

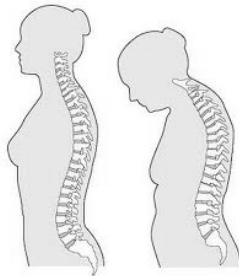
Prevention Strategies: Wisdom and Folly

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- ☞ What does it mean to you to feel well?
- ☞ How able are you to tolerate uncertainty?
- ☞ How do you feel about the medicalization of life?
- ☞ How do you assess risk?

“Presymptomatic”

- ☞ Pre-hypertension
- ☞ Osteopenia
- ☞ Pre- diabetes
- ☞ “Schizophrenia prodrome” – children more likely to become schizophrenic



Lies, Damned Lies, and Statistics

- ☞ Relative Risk (RR) = the ratio of the chance developing a disease among members of a population exposed to a factor compared with a similar unexposed population
- ☞ Absolute Risk Reduction (ARR) = event rate in *control* group – event rate in *intervention* group

Number needed to treat

$$\text{NNT} = \frac{1}{\text{ARR}}$$

$$\text{NNT} = 1$$

event rate in *control* group -
event rate in *intervention* group

THE NUMBER NEEDED TO TREAT

How well do drugs work? Ads and news stories usually say that a medicine slashes the risk of, say, heart attacks by a big number, like 50%. But that often overstates the benefit, because it fails to provide the *absolute* risk. If only 2 people in a group of 100 are expected to have a heart attack, then a drug that cuts the rate by 50% prevents just 1 heart attack when taken by all 100 people. That's why researchers favor using the "number needed to treat" (NNT). It shows how many people must take a drug for one person to benefit.

| DRUG | NNT | DETAILS |
|--|--|---|
| Antibiotic cocktail to eradicate ulcer-causing stomach bacteria (H. pylori) | 11 to eradicate bacteria | Bacteria will be eradicated in 10 of 11 people with 6 to 10 weeks of treatment. |
| Antibiotic cocktail to eradicate ulcer-causing stomach bacteria (H. pylori) | 5 to heal ulcers | Ulcers in 1 in 5 people will heal by the end of treatment. One in two will be cured in a year. |
| Lipitor and other cholesterol-lowering statins, when used in people who have had a heart attack or have signs of heart disease | 16-23 to prevent one heart attack | In clinical trials, with 5 years of treatment, 1 in 16-23 people is spared a coronary event. To prevent an actual death, the NNT is 48. |
| Lipitor and other cholesterol-lowering statins, when used in patients without heart disease, but who have risk factors such as high blood pressure | 70-250 to prevent one heart attack or stroke | Benefits with 5 years of treatment are smaller in those without existing disease, and the NNT increases with lower initial risk. |
| Lipitor and other cholesterol-lowering statins, when used in patients without heart disease, but who have risk factors such as high blood pressure | 500 to prevent death or serious medical conditions | In clinical trials, there was no significant reduction in deaths or serious events, so a precise NNT can't be calculated. |
| Avandia, which controls blood sugar | 1,000+ to prevent heart attacks, other effects of diabetes | The drug reduces blood sugar, but that does not translate into fewer problems, such as kidney failure, nerve damage, amputations. |
| Zetia, which lowers cholesterol | 1,000+ to prevent heart disease | Companies admit that it has not been shown to reduce heart disease or heart attacks. |

From: Bonfield, Therapeutics Institute, Boston/MSH

| Effect of BONIVA on the Incidence of Vertebral Fracture in the 3-year Osteoporosis Treatment Study* | | | | |
|---|--|------------------------------------|--|--|
| | Proportion of Patients with Fracture (%) | | | |
| | Placebo n=975 | BONIVA 2.5 mg Daily n=977 | Absolute Risk Reduction (%) 95% CI | Relative Risk Reduction (%) 95% CI |
| New Vertebral Fracture 0-3 year | 9.6 | 4.7 | 4.9 (2.3, 7.4) | 52** (29, 68) |
| New and Worsening Vertebral Fracture 0-3 year | 10.4 | 5.1 | 5.3 (2.6, 7.9) | 52 (30, 67) |
| Clinical (Symptomatic) Vertebral Fracture 0-3 Year | 5.3 | 2.8 | 2.5 (0.6, 4.5) | 49 (14, 69) |

*The endpoint value is the value at the study's last time point, 3 years, for all patients who had a fracture identified at that time; otherwise, the last postbaseline value prior to the study's last time point is used.
**p=0.0003 vs. placebo


| Patients with Osteoporosis | | | |
|----------------------------|-------------|--|----------|
| Medication | DOSE | 3 year NNT to prevent vertebral fracture | Trial |
| Aledronate (Fosamax) | 10 mg/d | 15/34 | FIT |
| Ibandronate (Boniva) | 2.5 mg/d | 21 | BONE |
| Risedronate (Actonel) | 5mg/d | 20 | VERTA-NA |
| Zoledronic Acid (Reclast) | 5mg IV q yr | 14 | HORIZON |
| Raloxifene (Evista) | 60 mg/d | 29 | MORE |
| Strontium ranelate | 2 g/d | 9 | SOTI |
| Teriparatide (Forteo) | 20 ug/d | 12 | |

