Baffled, Befuddled, and Bemused

How not to get fooled again, and again, and ,…

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4 questions????

Is a drug really needed?

Correct diagnosis, non-drug treatment, personal choice, magnitude of benefit, surrogate benefit

What is the best drug?

Evidence of long-term benefit, safety, cost

What is the lowest dose?

Don't use the CPS, genetic mongrels

Do I still need the drug?

Re-evaluate, drugectomy, slow reduction

"EVIDENCE"-BASED PRINCIPLES

Evidence

Values

Individualise

Decision-making

Evaluation

Negligence

Common sense

Economics

"EVIDENCE"-BASED PRINCIPLES

Evidence

Seek out evidence from reliable sources and familiarize yourself with the highest level of evidence for the common conditions you treat

Values

Identify and respect patient values and support their decisions

Do not promote fear of a risk – promote a sense of wellness

Individualise

Background risk; the added risk of a "risk factor"; reduction in risk from the therapy (along with the harm risk)

Identify specific goals - divided into immediate (symptoms) and theoretic

Always use the lowest dose that achieves the goal

Decision-making

Shared decision making not paternalism

"EVIDENCE"-BASED PRINCIPLES

Evaluation

Always re-evaluate on a regular basis – things change

Negligence

You get sued for negligence, not thoughtful and well documented shared decision-making

It is OK if you don't always follow the guidelines

Common sense

make it common

Economics

Use the lowest priced equally effective medication – cost is a side effect

Only order tests if the results will change what you would do and make sure the patients understands

Outcomes Are Not Created EQUAL
Surrogate - Subjective - Objective

Ask yourself: Can a patient feel the outcome?

If No - it is a surrogate marker

A Medical Tale: The Surrogate Heart

	Encainide/ Flecainide	Placebo
Mortality	7.7%	3.0%
Arrhythmia death or cardiac arrests	4.5%	1.2%

NEJM 1989;321:406-12

Surrogates: The Never-ending Consistently Inconsistent Story

The Marker	The Treatment
HDL	Torcetrapib[1] LDL down, HDL up CVD & mortality up
LDL	Niacin, Ezetimibe
Trigly	Fibrates
BP	Atenolol, Aliskiren, Doxazosin
A1c	Rosiglitazone - Almost any diabetes medications except Metformin
Homocysteine	Folate
CRP in CVD	Vitamin E, Rosiglitazone, etc.

N Engl J Med 2007;357:2109-22

Typically "evidence-based" guideline recommendations are not based on "solid" evidence

JAMA Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines
Pierluigi Tricoci; Joseph M. Allen; Judith M. Kramer; et al.
JAMA 2009;301(8):831-841 (doi:10.1001/jama.2009.205)

Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines
Dong Heun Lee, MD; Ole Vielemeyer, MD Arch Intern Med. 2011;171(1):18-22

Cardiology	LEVEL	Infectious disease
11%	Evidence Level (1 or A) based on RCTs	14%
48%	Evidence Level (3 or C) based on opinion	55%

17 "NEGATIVE" STUDIES IN A ROW

LIPIDS
AIM-HIGH, HPS2-THRIVE (niacin)
ACCORD (fibrates)
dalOUTCOMES (dalcetrapib)

BLOOD PRESSURE
ALTITUDE (aliskiren) - AQUARIUS?? (CHD+PreHTN)
VALISH, AASK, ACCORD (aggressive BP lowering)

DIABETES
ACCORD, ADVANCE, VADT (aggressive A1c lowering)
ROADMAP (olmesartan)
ORIGIN (insulin)
SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin)

GENERAL
ACTIVE (irbesartan/afib)
CRESCENDO (rimonabant)

1967

Effects of Treatment on Morbidity in Hypertension

Results in Patients With Diastolic Blood Pressures Averaging 115 Through 129 mm Hg

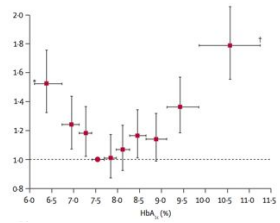
Veterans Administration Cooperative Study Group on Antihypertensive Agents

