Uncertainty and Risk

Lawrence G. Raisz, MD, Memorial Lecture
May 12, 2021

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Lawrence Gideon Raisz (1925 – 2010)

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Disclosure

- No direct compensation from potentially conflicting entities
- Employed by New Mexico Clinical Research & Osteoporosis Center, which has received the following in the past one year:
  - Research grant support from Amgen, Radius, Mereo
  - Consulting and scientific advisory board fees from Amgen, Radius, Alexion, Sandoz, Samsung Bioepis
  - Honoraria for speakers' bureaus of Alexion, Radius
  - Support for project development with University of New Mexico
  - Royalties from UpToDate for sections on DXA, fracture risk assessment, and prevention of osteoporosis
- Board positions with the NOF, ISCD, OFNM
- Guideline committees with NOF, ISCD, AACE, NAMS

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Objectives

- Understand the origins of risk and uncertainty in clinical medicine
- Describe the benefits and limitations of clinical trials
- Explain the application of evidence-based medicine to individualizing treatment decisions

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Risk

- General
  - Probability of harm
  - Probability of loss of that which we value
    - **RISK = HAZARD + OUTRAGE** *
- Osteoporosis
  - Untreated: probability of fracture and consequences of fracture vs. avoidance of medication side effects [feared side effects]
  - Treated: expected benefits vs. possible adverse effects and events attributed to medication but not causally related

* Covello VT. Center for Risk Communication. www.centerforriskcommunication.org. Schmid R. http://www.psandman.com/articles/zurich.pdf.

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“People are disturbed, not by things, but by the view they take of them.”

Epictetus

Greek stoic philosopher

(CE 35 - CE 135)

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Risk Perception

- Virtually no correlation between the ranking of hazards by experts and the ranking of the same hazards by how upsetting they are to the public
- Risk tolerance is highly variable - some people are terrified by things that are very unlikely to cause serious harm [osteoporosis medication?] but not bothered by things that kill many people [cars, fractures, COVID?]
- Risk communication is a science-based discipline that confronts this dilemma

Adapted from Covello VT, Sandman PM. http://www.psandman.com/articles/covello.htm.

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Risk Tolerance

Estimated Annual USA Deaths	
Motor vehicle accidents	40,000
Osteoporotic fractures	100,000
COVID Excess Deaths (2020)	522,000
Osteoporosis medications	0

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Risk Communication

"The study and practice of collectively and effectively understanding risks."

Crisis management
Natural disasters
Epidemics
Pandemics
Bioterrorism
Nuclear threats
OSTEOPOROSIS

Radonich M. http://www.cemp.dri.edu/cemp/workshop2006/presentations/Radonich-Communicating_Radiation_Risk_to_the_Public-Part_1.pdf.

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Goals of Healthcare Risk Communication

- Public health: To effectively inform the public about risk and encourage appropriate actions without causing panic (or disbelief) and counterproductive actions

- Patient care: To inform patients about the risks of treatment without frightening them so much that they don’t take it

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Obstacles to Effective Risk Communication

- Uncertainty, complexity, and incompleteness of data
- Statistical illiteracy
- Distrust of experts, government, industry
- Selective reporting by news media - anecdotes that generate outrage
- Politicization of vaccines and public health recommendations

Adapted from Covello VT, Sandman PM. http://www.psandman.com/articles/covello.htm.

Risk Information Sources

Professionals

- Health statistics
- Mortality studies
- Randomized controlled trials
- Mentors
- Probabilistic risk assessment*

Public

- Observation
- Experiences
- Systems of trust and belief
- Anecdotes
- Social media, news media

Cable news network XXX vs. YYY

*Methodology to evaluate risk severity and probability for complex technology (ie, nuclear power plant)

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Social Media / Traditional Media

- Tremendously important for rapid communication of important health issues
  - COVID and COVID vaccinations
  - Osteoporosis and osteoporosis treatment
- Great potential harm when public is misinformed about the balance of benefits and risks
  - COVID and COVID vaccinations
  - Osteoporosis and osteoporosis treatment

