<td>5 250 250</td>
<td>6.00</td>
<td>1.91 (0.80, 4.50)</td>
<td></td>
</tr>
<tr>
<td>Annecy, 2009</td>
<td>25 210 210</td>
<td>2.50</td>
<td>2.29 (0.68, 4.00)</td>
<td></td>
</tr>
<tr>
<td>Athens, 2010</td>
<td>59 230 230</td>
<td>1.00</td>
<td>1.00 (0.72, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Pallas, 2011</td>
<td>21 180 180</td>
<td>2.00</td>
<td>2.00 (0.66, 4.00)</td>
<td></td>
</tr>
</tbody>
</table>

Bayesian approach – The totality of the evidence

Even if it kills, it is still cost effective!

Cost-Effectiveness of Dronedarone in Atrial Fibrillation: Results for Canada, Italy, Sweden, and Switzerland

Conclusions: Dronedarone on top of SOC appears to be a cost-effective treatment for atrial fibrillation compared with SOC alone. Despite the differences in the local settings considered, the results were consistent across all the countries included in the study.

The study was funded by sanofi-aventis, Paris, France.

CDN 2012 guidelines

RECOMMENDATION

We recommend that dronedarone not be used in patients with permanent AF nor for the sole purpose of rate control (Strong Recommendation, High-Quality Evidence).

We recommend dronedarone not be used in patients with a history of heart failure or a left ventricular ejection fraction ≤ 0.40 (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. Dronedarone is a reasonable choice for rhythm control in selected patients with AF. Typically, these would be patients with nonpermanent (predominantly paroxysmal) AF with minimal structural heart disease. Consideration should be given to monitoring for liver enzyme elevations within 6 months of initiating therapy with dronedarone.

Reasonable conclusion?

- Implies that no sharing of information between studies is possible, even though same drug, and all with cardiac history
- OK for paroxysmal AF or persistent less than 6 months duration but dangerous if AF lasts longer – can we accurately measure this?
- OK if EF is >41% but may kill you if <40%
- Bottom line therapeutic window very narrow and other safer choices exists
- So, why are we still recommending this drug which is also 5-8 times more expensive than other agents?
**CDN Guidelines New Anticoagulants**

**RECOMMENDATION (Fig. 1)**

We recommend that all patients with AF or AFL (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk (eg, CHADS₂) and for the risk of bleeding (eg, HAS-BLED), and that most patients should receive either an OAC or ASA (Strong Recommendation, High-Quality Evidence).

We suggest that when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban (once approved by Health Canada), in preference to warfarin (Conditional Recommendation, High-Quality Evidence).

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**Apixaban – the best?**

**The NEW ENGLAND JOURNAL of MEDICINE**

**Apixaban versus Warfarin in Patients with Atrial Fibrillation**

**CONCLUSIONS**

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984)

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**Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban N=9120</th>
<th>Warfarin N=9081</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSE (Primary outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>212 (2.3)*</td>
<td>265 (2.9)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.80 [0.67, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Ischemic or unspecified stroke</td>
<td>162 (1.78)</td>
<td>175 (1.93)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.92 (0.74, 1.13)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>40 (0.44)</td>
<td>78 (0.86)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.51 (0.35, 0.75)</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>15 (0.16)</td>
<td>17 (0.19)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.87 (0.44, 1.75)</td>
<td></td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>603 (6.6)*</td>
<td>669 (7.4)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.89 [0.81, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>308 (3.4)</td>
<td>344 (3.8)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.89 (0.76, 1.04)</td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td>3182 (35.0)*</td>
<td>3302 (36.5)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.96 [0.92, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>327 (3.6)*</td>
<td>462 (5.1)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>0.70 [0.61, 0.81]</td>
<td></td>
</tr>
</tbody>
</table>

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**Different view of results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban N=9120</th>
<th>Warfarin N=9081</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSE (Primary outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal. rate</td>
<td>1.27%</td>
<td>1.60%</td>
</tr>
<tr>
<td>Difference</td>
<td>3.3 / 1000 treated</td>
<td></td>
</tr>
<tr>
<td>NNT (95%CI)</td>
<td>333 (185-1250)</td>
<td></td>
</tr>
<tr>
<td>All-cause deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal. rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNT (95%CI)</td>
<td>238 (127-2500)</td>
<td></td>
</tr>
</tbody>
</table>

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**Other points to consider**

- Real world compliance for BID vs. daily Rx
- New agents, no means of measuring compliance, no means of reversing effect
- Cost is $3/day vs. $0.16 / day
- Given >1 MM with AF, additional budget impact for general use is $ 1 B annually
- Full economic analysis is req’d but would a target approach not make more sense?
Conflict of interest

Only 1 of 10 authors had no COI.

COI? Which affiliations count more?

CDN Guidelines

More or less believable guidelines?

Off label promotion fines

Overpromoted pills

Company | Date | Drug | Promoted as a treatment for:
--- | --- | --- | ---
Abbott Laboratories | May 2012 | 3,5 | Acute respiratory distress syndrome, sepsis, shock
Abbott Laboratories | June 2011 | 1,6 | Acute respiratory distress syndrome, sepsis, shock
Actavis | Aug 2012 | 0.5 | Acute respiratory distress syndrome, sepsis, shock
Abbott Laboratories | May 2012 | 3,5 | Acute respiratory distress syndrome, sepsis, shock
Abbott Laboratories | June 2011 | 1,6 | Acute respiratory distress syndrome, sepsis, shock

Sources: US Department of Justice, ProPublica, The Economist

Astro-turfing

- **Astroturfing** refers to political, advertising or public relations campaigns that are designed to mask the sponsors of the message to give the appearance of coming from a disinterested, grassroots participant.
- In our context, academic MDs, or even patient groups providing the work for industry whose goals of profit are not necessarily aligned with those of the medical system (value).
<table>
<thead>
<tr>
<th>My biggest concerns today</th>
<th>What to do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lunches, dinners, and conferences sponsored (and organized) by industry</td>
<td>• Be aware of the problem</td>
</tr>
<tr>
<td>• Academics who downplay or hide their conflict of interests (including $ and ghost writing)</td>
<td>• Easy steps – no free lunch, no gifts, no to CME drug sponsorship</td>
</tr>
<tr>
<td>• Impact of COI on guidelines and editorial decisions</td>
<td>• Moderate – full declaration, local full disclosure of research interests, guidelines without COI</td>
</tr>
<tr>
<td>• Pressure groups (patient advocacy groups) that follow an industry agenda</td>
<td>• Difficult – Canadian Sunshine Act (covers speakers’ bureau, consulting, etc), change our culture, improve our critical evaluative skills</td>
</tr>
<tr>
<td>• All lead to inappropriate spending and lack of value for our limited resources</td>
<td></td>
</tr>
</tbody>
</table>

Thank you