Lower BP in patients with average DBP of 121 mmHg - 19 months

Placebo - 70 patients - 27 CVD events - 4 deaths

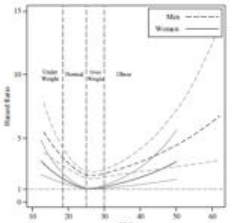
Drug - 73 patients - 2 events - 0 deaths

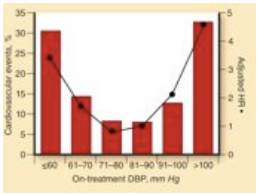
What goes down must come up



A1C[1]

BMI[3] over 65



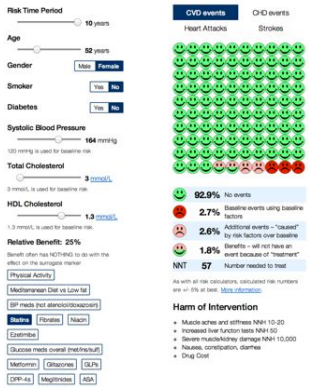


Diastolic BP[2]

Similar data for
25-59 years of age
JAMA 2007;298:2028-37

1) Lancet 2010; 375: 481–89
2) Curr Hypertens Rep (2010) 12:290–295
3) J Am Geriatr Soc 2010; 58:234–241

Cardiovascular Risk/Benefit Calculator



http://bestsciencemedicine.com/chd

632 JAMA, Feb 23, 1963

Effectiveness of Estrogens for Therapy of Myocardial Infarction in Middle-Age Men

10 mg versus placebo - over 5 years
Cardio/renal event - first 3 months - 22% vs 5% - but mortality lower at 5 years therefore a new trial suggested
"Feminizing effect" - 40% vs 30% JAMA 1963;183:106-12

The Coronary Drug Project

Initial Findings Leading to Modifications of Its Research Protocol

The Coronary Drug Project Research Group

Terminated early

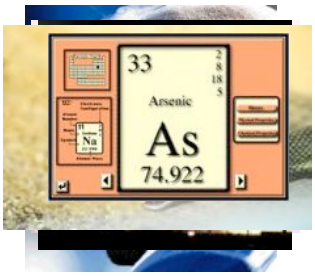
5 mg versus placebo - over 18 months
Definite non-fatal MI - 6.2% vs 3.2%
Pulmonary embolism - 1.5% vs 0.4%
Excessive shopping - 80% vs 3% JAMA 1970;214:1303-13

BMJ EDITORIALS

"If you say it enough it becomes the truth" 2012)

"a reasonable approach for most primary care infections would be to tell the patient to continue the antibiotic until they have been asymptomatic or afebrile for 72 hours and then to stop"

Medical Myths



Sugar makes kids

You lose most of your body heat through your

You should drink at least glasses of water a day

Carrots can improve your

Low fat diets help you lose

Natural products are

WHERE DO SUPPOSITORIES FIT IN?

INSERT THE A OR B END FIRST?

A = 83% needed to introduce finger - 3% expulsion

B = 1% needed to introduce finger - 0% expulsion - 98% found this method easier

Lancet 1991;338:798-800

Regularly repeating BMD, LDL, and SBP is BAD medicine

CMAJ REVIEW

2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary

"For patients who are undergoing treatment, repeat measurement of bone mineral density should initially be performed after one to three years; the testing interval can be increased once therapy is shown to be effective"

"For individuals with low risk of fracture and without additional risk factors for rapid loss of bone mineral density, a testing interval of 5–10 years may be sufficient"

Evidence for Targets

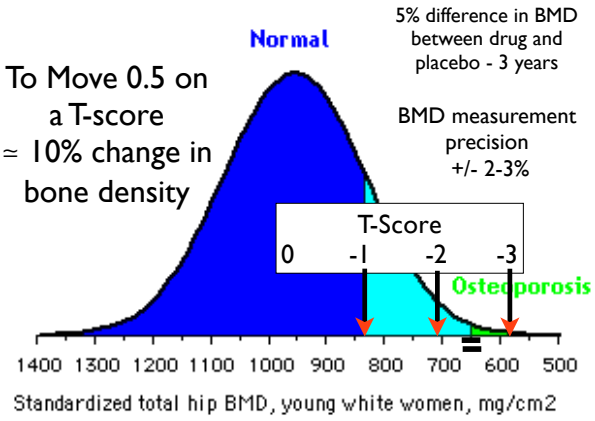
BONE DENSITY
There are NO studies that have looked at getting patients to different BMDs and seeing if that makes a clinically important difference