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Politcal Conspiracy Theories Abound

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Different Medical World Views

Category	Professionals	Patients
Risk	Probability that an event will occur (P value, odds ratio, …)	It will happen to me (nocebo effect)
Uncertainty	Competing guidelines Indecisiveness Inconsistent clinical decisions	Amusement Distrust Fear

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Placebo and Nocebo Effects

Variations in response to treatments in clinical trials and clinical practice may be partly attributable to placebo and nocebo effects

- **Placebo effect: placebo makes you feel better**
  - Many double-blind studies of treatments for pain report similar effects of placebo and active treatment
  - Associated with release of endogenous opioids, endocannabinoids, dopamine, oxytocin, and vasopressin
- **Nocebo effect: placebo makes you feel worse**
  - Up to 29% of elderly persons taking placebo report side effects
  - Associated with release of other neurotransmitters, such as cholecystokinin, that may be blocked by diazepam

Colloca L, Barsky AJ. N Engl J Med. 2020;382:554-561.

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Nocebo Dilemma in Clinical Practice

- Patients must be informed of all potentially serious side effects and encouraged to report them, while expectation of these effects makes them more likely to happen
- Nocebo effects are influenced by prior treatment experiences, the experiences of others, news media reports, and ”framing” of drug benefits and risks
- One approach is “contextualized informed consent” or “authorized concealment” – explaining the nocebo effect and asking patients whether they want to be informed of possible benign non-specific side effects

Colloca L, Barsky AJ. N Engl J Med. 2020;382:554-561.

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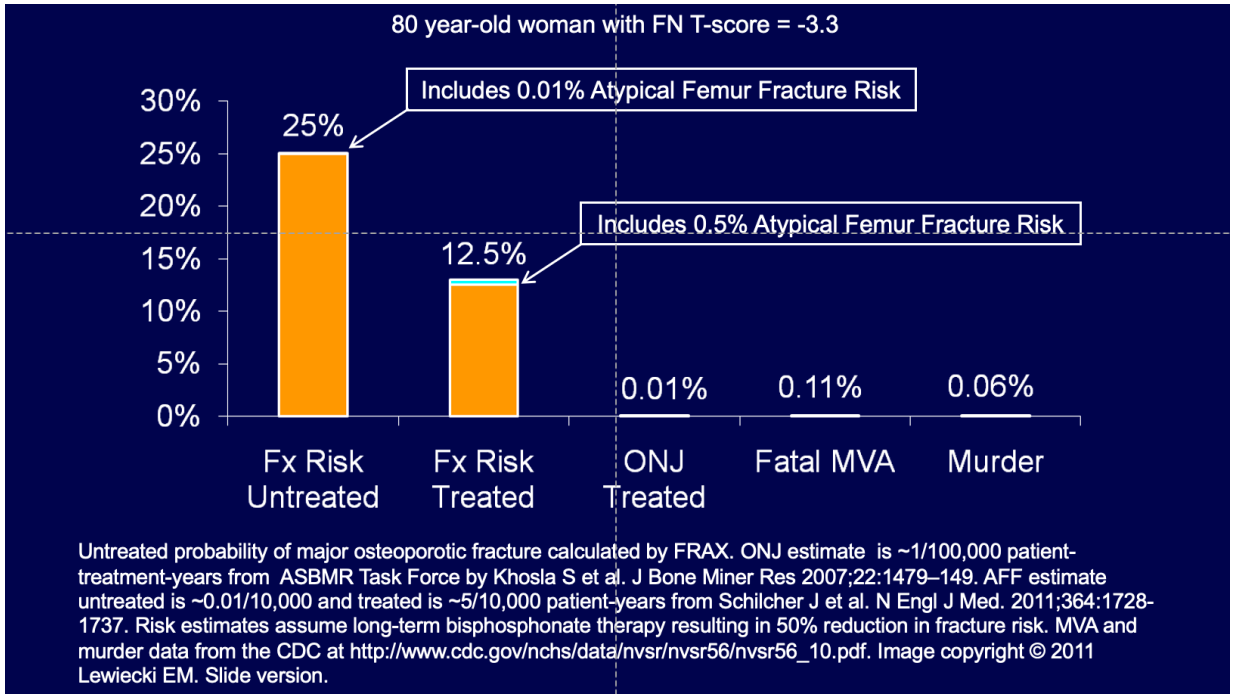
Decision Aid: Focus on AFF and ONJ



