Sacred Monsters: Evidence, Guidelines and the Nature of Good Primary Care

V International Conference on Primary Care
Rio De Janiero Brazil 2010
Dee Mangin
• The nature of evidence
• The nature of guidelines
• The nature of patients
Some of the witnesses we have had have described these guidelines as a framework, within which to work... Does that fit in with how you saw the guidelines?

MT They are exactly what they say, guidelines, they are not the law. They are guidelines

Did they have to be followed?

MT Of course they have to be followed, but they are not strict law. That is why they are guidelines and not law and, of course, they have to be applied according to the relevant circumstances.

They are expected to be followed?

MT Of course they have to be followed. They need to be followed for what they are, guidelines
Effective Care

Recognition of the patients needs

Consideration by doctor and patient of the best that medical science has to offer

Context a continuous and comprehensive relationship that will maximise the therapeutic effect of using or not using treatments
Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values


Dave Sackett
Guidelines and EBM

Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values.
Clinical state and circumstances

Research evidence

Patients’ preferences and actions

Improved health outcomes
Focus on the disease

Guidelines, targets and pay for performance structures designed to drive this along single disease / specialist lines

Aim for standardisation and adherence

Premise that it doesn’t matter who does it as long as it gets done
The focus has shifted from patients and the diseases that make them suffer, to the diseases themselves and their measurement within the patient.
Evidence based medicine

risks becoming

Scientific - bureaucratic medicine
Guidelines as targets

Appropriate
- immunisation
- hand washing
- measuring BP in both arms

Inappropriate
- chronic disease
Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Data Extraction The number of recommendations and the distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were deter-
Clinical trials: bias

• Largely commercially driven
  – 1/2 of efficacy and 2/3 of harm outcomes incompletely reported
  – 2/3 of trials had a primary outcome that was changed
  – results and conclusions biased in favour of the funding company’s drug

• Generated in highly selected populations
  – secondary and tertiary care
  – exclude multiple comorbidities
  – exclude older patients

Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry

Niteesh K. Choudhry, MD, FRCPC
Henry Thomas Stelfox, MD, FRCPC
Allan S. Detsky, MD, PhD, FRCPC

Interactions between physicians and the pharmaceutical industry have received increasing amounts of attention over the last several years. Several authors have described significant contact between the

Context Increasing contact has been reported between physicians and the pharmaceutical industry, although no data exist in the literature regarding potential financial conflicts of interest for authors of clinical practice guidelines (CPGs). These interactions may be particularly relevant since CPGs are designed to influence the practice of a large number of physicians.

Objective To quantify the extent and nature of interactions between authors of CPGs and the pharmaceutical industry.

Design, Setting, and Participants Cross-sectional survey of 192 authors of 44 CPGs endorsed by North American and European societies on common adult diseases published between 1991 and July 1999. One hundred authors (52%) provided us
Pursuing New Revenue Growth Opportunities
Emerging Markets

Global Pharma Sales

<table>
<thead>
<tr>
<th>Market CAGR</th>
<th>2007</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>$713</td>
<td>$950</td>
</tr>
<tr>
<td>10%</td>
<td>80</td>
<td>156</td>
</tr>
<tr>
<td>3%</td>
<td>633</td>
<td>794</td>
</tr>
</tbody>
</table>

Emerging Markets: $713 Billion in 2007; $950 Billion in 2012
Developed Markets: $633 Billion in 2007; $794 Billion in 2012

Goal:
- Top 5 in each market

Keys to Success:
- Focus on China, Brazil, Turkey, India, South Korea, Poland and Russia
- Internal and external growth opportunities
- Investment commensurate with the opportunity
- Contribution to current earnings while accelerating growth
- Significant local presence

Source: IMS Health, Market Prognosis, September 2008

Emerging Markets* will represent 16% of the global pharma market by 2012

*Emerging Markets are defined as China, Brazil, Turkey, India, South Korea, Poland and Russia.

http://google.brand.edgar-online.com/EFX_dll/EDGARpro.dll?FetchFilingHtmlSection1?SectionID=6289965-43085-189819&SessionID=09R1HCgZHm27HR7 accessed 26 Feb 2010
# Intermediate Indicators and Good Care

<table>
<thead>
<tr>
<th>↓ LDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ LDL cholesterol</td>
</tr>
<tr>
<td>↓ LDL cholesterol</td>
</tr>
<tr>
<td>Better glucose control</td>
</tr>
<tr>
<td>Lower HbA1C</td>
</tr>
<tr>
<td>Better kidney function</td>
</tr>
<tr>
<td>Lower blood pressure</td>
</tr>
<tr>
<td>Treatment/Condition</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Adding torcetrapib to atorvastatin</td>
</tr>
<tr>
<td>HRT</td>
</tr>
<tr>
<td>Adding ezitimbe to simvastatin</td>
</tr>
<tr>
<td>Rosiglitazone for diabetes</td>
</tr>
<tr>
<td>Tighter glucose control</td>
</tr>
<tr>
<td>Lower glucose control target</td>
</tr>
<tr>
<td>Adding an ACE blocker to and ACE inhibitor</td>
</tr>
</tbody>
</table>
# Perils of intermediate targets as quality indicators