Ringe Jdet al. *Rheumatol Int* (2010) 30:863-869
MacLaughlin EJ et al. *Am J Health-Syst Pharm*. 2008; 65:343-57

| Patients with Osteoporosis | | | |
|----------------------------|------------|-------------------------------|---------|
| Medication | Dose | NNT to prevent a hip fracture | Trial |
| Aledronate | 10 mg /d | 91 | FIT |
| Risedronate | 2.5-5 mg/d | 91 | HIP |
| Zoledronic Acid | 5 mg iv | 91 | HORIZON |
| Strontium Ranelate | 2 g/d | 48 | TROPOS |

Ringe Jdet al. *Rheumatol Int* (2010) 30:863-869
MacLaughlin EJ et al. *Am J Health-Syst Pharm*. 2008; 65:343-57

Patient and practitioner are partners in the healing process



Shared decision making process

New tools

- ⌘ Hip fracture risk calculators
 - <http://riskcalculator.fore.org/>
- ⌘ Heart Attack risk assessment tool

Framingham Heart Study

- <http://hp2010.nhlbi.nih.net/atpiii/calculator.asp>
- www.myoptumhealth.com/portal/ManageMyHealth/Heart+Attack



| The Number Needed to Treat is time-dependent | | | | | |
|--|---------------------------|--------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Table 1: Example calculations for a trial evaluating the impact on fatal and nonfatal myocardial infarctions of statins for patients with hypertension and other cardiovascular risk factors* | | | | | |
| Time | Event rate in placebo arm | Event rate in intervention arm | Relative risk reduction* (95% CI) | Absolute risk reduction† (95% CI) | Number needed to treat‡ (95% CI) |
| 90 d | 21/5121 | 7/5184 | 0.67 (0.23-0.86) | 0.28 (0.07-0.48) | 364 (210-1362) |
| 12 mo | 61/5121 | 34/5184 | 0.45 (0.16-0.64) | 0.54 (0.17-0.92) | 186 (109-601) |
| 3.3 yr (study end) | 154/5121 | 100/5184 | 0.36 (0.18-0.50) | 1.08 (0.48-1.69) | 93 (59-208) |

Note: CI = confidence interval.
*Relative risk reduction = 1 - (event rate in intervention arm/event rate in placebo arm). For example, at 90 days, relative risk reduction = 1 - (7/5184) / (21/5121).
†Absolute risk reduction = event rate in placebo arm - event rate in intervention arm. For example, at 90 days, absolute risk reduction = 21/5121 - 7/5184.
‡Number needed to treat = 100/absolute risk reduction. It can also be calculated as number needed to treat = (1/absolute risk reduction) × 100. For example, at 90 days, number needed to treat = 1000.3.

McAlister FA *CMAJ* 2008;179:549-553

Weighing the evidence for prevention

- ⌘ Amount
- ⌘ Quality
- ⌘ Relative benefit
- ⌘ Relative harm



Prevention concepts

- ⌘ Screening
 - ⌘ BP and cholesterol
- ⌘ Early detection
 - ⌘ Colon polyps
 - ⌘ Cervical cancer
 - ⌘ Mammogram and PSA
- ⌘ Primary prevention, secondary prevention, tertiary prevention



US Preventive Services Task Force recommendation categories

| | |
|---|---|
| A | The USPSTF recommends the service. There is high certainty that the net benefit is substantial. |
| B | The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. |
| C | The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small. |
| D | The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. |
| I | The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the services. Evidence is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined. |

Internet Citation: U.S. Preventive Services Task Force Ratings. June 2007. Agency for Healthcare Research and Quality, Rockville, MD.
<http://www.ahrq.gov/clinic/uspstf07/ratingsv2.htm>. Accessed May 27, 2010

- ⌘ After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group
- ⌘ The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group
- ⌘ Conclusions After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups.

N Engl J Med 2009;360:1310-9.

October 2011

- ⌘ The USPSTF recommends against prostate-specific antigen (PSA) based screening for prostate cancer. This is a grade D recommendation
- ⌘ There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits

Risks of Prostate Cancer Treatment

- ⌘ For every 1,000 men treated for prostate cancer
 - ⌘ 5 die of perioperative complications
 - ⌘ 10-70 suffer significant complications but survive
 - ⌘ 200-300 suffer long-term problems, including urinary incontinence, impotence or both.