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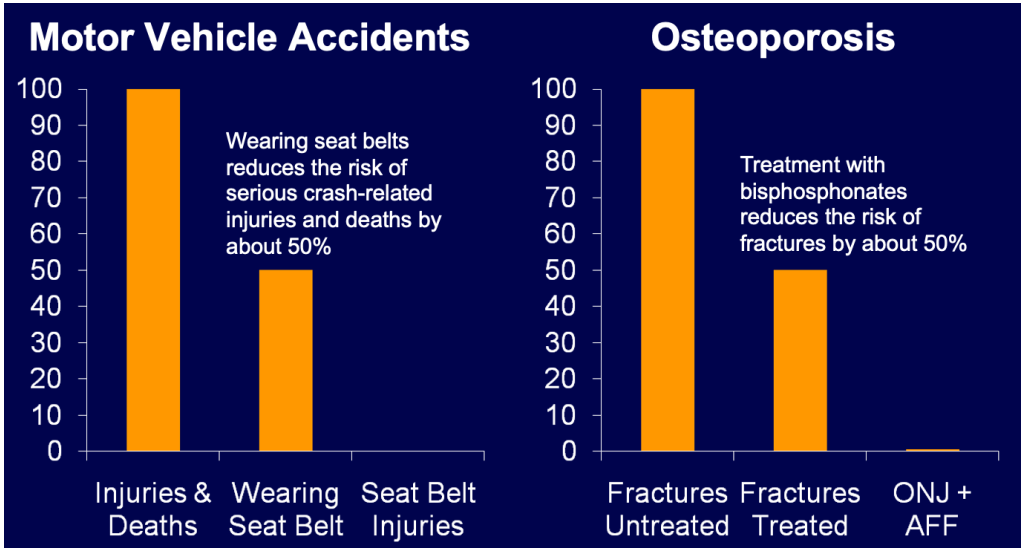
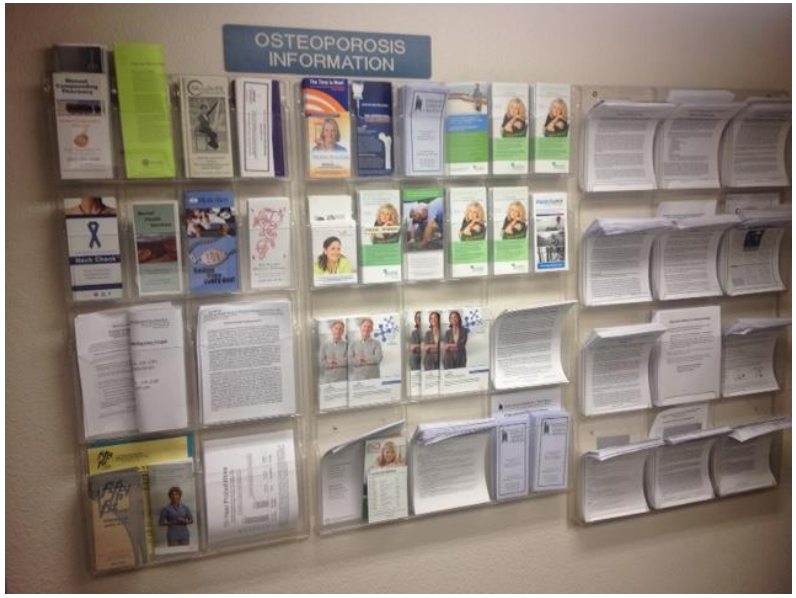
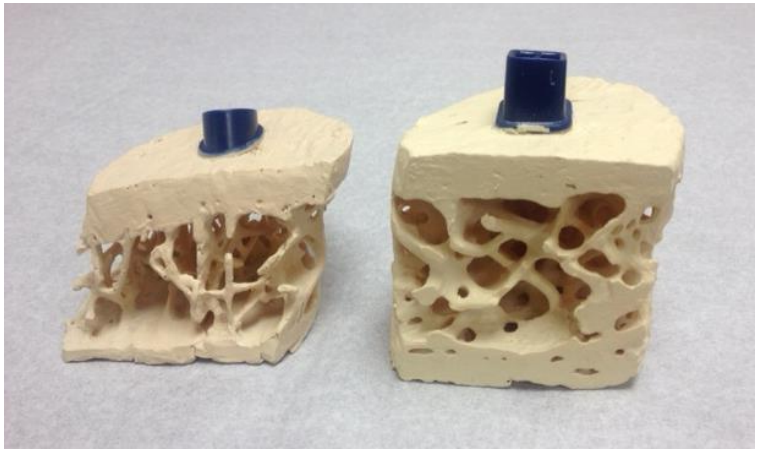
Decision Aid: “Framing” with Seat Belt Analogy