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect on LDL cholesterol</th>
<th>Effect on death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adding torcetrapib to atorvastatin</td>
<td>↓ LDL cholesterol</td>
<td>Higher death rate</td>
</tr>
<tr>
<td>HRT</td>
<td>↓ LDL cholesterol</td>
<td>Higher death rate</td>
</tr>
<tr>
<td>Adding ezitimbe to simvastatin</td>
<td>↓ LDL cholesterol</td>
<td>No change in death rate</td>
</tr>
<tr>
<td>Rosiglitazone for diabetes</td>
<td>Better glucose control</td>
<td>Higher rate of heart attacks and deaths</td>
</tr>
<tr>
<td>Tighter glucose control</td>
<td>Lower HbA1C</td>
<td>Higher death rate</td>
</tr>
<tr>
<td>Lower glucose control target</td>
<td>Better kidney function</td>
<td>More hypoglycemic episodes</td>
</tr>
<tr>
<td>Adding an ACE blocker to and ACE inhibitor</td>
<td>Lower blood pressure</td>
<td>Higher adverse events with no change in CV events</td>
</tr>
</tbody>
</table>
The nature of patients
Real populations

In primary care 40% of new presentations never fit criteria for any known diagnosis.

In primary care 40% of patients have multiple comorbid conditions.
About half of people over 65 years old have at least 3 coexisting chronic conditions

About one in five have 5 or more
Hypothetical >70 year old woman

- COPD
- Type 2 diabetes
- Hypertension
- Osteoarthritis
- Osteoporosis
• 19 doses of 12 different medications
• Taken at five times during the day
• 14 non pharmacological activities
• 10 different possibilities for significant medicine interactions either with other medicines or other diseases
“Standards that define quality of patient care…by placing emphasis on high rates of adherence to guidelines and targets rather than weighing the burden, risks and benefits of complex therapies in shared decision making could ultimately undermine quality of care.”

Boyd et al JAMA 2005; 294:716-24
## Individual GP Data

*patients > 75y
#this is a subset of patients on > 5 meds

### Polypharmacy Report on Total Patients aged 75 years and over from 1st Oct 2008 to 31st Mar 2009

<table>
<thead>
<tr>
<th>Name</th>
<th>No. enrolled pts &gt; 75y</th>
<th>No. pts* on &gt;5 meds (%)</th>
<th>No. pts* on &gt; 10 meds# (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>162</td>
<td>50 (30.86%)</td>
<td>8 (4.94%)</td>
</tr>
<tr>
<td></td>
<td>132</td>
<td>52 (39.39%)</td>
<td>13 (9.85%)</td>
</tr>
<tr>
<td></td>
<td>519</td>
<td>139 (26.78%)</td>
<td>30 (5.78%)</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>3 (15.79%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td></td>
<td>271</td>
<td>45 (16.61%)</td>
<td>8 (2.95%)</td>
</tr>
<tr>
<td></td>
<td>89</td>
<td>28 (31.46%)</td>
<td>2 (2.25%)</td>
</tr>
<tr>
<td></td>
<td>217</td>
<td>51 (23.50%)</td>
<td>9 (4.15%)</td>
</tr>
<tr>
<td></td>
<td>293</td>
<td>122 (41.64%)</td>
<td>58 (19.80%)</td>
</tr>
<tr>
<td></td>
<td>362</td>
<td>134 (37.02%)</td>
<td>37 (10.22%)</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>23 (31.08%)</td>
<td>4 (5.41%)</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>13 (17.11%)</td>
<td>1 (1.32%)</td>
</tr>
<tr>
<td></td>
<td>129</td>
<td>31 (24.03%)</td>
<td>10 (7.75%)</td>
</tr>
<tr>
<td></td>
<td>189</td>
<td>75 (37.69%)</td>
<td>13 (6.53%)</td>
</tr>
<tr>
<td></td>
<td>315</td>
<td>63 (20.00%)</td>
<td>6 (1.90%)</td>
</tr>
</tbody>
</table>

No pts > 75y in the PHO are 50596
Of these there are 15168 patients on > 5 meds (30%) and 6151 patients on > 10 meds (12%).
People >70yrs who were dispensed one or more medicines (March - Aug 2007).