Controversies in Screening

- ⊗ Screening mammography
 - ⊗ Effective age 50-69
 - ⊗ ? Age 40-49
- ⊗ Clinical breast exam
- ⊗ Self breast exam



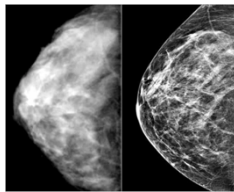
Risks of Mammography:

- ⊗ Overdiagnosis
- ⊗ Autopsy studies show undetected breast cancer in 37% of women who died of other causes
- ⊗ Study of 42,238 Norwegian calculated that 22% of symptom-free cancers found on a screening mammogram naturally regressed on their own
- ⊗ For every 2,000 women screened by mammography over 10 years:
 - ⊗ 1 will avoid dying from breast cancer
 - ⊗ 10 others will receive treatments for a cancer that would have never become life-threatening

Zahl, Moehlan, Welch *Archives of Internal Medicine* 2008
Jørgensen, K. *BMJ* 2009;339:b2587

November 2009: USPSTF change in recommendations

- ⊗ Biennial screening mammography for women aged 50 to 74 years.
Grade: B recommendation
- ⊗ Screening mammography before age 50 should be an individual decision.
Grade: C recommendation



Diabetes Prevention Program (DPP)

- ⊗ Goal: to determine whether diet + exercise or metformin could prevent or delay the onset of type 2 diabetes
 - ⊗ 1996-2001 multisite study
 - ⊗ 3,234 study participants all overweight with pre-diabetes
- ⊗ Intensive lifestyle modification program
 - ⊗ lose 5-7% body weight
 - ⊗ healthy low-calorie, low-fat diet
 - ⊗ 30 minutes of physical activity 5 days a week
- ⊗ Standard lifestyle recommendations plus metformin
- ⊗ Standard lifestyle recommendations plus placebo twice daily

DPP Research Group. *N Engl J Med* 2002, Vol.346, No. 6.

Incidence of Diabetes



Half of the people who suffer a first heart attacks have normal serum cholesterol

- ⊗ Statins effect:
 - ⊗ ↓ LDL
 - ⊗ do not ↑ HDL
 - ⊗ do not ↓ triglycerides
 - ⊗ do not address modifiable risk factors:
 - Diet
 - Lack of physical activity
 - Stress
 - Uncontrolled anger



Research Evidence

- ✧ Mediterranean diet reduces risk of death from heart disease by 72% (and reduces risk of cancer by 61%)
Lyon Heart Trial Circulation 1999

- ✧ Statin medicines reduce risk of death from heart disease by 42%
Scandinavian Simvastatin Survival Study Lancet 1995

- ✧ Daily serving of green leafy vegetables reduce risk of death from heart disease by 23%
Annals of Internal Medicine 2001



Mediterranean Diet

- ✧ High intake of vegetables, legumes, fruits, and (unrefined) cereals
- ✧ Moderate to high intake of fish
- ✧ Low intake of saturated fats
- ✧ High intake of mono-unsaturated especially olive oil
- ✧ Low to moderate intake of dairy, mostly cheese and yogurt
- ✧ Low intake of meat
- ✧ Modest intake of alcohol, mostly as wine



Mediterranean diet mechanisms

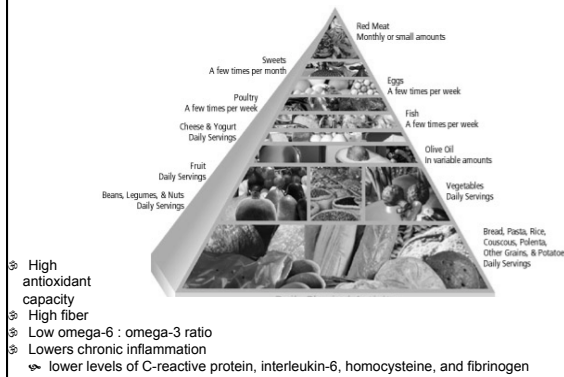
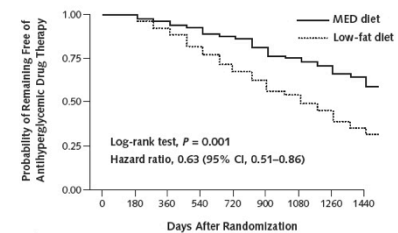


Figure 2. Probability of remaining free of antihyperglycemic drug therapy.

Ann Intern Med. 2009;151:306-314

NNT = 4



| At risk, n | | Days After Randomization | | | | | | | | |
|--------------|-----|--------------------------|-----|-----|-----|-----|-----|------|------|------|
| | | 0 | 180 | 360 | 540 | 720 | 900 | 1080 | 1260 | 1440 |
| MED diet | 108 | 108 | 105 | 101 | 89 | 80 | 77 | 66 | 52 | 49 |
| Low-fat diet | 107 | 107 | 98 | 87 | 72 | 64 | 54 | 45 | 35 | 29 |

MED = low-carbohydrate, Mediterranean-style.