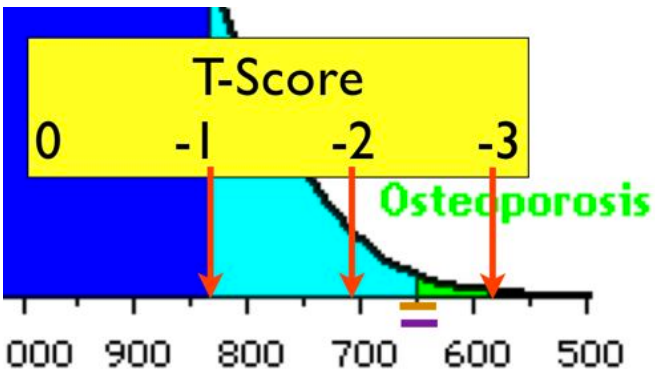
Bone density reports that state a change in bone density has been seen

"Lumbar spine measurements have increased by 3.5%"

"Right total femur measurements have decreased by 4.1%"

To Move 0.5 on a T-score ≃ 10% change in bone density





Other Smarter People

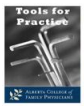
Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data

Katy J L Bell, Andrew Hayen, Petra Macaskill, Les Irwig, Jonathan C Craig, Kristine Ensrud and Douglas C Bauer

BMJ 2009;338;b2266;

"Monitoring BMD in the first 3 years after starting treatment with a bisphosphonate is unnecessary and may be misleading"

BMJ 2009;338;b2266



Bone Mineral Density – Too much of a good thing?

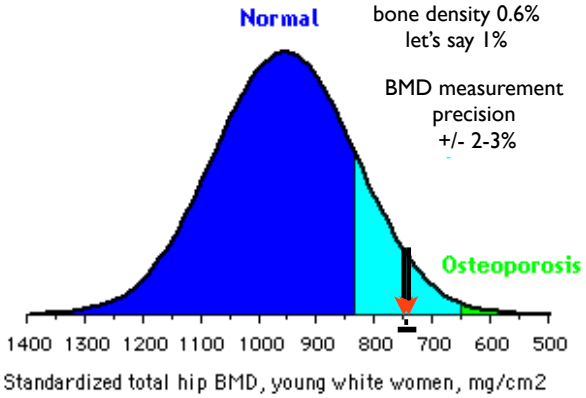
Clinical Question: Once we have initiated bisphosphonate therapy, how frequently should we check bone mineral density (BMD)?

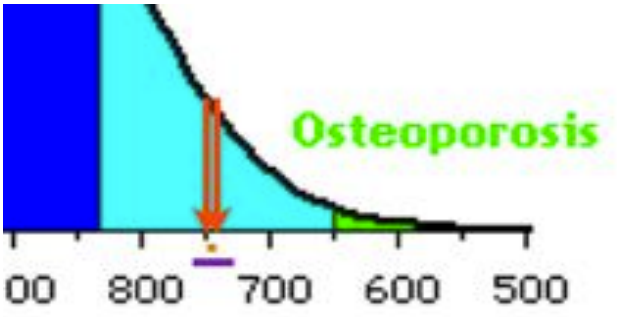
#32 Christina Korownyk & Michael R. Kolber

"Repeating BMD in the first three years after starting treatment with a bisphosphonate is unnecessary and potentially confusing. The vast majority of patients taking a bisphosphonate will get an adequate increase in BMD after three years and have a reduced fracture risk regardless of BMD changes"

Average yearly reduction in bone density 0.6%
let's say 1%

BMD measurement precision
+/- 2-3%





Other Smarter People

Evaluating the Value of Repeat Bone Mineral Density Measurement and Prediction of Fractures in Older Women

The Study of Osteoporotic Fractures

Teresa A. Hillier, MD, MS; Katie L. Stone, PhD; Doug C. Bauer, MD; Joanne H. Rizzo, MS; Kathryn L. Pedula, MS; Jane A. Cauley, DrPH; Kristine E. Ensrud, MD, MPH; Marc C. Hochberg, MD; Steve R. Cummings, MD

Arch Intern Med. 2007;167(2):155-160.