Most are on >4 medicines
• Hospitalisation from inappropriate medication use in older adults estimated at 17%
• 6x the general population rate
• Adverse drug reactions 4-6th most common cause of death (US)
• Rate goes up sharply with the number of drugs taken

Nananda C et al Archives of Internal Medicine, Vol. 150, No.4 (Apr. 1990)
Lombardi & Kennicutt. Med Pharm 2 (1), 2001
Paying for performance

“I find myself considering whether to start an elderly female patient on a fourth antihypertensive in order that she will fall as I predict she will and I can then exception report her in order to maintain the QOF target”

UK Professor of General Practice
Persuasion or coercion

“Some patients will come to you and they’ll plead with you ‘please don’t give me any tablets I’ll bring my blood pressure down, I’ll do everything, I’ll bring it down’ and they’re not horrendously high they’re like 140/90 or whatever …but we’re saying to them ‘well, look we’ve checked it three times now and it remains raised, you’re clinically classed as hypertensive, we follow these guidelines and this is what we should be doing with you”
The nature of individuals
Patient priorities

“Life itself is not the most important thing in life. Some cling to it as a miser to his money and to as little purpose. Some risk it for a song, a hope, a cause, for wind in their hair.”

Sir Theodore Fox
Shared decision making
## Causes of Death

<table>
<thead>
<tr>
<th>Causes</th>
<th>Deaths (000)</th>
<th>(%)</th>
<th>Years of Life Lost (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>122</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>139</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>129</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Perinatal conditions</td>
<td>70</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Violence</td>
<td>57</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>53</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>51</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>46</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>36</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>34</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Inflammatory heart diseases</td>
<td>22</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: [Death and DALY estimates by cause, 2002](http://www.who.int/entity/healthinfo/statistics/bodgbdddeathdalyestimates.xls)
HEART DISEASE
EPIDEMIC
Patient priorities: Perverse incentives and unethical outcomes
People aged ≥75 years should be treated in the same way as younger people.

Older people gain a similar relative benefit from cholesterol lowering, but are more likely to benefit in absolute terms because of their much higher pretreatment cardiovascular risk.
Cholesterol drugs over age 70

Shepherd J et al. *Lancet* 2002;360
Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

James Shepherd, Gerard J Blauw, Michael B Murphy, Edward L E M Boileen, Brendan M Buckley, Stuart M Cobbe, Ian Ford, Allian Gaw, Michael Hyland, J Wouter Jukema, Adriaan M Kamper, Peter W Macfarlane, A Edz Melinders, John Norrie, Chris J Packard, Ivan J Perry, David J Stott, Brian J Sweeney, Clillian Twomey, Rudi G J Westendorp, on behalf of the PROSPER study group*

Summary

Background Although statins reduce coronary and cerebrovascular morbidity and mortality in middle-aged individuals, their efficacy and safety in elderly people is not fully established. Our aim was to test the benefits of pravastatin treatment in an elderly cohort of men and women with, or at high risk of developing, cardiovascular disease and stroke.

Methods We did a randomised controlled trial in which we assigned 5804 men (n=2804) and women (n=3000) aged 70–82 years with a history of, or risk factors for, vascular disease to pravastatin (n=2913). Baseline 4·0 mmol/L to 9·0 mmol/L, the average and our patients, was 6·0 mmol/L. Coronary death, non-fatal myocardial infarction, and non-fatal stroke. Analyzed were the effects of pravastatin on the primary composite end point (coronary death plus non-fatal myocardial infarction) and on non-fatal stroke. New cancer diagnoses were more frequent on pravastatin than on placebo (1·25, 1·04–1·51, p=0·020).

Findings Pravastatin reduced coronary death and myocardial infarction by 34% and reduced non-fatal stroke by 21% (relative risk 0·85, 95% CI 0·78–0·93; p=0·0008). The reduction in risk was unaffected (1·03, 0·81–1·31, p=0·8), but the hazard ratio for transient ischaemic attack was 0·75 (0·55–1·00, p=0·051). New cancer diagnoses were more frequent on pravastatin than on placebo (1·25, 1·04–1·51, p=0·020).

Interpretation Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals. PROSPER therefore extends to elderly individuals the treatment strategy currently used in middle aged people.

However, incorporation of this finding in a meta-analysis of all pravastatin and all statin trials showed no overall increase in risk. Mortality from coronary disease fell by 24% (p=0·043) in the pravastatin group. Pravastatin had no significant effect on cognitive function or disability.