There are about 2.3 million adults treated in ERs each year for injuries from MVAs and about 2 million osteoporotic fractures each year. The risk of seat belt injuries and serious side effects from osteoporosis treatment is very small in proportion to the benefits. Data from multiple sources.

Decision Aids: Handouts and Models





Videos and websites . . .
www.nof.org

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“Medicine is the science of uncertainty and an art of probability.”

Sir William Osler

(1849 – 1919)

Canadian with medical career in Canada, USA, and UK
“Father of modern medicine”
“One of the greatest diagnosticians ever”
One of the 4 founding professors at Johns Hopkins Hospital
First chief of medicine at Johns Hopkins
Created first formal journal club (at McGill)
Created first medical residency program
Created grand rounds
Established bedside learning as a standard teaching method

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Addressing Uncertainty with “The Scientific Method”

1. Uncertainty
2. Question
3. Hypothesis
4. Experiment
5. Analyze data
6. Conclusions
7. Independent peer review
8. Reported / published
9. Reviewed by many
10. Replication

Not the same as patient care

- Medical history
- Physical exam
- Laboratory tests
- Imaging
- Discussion of results
- Recommendation
- Shared decision making
- Preferences
- Negotiation

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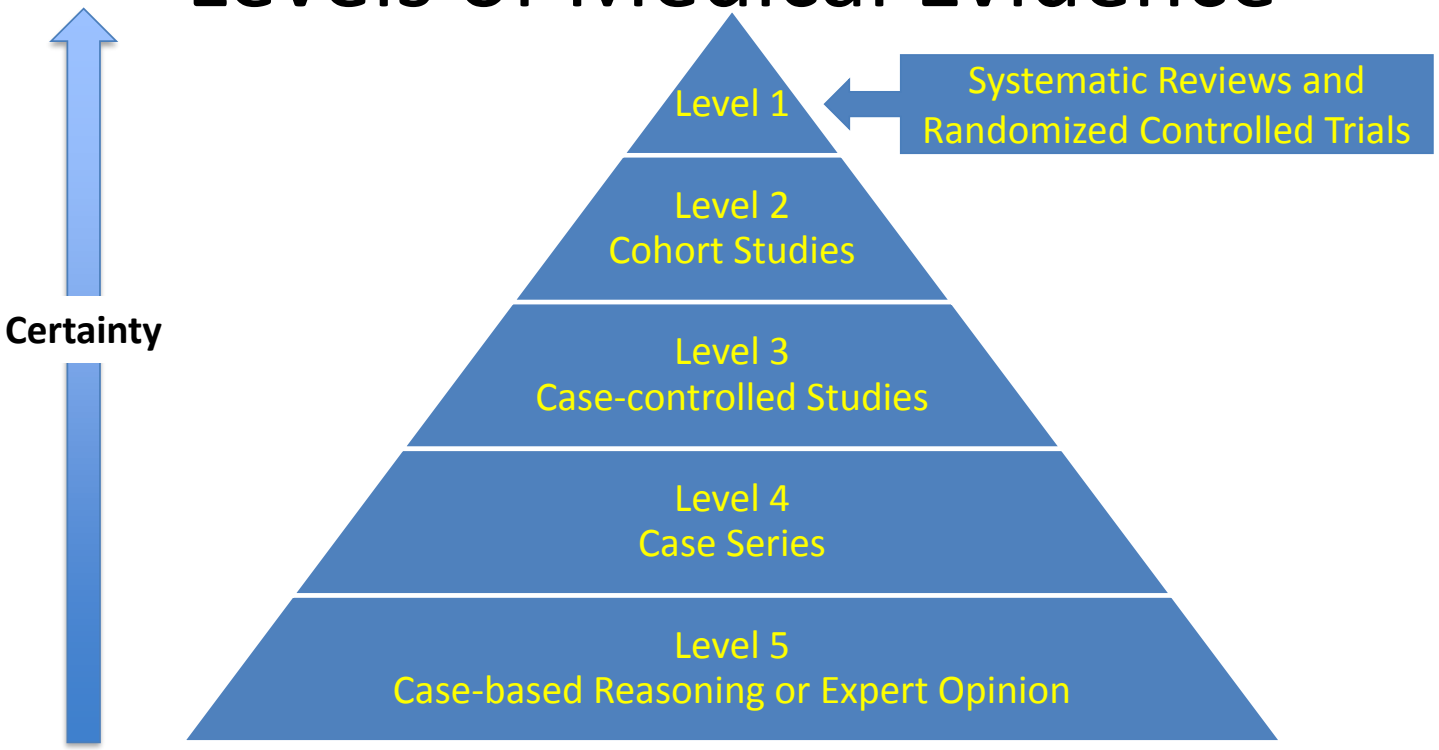
Levels of Medical Evidence



From the Oxford Centre for Evidence-based Medicine

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When RCTs and systematic reviews agree on an outcome, we have achieved the highest level of medical evidence.

Do we now know that the outcome is true?

Truth is elusive, certainty is not absolute, and patient care is complex.

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1965 Heberden Oration: "Reflections on the Controlled Trial"

- Blind acceptance of RCTs without critical evaluation can mislead as well as lead
- RCT may show that treatment A is on average better than treatment B in comparable groups of highly selected clinical trial subjects, but what you want to know is . . .
- **"What is the most likely outcome when I give this drug to my patient?"**

Sir Austin Bradford Hill
1897-1991
English Epidemiologist and Statistician

Hill AB. Ann Rheum Dis. 1966;25:107-113.

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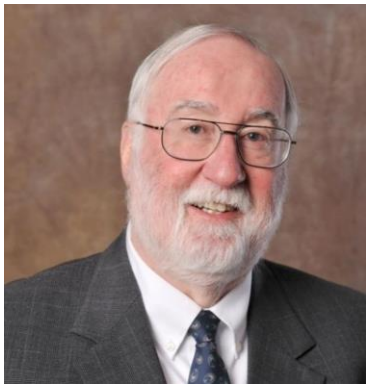
Evidence-based Medicine*

- EBM ≠ RCT
- EBM = “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”



David Sackett, MD
1934-2015
“Father of Evidence-based Medicine”

Sackett DL et al. BMJ. 1996;312:71-72.