"repeat BMD [8 years] measurement provides little additional benefit as a screening tool"

Average bone loss/year 0.6%

Arch Intern Med 2007;167:155-60

2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

"The frequency of follow-up measurements is debated but should probably be performed semiannually, or with any changes in lipid-lowering therapy"

CHOLESTEROL

There are NO large studies that have looked at getting patients to different cholesterol levels

Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes
The SANDS Randomized Trial

3 years - 499 American Indian men and women aged 40 years or older with type 2 diabetes and no prior CVD events
Results - surrogates improved - no change in clinical outcomes

JAMA 2008;299:1678-89

ARTICLE | Annals of Internal Medicine

Monitoring Cholesterol Levels: Measurement Error or True Change?

Paul P. Glasziou, MBBS, PhD; Les Irwig, MBBS, PhD; Stephane Heritier, PhD; R. John Simes, MBBS, MD; and Andrew Tonkin, MBBS, MD, for the LIPID Study Investigators

Background: Cholesterol level monitoring is a common clinical activity, but the optimal monitoring interval is unknown and practice varies.

Objective: To estimate, in patients receiving cholesterol-lowering medication, the variation in initial response to treatment, the long-term drift from initial response, and the detectability of long-term changes in on-treatment cholesterol level ("signal") given short-term, within-person variation ("noise").

Design: Analysis of cholesterol measurement data in the LIPID

of variation, 7%) to 0.60 mmol/L (23 mg/dL) (coefficient of variation, 11%), but it took almost 4 years for the long-term variation to exceed the short-term variation. This slow increase in variation and the modest increase in mean cholesterol level, about 2% per year, suggest that most of the variation in the study is due to short-term biological and analytic variability. Our calculations suggest that, for patients with levels that are 0.5 mmol/L or more (>19 mg/dL) under target, monitoring is likely to detect many more false-positive results than true-positive results for at least the first 3 years after treatment has commenced.

"After initial change only measure every 3-5 years"

Average increase in chol is 0.5-1%/year

Within-person coefficient of variation is ~7%
Single measurement - 95% CI
Total chol ~ - 0.80 to 0.80 mmol/L (~30 mg/dL)
LDL chol ~ - 0.5 to 0.5 mmol/L (~20 mg/dL)

Ann Intern Med 2008;148:656-61

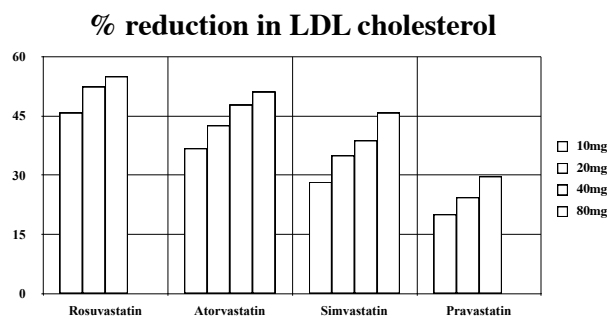
RESEARCH

When to remeasure cardiovascular risk in untreated people at low and intermediate risk: observational study

BMJ 2013; 346 doi: http://dx.doi.org/10.1136/bmj.f1895 (Published 3 April 2013)
Cite this as: *BMJ* 2013;346:f1895

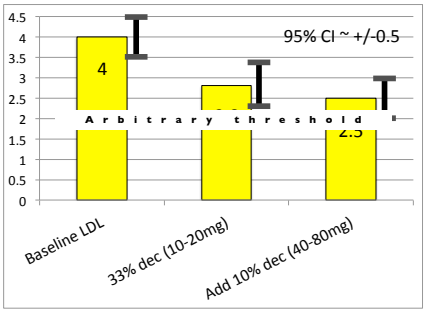
"Repeat risk estimation before 8-10 years is not warranted for most people initially not requiring treatment"