University Department of Pathological Biochemistry
(Prof J Shepherd mD, A Gaw mD, Prof C J Packard BSc), North Glasgow University NHS Trust; Robertson Centre for Biostatistics
(Prof I Ford PhD, J Norrie MD), and Division of Cardiovascular and Medical Sciences (Prof S M Cobbe MD, Prof P W Macfarlane BSc, University of Glasgow, Glasgow, UK. *Members listed at end of paper


increasing age. However, investigators of previous statin trials have reported benefits on stroke, and results of observational studies have raised the possibility that statins could reduce the rate of cognitive decline in elderly people. However, in the oldest old people, low plasma cholesterol is associated with increased mortality. In view of these conflicting observations, we concluded that the balance of the efficacy and safety of cholesterol reducing drug therapy in elderly people is not yet favorable.
D Mangin, K Sweeney, I Heath BMJ 2007;335;285-7
01 CHD death or non-fatal MI or fatal or non-fatal stroke
   PROSPER

02 CHD death or non-fatal MI
   PROSPER

03 fatal or non-fatal stroke
   PROSPER

04 all cause mortality
   PROSPER

05 cancer death
   PROSPER

06 new cancer diagnosis
   PROSPER
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Findings Pravastatin reduced the risk of death from coronary heart disease by 34% and reduced the risk of hospitalisation because of heart disease by 24% (95% CI 18–34, p<0·0001) in elderly people with or at high risk of vascular disease. However, incorporation of this finding in a meta-analysis of all pravastatin and all statin trials showed no overall increase in risk. Mortality from coronary disease fell by 24% (p=0·043) in the pravastatin group. Pravastatin had no significant effect on cognitive function or disability.

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Lancet 2002; 360: 1623–30. Published online Nov 19, 2002
http://image.thelancet.com/extras/02an8325web.pdf

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Conflict of interest statement
The authors declare the following arrangements with the sponsoring company or other companies, or both, making competing products. Consultancy agreements: J Shepherd, M B Murphy, I Ford, B M Buckley, S M Cobbe, J W Jukema, C J Packard. Research support, honoraria, travel grants: J Shepherd, G J Blauw, M B Murphy, E L E M Bollen, B M Buckley, S M Cobbe, I Ford, A Gaw, M Hyland, J W Jukema, P W Macfarlane, A E Meinders, J Norrie, C J Packard, D J Stott, R G J Westendorp.

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We thank Sheena Brownlie for her administrative and secretarial help, and the following individuals and their staff, all of whom have worked with great enthusiasm and professionalism, contributing to the successful completion of this trial: recruitment of patients—Melvyn Percy, Karen McIntyre, Bernadette Stierhout, Helen Walsh, on behalf of all staff within the trial centres in Glasgow, Leiden, and Cork, and the Irish College of General Practitioners; psychometric testing—Peter Houx; MRI scanning—Mark A van Buchem; central laboratory—M Anne Bell, Christine Gourlay; ECG laboratory—Julian Allan, Louise Inglis, J Kennedy, Shahid Latif, Kathryn McLaren, Pamela Reay, Marianne Sneddon, Jean Watts; Robertson Centre for Biostatistics—Liz Anderson, Sharon Kean, Jan Love, Anne Nears, Michele Robertson; Biobank—Marinke Frölich; PROSPER administration centres—Liz Ronald, Jane Kent, Moira Mungall, Eleanor Dinnett, Jane Rush, Claire Gordon, Eileen McCafferty, Margaret McMurrough, Elizabeth Brown, Kirsty Simpson, Marjan Hornstra Moedt, Ilse van Gils, Natascha Zimmermann, Maria-Teresa Carroll, Maura Fallon, Leona Heaphy, Lisa Drinan, Ciara Roe, Denise Murphy, Nicholas Hern, Suzanne Doyle, Niamh O’Dwyer, Michelle Kavanagh, Gobnait Lynch, Noirin Deasy, Margaret O’Donoghue, Sinead Murphy, Eimear Singleton, Imelda O’Meara, Shirley O’Donoghue, Emma Clarke, Annette O’Gorman, Clare Mills, Carmel Buckley, and the staff of the three administrative centres.

This work was supported by an investigator initiated grant from Bristol-Myers Squibb, USA.
The Empty Mailbox

T Moffitt
OK Grandad, You Look Out the Window and I’ll be Back in 3 Hours

T. Moffitt
‘I can’t say I’m particularly bothered about heart disease. To a certain extent I’d rather go with a heart attack than drag on.’

‘certainly something you dread, you know (cancer)...a really unpleasant way to go ... I wouldn’t wish it on anyone’

Discriminatory Prescribing

“It is an art of no little importance to administer medicines properly: but, it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them.”

Philippe Pinel (1745-1826)
Treatise on Insanity
Guidance to inform practice rather than guidelines to drive it
To improve the individual’s experience of healthcare we must not define people by their sicknesses but rather think of them as a sick person.