*Term coined by Gordon Guyatt, MD, in 1992

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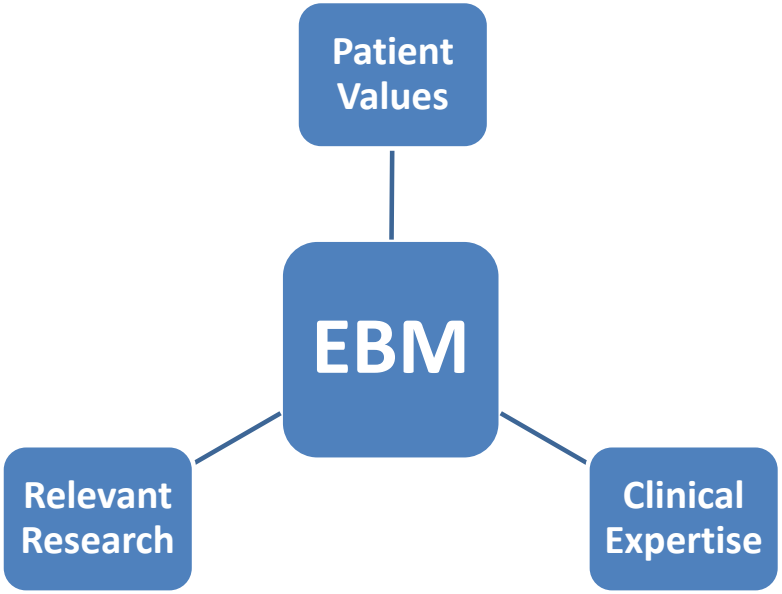
Combining Medical Evidence and Clinical Judgment

- "Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable or inappropriate for an individual patient."
- "Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients."



Sackett DL et al. BMJ. 1996;312:71-72.

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GRADE Working Group

Grading of **R**ecommendations **A**ssessment, **D**evelopment, and **E**valuation

- Established in 2000 → community of over 600 members in 40 countries
- Aim is to create systematic frameworks for assessing certainty [or uncertainty] of evidence used for making healthcare decisions
- Considers risk of bias, imprecision, inconsistency, indirectness, and publication bias
- Certainty rating of high, moderate, low, very low

Brozek JL et al. J Clin Epidemiol. 2021;129:138-150.

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Examples of Osteoporosis Uncertainty

- Diagnosis
- BMD testing
- Assessment of fracture risk
- Calcium
- Clinical practice guidelines

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3 Ways to Diagnose Osteoporosis

- BMD
  - T-score ≤ -2.5 at LS, TH, FN, or 33%R
- Fracture
  - Especially hip, spine, forearm
- FRAX
  - MOF risk ≥ 20% or HF risk ≥ 3%

- Uncertainties
  - Was the BMD test accurate, done according to current best practices, and correctly interpreted?
  - Were other causes of low BMD considered and eliminated (e.g., osteomalacia)?
  - Were other causes of fracture considered and eliminated (e.g., myeloma)?
  - Was FRAX correctly calculated (e.g., did the patient have RA or OA?)

NOF Clinician's Guide. Osteoporos Int. 2021;In press.

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Uncertainty and LSC with DXA BMD

- Short-term precision
  - ISCD Official Position: “Each DXA facility should determine its precision error and calculate the LSC.”
  - If LS LSC = 0.030 g/cm^2, what does change of 0.029 mean?
  - Most DXA facilities don’t do precision assessment

- Long-term precision
  - Techs change, skill levels change, patients change (weight gain or loss)
  - Calibration may not be done or not done correctly
  - Long-term precision study over 4 years found BMD shifts of 1.5% to 2.1%, suggesting that short-term LSC may need to be adjusted (1)
  - Long-term precision study over 16 years found that long-term precision errors were 50% larger than short-term precision errors (2)

1. Hangartner TN. Osteoporos Int. 2007;18:513-523.
2. Rajamanohara R et al. Osteoporos Int. 2011;22:1503-1512.

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FRAX® Fracture Risk Assessment Tool

Released February 21, 2008, 12 Noon

- Probability
  - Point estimate of fracture risk validated in large cohorts of women and men age 40 to 90
  - Calibrated for country-specific hip fracture risk and mortality
  - 71 models in 66 countries with 35 languages for 80% of world's population
  - Part of more than 80 clinical practice guidelines worldwide

- Uncertainty
  - Algorithm not publicly released for peer review
  - 4 ethnicities in the US – Caucasian, Black, Hispanic, Asian
  - Range of error not known
  - Incorrect input of risk factors
  - Dichotomous input for 7 clinical risk factors
  - Some risk factors not included

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Uncertainty Begets Controversy: The Calcium War

Does calcium supplementation increase the risk of cardiovascular disease?