"The lipid re-screening interval should be more than 3 years for those not taking cholesterol-lowering drugs" Heart 2010;96: 448-52



LDL cholesterol mmol/L

2 mmol/L~80mg/dL



Statins in secondary prevention

10-20 mg - 5-6% ARR in MIs and strokes

Inc. dose 4-8X you get an additional 1-2% ARR

short-term variability - a combination of analytic variability and week-to-week biological fluctuation around a stable average

BLOOD PRESSURE
Less than 135/85 "Despite a -4/-3 mmHg greater achieved reduction in systolic/diastolic BP, attempting to achieve "lower targets" instead of "standard targets" did not change total mortality, MI, stroke, CHF, major CV events or ESRD"

Cochrane Review 2009;Issue 3:CD004349

"the oft-cited <140 mm Hg systolic threshold used to define hypertension has admittedly been arbitrarily chosen as a 'compromise' and one could make a strong case for a lower threshold in high-risk patients and a higher threshold in those at lower risk"

"'treatment' refers to both lifestyle modifications and pharmacologic therapy"

Canadian Hypertension Education Program and Recommendations Task Force - Can Fam Physician January 2013 59: 19-21

Need changes of at least 10/5 mmHg before you can say there has been a change

Am J Hyper 2008;21:3–4

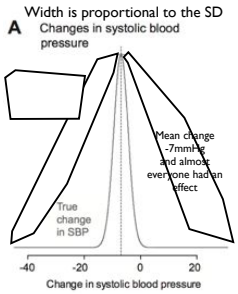
"clinicians cannot identify individuals who have good or poor responses to drugs"

"coefficients of variation for systolic office, ambulatory, and self-monitored blood pressure, compared at baseline and 6 weeks, were 8.6%, 5.5%, and 4.2% respectively"

Br J Gen Pract 2010; 60: 675–80

"a single careful blood pressure measurement taken a few months after the start of treatment is not useful for monitoring"

BMJ 2009;338:b1492



28,000 patients from ACEI studies

Hypertension 2010; 56: 533-539

"Instead of using a "treat-to-target" approach of lowering blood pressure to a specific target, recent evidence suggests that a "fire and forget" approach may be preferred."

"we estimate that it would be necessary to average >90 measurement occasions both before and after starting treatment to be 95% certain that an apparent decrease of >4 mm Hg in systolic blood pressure indicates a true decrease of >4 mm Hg (ie, to be certain that treatment is having a substantial effect)"

SYSTOLIC BLOOD PRESSURE - changes

Take the average of 2-3 measurements at a visit - coefficient of variation is ~10%

Start medication - avg 9mmHg

Increase dose - avg 2-5mmHg

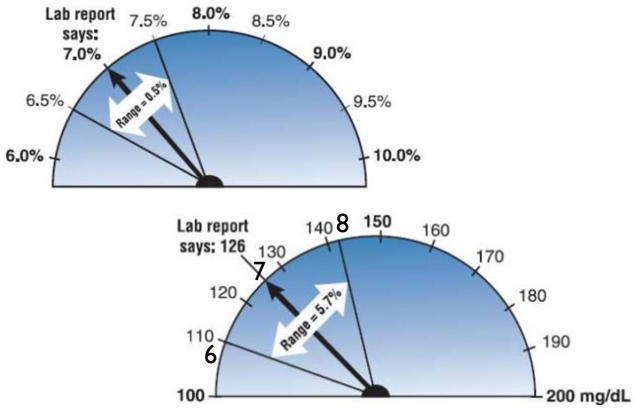
Seasonal differences - avg 8mmHg lower when warm

Age related (per year) - avg 0.5-0.8mmHg

Sample size calculation - 40 office measurements before and after treatment to be reasonable confident that a 5 mmHg change has occurred

	Bone density	Cholesterol	Blood pressure
Before treatment	If pt would consider treatment one time measurement translate T-score into 10-year fracture risk	If pt would consider treatment one time measurement translate cholesterol into 10-year CVD risk	Easy to measure BUT many, many repeat measurements unless VERY high
After treatment	Don't bother as the test just isn't precise enough	"fire and forget" approach Don't bother because all you can do is raise the statin dose - that decision should be based on magnitude of CVD reduction not cholesterol	"fire and forget" approach????