215 overweight people with newly diagnosed type 2 diabetes never treated with anti-hyperglycemic drugs
HbA1c < 11%

Optimal Population-based Prevention:

Maintain "ideal" risk factor profile:

1. Not currently smoking
2. BMI <25
3. ≥ 150 min/wk moderate or ≥ 75 min/wk vigorous or combination
4. Healthy diet
5. Total cholesterol <200
6. Blood pressure <120/<80
7. Fasting blood sugar <100

Lloyd-Jones DM, et al., Defining and setting national goals for CV health promotion and disease reduction: the AHA's Strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121

Optimal Population-based Prevention:

Maintain "ideal" risk factor profile:

- ✧ Add 10 years of longevity
- ✧ Enhance health related quality of life
- ✧ Reduce Medicare costs
- ✧ 90% of CV deaths could be prevented
- ✧ But... only 5% of Americans have this phenotype

Lloyd-Jones DM, et al Prediction of lifetime risk for CVD by risk factor burden at 50 years of age. *Circulation*. 2006;113(6):791-798
Capewell S, et al Cardiovascular risk factors and potential for reducing CHD mortality in the US. *Bull World Health Organ*. 2010;88(2):120-130

The Healthy Ageing: a Longitudinal study in Europe (HALE)

- ⌘ 2339 healthy men and women, aged 70 to 90 years from 11 European countries
- ⌘ Ten-year mortality from all causes
- ⌘ Investigated the effect of Mediterranean diet, physical activity, moderate alcohol use, and nonsmoking
- ⌘ 935 participants died: 371 from cardiovascular diseases, 233 from cancer, 145 “other,” 186 unknown
 - ↪ Mediterranean diet (HR 0.77)
 - ↪ Moderate alcohol use (HR, 0.78)
 - ↪ Physical activity (HR, 0.63)
 - ↪ Nonsmoking (HR, 0.65)
 - ↪ All four combined: (HR 0.35)

JAMA. 2004;92:1433-1439.

“Healthy living is the best revenge”

- ⌘ 23,000 people – 4 behaviors
 - ↪ *not smoking*
 - ↪ *exercising 3.5 hours a week*
 - ↪ *eating a healthy diet (fruits, vegetables, beans, whole grains, nuts, seeds, and low meat consumption)*
 - ↪ *keeping a healthy weight (BMI <30)*
- ⌘ Prevention of 78% of chronic disease: 93% of diabetes, 81% of heart attacks, 50% of strokes and 36% of all cancers

Arch Intern Med. 2009;169(15):1355-1362.

Exercise

- ⌘ **Benefits**
 - ↪ ↓ coronary heart disease
 - ↪ ↓ cancer incidence
 - ↪ ↓ diabetes
 - ↪ ↓ falls
 - ↪ ↑ mood
 - ↪ ↑ cognitive function
- ⌘ **How much?**
 - ↪ 150 minutes/week disease prevention
 - ↪ 60 minutes/day weight maintenance
 - ↪ 90 minutes/day weight loss



Mechanisms

- ⌘ **Systemic effects**
 - ↪ Regulates energy balance and fat distribution
 - ↪ Modifies metabolic hormones (insulin, glucose) and growth factors (IGF)
 - ↪ Improves anti-tumor defense system
 - ↪ Improves antioxidant defense and DNA repair activity



Happiness is protective

- 8000 British civil servants in Whitehall II
 - ↪ Average age 49 years old
 - ↪ Rated satisfaction on seven specific areas: love relationships, leisure activities, standard of living, job, family, sex, and one's self
 - ↪ Higher average life satisfaction associated with 13% a reduced risk of total coronary heart disease (HR 0.87; 95% CI: 0.78 – 0.98)

European Heart Journal

Stress reduction practices



- ⌘ Breathing practices
- ⌘ Meditation
- ⌘ Active forms of relaxation
 - ↪ Yoga
 - ↪ Tai chi
 - ↪ Exercise

As you weigh evidence for prevention

- ⌘ Relative benefits (NNT)
- ⌘ Relative harm (NNH)
- ⌘ Quality of the evidence
- ⌘ Side effects and side benefits



Resources

- ⌘ *Why Our Health Matters: A Vision of Medicine That Can Transform Our Future* Andrew Weil MD
- ⌘ *The Truth About the Drug Companies* Marcia Angell MD
- ⌘ *Overdosed America: The Broken Promise of American Medicine* John Abramson MD
- ⌘ Arizona Center for Integrative Medicine
www.integrativemedicine.edu