NO

From Perth, RCT: no increase of risk, and perhaps reduced mortality in patients with pre-existing ASVD (2)

LACK OF EVIDENCE FOR INCREASED RISK

NOF and ASPC reviewed the data and determined there was moderate quality evidence for no relationship between dietary/supplemental calcium and CVD and no plausible mechanism for increased risk. Safe ULN 2000-2500 mg/day (3).

YES

From Auckland, meta-analysis of RCTs: increased risk of myocardial infarction (1)

More studies. More meta-analyses. Passionate debates. Pleas to halt meta-analyses.

1. Bolland MJ et al. BMJ. 2010;341:c3691.
2. Lewis JR et al. J Bone Miner Res. 2011;26:35-41.
3. Kopecky SL et al. Ann Intern Med. 2016;165:867-868.

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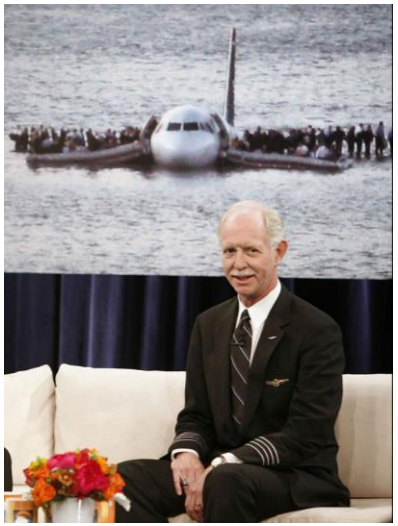
Miracle on the Hudson: Decisiveness in the Face of Uncertainty



US Airways Flight 1549
January 15, 2009
Captain ”Sully” Sullenberger

- No RCT showing what to do when a flock of Canada geese shuts down both engines 100 seconds after takeoff from LaGuardia Airport
- Automation does not eliminate errors
- Follow procedures when appropriate but deviate when necessary

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All guidelines are wrong, but good ones are useful

	ACP (2017)[1]	NOF (2015)[2]
Treatment		
Women	ALN, RIS, ZOL, Dmab (Not RLX, anabolic)	All approved agents
Men	BP	All approved agents
Duration		
Women	5 years	According to label
Men	Not stated	According to label
Monitoring		
Women	Do not repeat DXA	DXA Q2Y or more often as needed
Men	Not stated	DXA Q2Y or more often as needed

ACP used the GRADE methodology to grade the strength of each recommendation and the quality of the evidence. NOF did not.

1. Qaseem A et al. Ann Intern Med. 2017;166:818-839.
2. Cosman F et al. Osteoporos Int. 2015;26:2045-2047.

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Guideline Conundrum

Scientifically Rigorous	vs.	**Clinically Useful**
• Evidence-based		• Evidence-based + expert opinion
• RCTs		• Intuitive
• Cost-utility analysis		• Flexible
• Often very detailed		• Memorable
• Limited applicability		• Broadly applicable
• Overly complex		• Allow for clinical judgment
• Difficult to remember		• Not tied to reimbursement
• Less bias		• More bias
• Individualize treatment decisions		• Individualize treatment decisions

Healthcare payers may not see the bottom line.

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Guideline Harmonization

Core principles for fracture prevention: North American Consensus from the National Osteoporosis Foundation, Osteoporosis Canada, and Academia Nacional de Medicina de Mexico

E.M. Lewiecki[1] · N. Binkley[2] · P. Clark[3] · S. Kim[4] · W.D. Leslie[5] · S.N. Morin[6]

- Small step toward harmonization, addressing . . .
- Evaluation
- Assessment of fracture risk
- Treatment
- Monitoring

Lewiecki EM et al. Osteoporos Int. 2020;31:2073-2076.