Similar Issue With A1c



Risk: Relative, Absolute & NNT

If you don't know where you start, it's hard to know where you finish.

- If you don't know where you start, it's hard to know where you finish.
- Zoster Vaccine reduces shingles up to 70%

Zoster Vaccine reduces shingles up to 70%

Study	Placebo	Zoster Vac	Benefit	NNT (3 yrs)
Age 50-59 (3 yrs)	2.03%	0.62%	1.41%	71
Age ≥60 (3 yrs)	3.42%	1.67%	1.75%	58

Bottom-Line: Over 3 years, one in 60-70 patients will avoid shingles due to the vaccine

- One in 350 for post-herpetic neuralgia

Tools for Practice Nov 12, 2012

Heartburn

Patients who respond in the PPI group

≈ 65% at 4 weeks, 85% at 8 weeks

Patients who respond to H2RA

≈ 40% at 4 weeks, 55% at 8 weeks

Patients who respond in the placebo group

≈ 15% at 4 weeks, 30% at 8 weeks

8-9/10 patients will respond to a PPI
3 of these improved not because of a drug
an additional 2-3 of these would have improved with an H2RA

Cochrane Library CD003244

Depression

Patients who respond in the SSRI group ≈ 60% - 40% in primary care? Am J Psychiatry 2009; 166:599–607

Patients who respond in the placebo group ≈ 45%

6/10 patients will respond to an antidepressant

4-5 of these 6 improved not because of the drug - NNT of 6-7

Cochrane Library CD007954

Erectile dysfunction

"Successful" attempts in the sildenafil group ≈ 70%

"Patients" who "responded" in the placebo group ≈ 20%

7/10 "patients" will "respond" each time to sildenafil

2 of these 7 "responded" not because of the drug - NNB of 2

10% headache, 15%flushing, 10% dyspepsia <1% stopped drug due to side effects

N Engl J Med 1998;338:1397-404

Doxepin (Sinequan)

Depression - start 25-50 mg - optimal 75mg -150mg up to 300mg

Doxepin in the Treatment of Primary Insomnia: A Placebo-Controlled, Double-Blind, Polysomnographic Study — J Clin Psychiatry 2001;62:453-63

"The results support the effectiveness of low doses (25-50 mg) of doxepin to improve sleep"

INSOMNIA — Sleep 2007; 30: 1555–61

Efficacy and Safety of Three Different Doses of Doxepin in Adults with Primary Insomnia

All three doses worked better than placebo
AND
NO side effects over placebo

A recommended low dose was still 25-50 times TOO HIGH

Beware of "qualitative quantification"

Qualitative descriptor	EU assigned frequency	Mean frequency estimated by participants (n=200)
Very common	>10%	65% (24·2)
Common	1–10%	45% (22·3)
Uncommon	0·1–1%	18% (13·3)
Rare	0·01–0·1%	8% (7·5)
Very rare	<0·01%	4% (6·7)

Values are mean (SD).

Lancet 2002;359:853–54

Minimally Disruptive Medicine

1. Establish burden of therapy
2. Encourage coordination in clinical practice
3. Acknowledge comorbidity in clinical evidence
4. Prioritize from the patient perspective

1. NEWER IS RARELY BETTER - WAIT 5 YEARS
2. SURROGATES CAN BREAK YOUR HEART
3. VERY HIGH IS BAD BUT AGGRESSIVE LOWERING RARELY SEEMS TO DO MUCH
4. COLLATERAL DAMAGE CAN COME FROM SHOOTING AT TARGETS
5. LEAVE PHYSIOLOGICAL MECHANISMS TO PHYSIOLOGISTS
6. START WITH VERY LOW DOSES
7. MEASUREMENT OBSESSION
8. RECONSIDER HOW YOU USE "RISKY" WORDS
9. HEALTHY SKEPTICISM AND BASIC CRITICAL APPRAISAL SKILLS ARE ESSENTIAL FOR STUDENTS/PRACTITIONERS