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When the GRADE methodology gives a high rating of certainty to RCTs, systematic reviews, and clinical practice guidelines, do we now know how to manage our patient?

Maybe

Maybe not

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PROBLEM

Many or most patients in clinical practice would probably not qualify for participation in the clinical trials used to approve the drugs we use to treat them. And we often use drugs in clinical practice for longer than the duration of the clinical trials.

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Differences Between Clinical Practice Patients and Subjects in RCTs

- Retrospective chart review of 120 consecutive women with T-scores < -2.0 and/or fragility fractures, seen as new patients at an academic osteoporosis center

- Evaluated for eligibility in 4 typical RCTs of drugs for treatment of osteoporosis
  - Inclusion criteria varied by age range, skeletal site of BMD measurement, T-score, type and number of prevalent fractures, etc.
  - Exclusion criteria varied by allowable drugs, washout periods, co-morbidities, etc.

Standard Criteria for Drug Therapy	Eligible for Participation in Drug Study			
	A	B	C	D
100%	3%	4%	21%	7%

Reasons for Exclusion from Drug Studies	
Too young	28%
Too old	8%
Disease too severe	19%
Co-morbid conditions	60%
Medications	60%
Other	3%

Dowd R, Recker RR, Heaney RP. Osteoporos Int. 2000;11:533-536.

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Differences Between Clinical Practice Patients and Subjects in RCTs

- Conclusion
  - Many clinical practice patients with osteoporosis who were candidates for treatment did not qualify for participation in typical RCTs of osteoporosis drugs
- Implication
  - Uncertainty whether efficacy and safety findings of RCTs for approved drugs can be generalized to some patients we see in clinical practice, with special regard to age, comorbidities, and concomitant medications
- Questions
  - How can we apply the data from RCTs to the care of individual patients?
  - How can we communicate the uncertainty to the patients who need treatment?
  - Should clinical trials be designed differently to be more relevant to our patients?

Dowd R, Recker RR, Heaney RP. Osteoporos Int. 2000;11:533-536.

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What we don't know about osteoporosis

E. M. Lewiecki[1] · N. Binkley[2]

- Bone remodeling
- Calcium and vitamin D
- Medications
- ONJ
- AFF
- Treatment gap
- Clinical practice guidelines
- Defining Osteoporosis

Lewiecki EM, Binkley N. J Endocrinol Invest. 2016;39:491-493.

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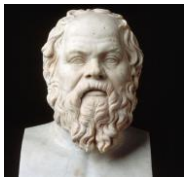
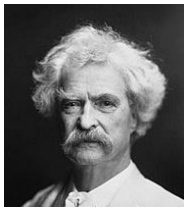
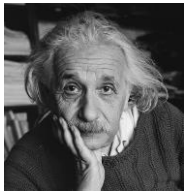
“True knowledge exists in knowing that you know nothing.”
Socrates



“It ain’t what you don’t know that gets you into trouble. It’s what you know for true that just ain’t so.”
Mark Twain



“A true genius admits that he/she knows nothing.”
Albert Einstein



“We know there are some things we do not know. But there are also unknown unknowns - the ones we don't know we don't know.”
Donald Rumsfeld

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But we need to effectively share the knowledge that we do have . . .

- Mission: To expand global capacity to deliver best practice skeletal healthcare
- Strategy: To share knowledge across many medical disciplines using technology-enabled collaborative case-based learning
- Common themes for discussions: individualizing patient care when evidence is insufficient and guidelines may not apply, making treatment decisions despite uncertainty, communicating risk
- Many ECHO programs in the US and internationally with more to follow

If you are passionate about osteoporosis and love to teach, you could start your own ECHO program

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Final Thoughts

- Be intellectually humble – ask questions and listen
- Recognize that most clinical decisions are made with evidence that is insufficient, conflicting, or absent
- Understand that clinical practice guidelines and RCTs can be helpful but may not the final answer
- Accept the presence of uncertainty – it will never go away
- Reduce uncertainty by advancing your knowledge
- Individualize patient management decisions

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