Osteoporosis : The Benefits and Harms of Treatment - Making No Bones About It

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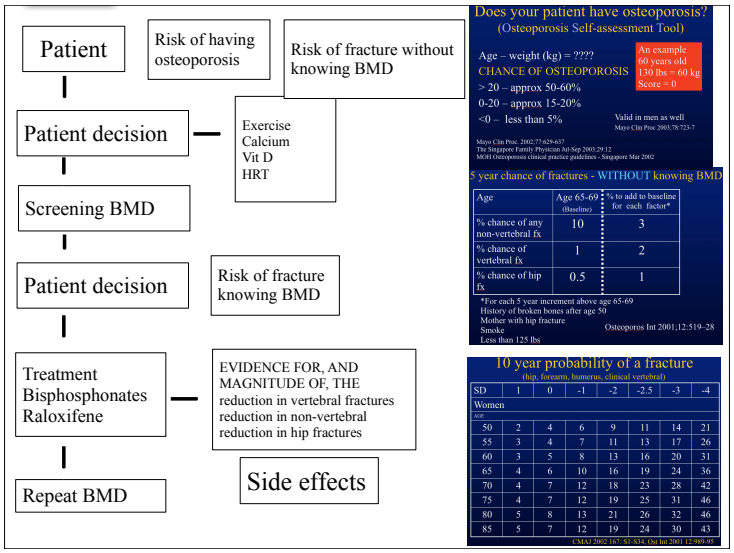


Decisions that can be made without a BMD

Exercise
Calcium
Vitamin D
HRT?

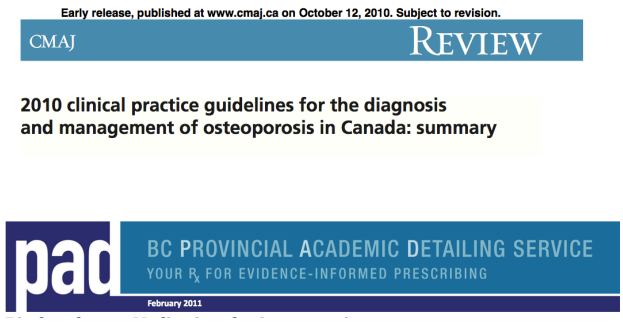
Exercise Evidence

"In summary, routine physical activity appears to be important in preventing loss of bone mineral density and osteoporosis, particularly in postmenopausal women. The benefits clearly outweigh the potential risks, particularly in older people."

CMAJ 2006;174:801-9

Talk to your patient

Before you do a BMD ask patient if they would take therapy – cost, benefit, side effects etc.



A simple tool for assessing the chance of your patient having osteoporosis

Does your patient have osteoporosis?

(Osteoporosis Self-assessment Tool)

Age – weight (kg) = ????

CHANCE OF OSTEOPOROSIS

> 20 – approx 50-60%

0-20 – approx 15-20%

<0 – less than 5%

An example
60 years old
130 lbs = 60 kg
Score = 0

Valid in men as well

Mayo Clin Proc 2003;78:723-7

Mayo Clin Proc. 2002;77:629-637
The Singapore Family Physician Jul-Sep 2003;29:12
MOH Osteoporosis clinical practice guidelines - Singapore Mar 2002

A simple tool for estimating chance of fractures without a BMD

5 year chance of fractures - WITHOUT knowing BMD

Age	Age 65-69 (Baseline)	% to add to baseline for each factor*
% chance of any non-vertebral fx	10	3
% chance of vertebral fx	1	2
% chance of hip fx	0.5	1

*For each 5 year increment above age 65-69
History of broken bones after age 50
Mother with hip fracture
Smoke
Less than 125 lbs

Osteoporos Int 2001;12:519–28

TABLE 5. Ten-Year Absolute Risk of Hip Fracture in Women, ≥60 yr of Age Among Different Levels of the Risk Score

	*Number of risk factors**			
	0	*1*	*2*	*3 of 4*
60–69 yr	1.4%	3%	6%	NA
70–79 yr	6%	8%	15%	22%
80+ yr	15%	22%	29%	25%
Corticosteroid use	NA			

Gray area means at high risk.
* Number of the following four risk factors: any prior fracture since age 50, body weight <64 kg, use of a walking aid, and smoking.
NA, not applicable because of too low power.

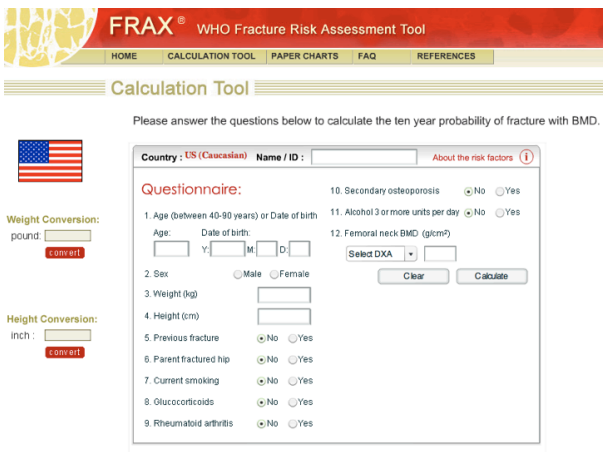
TABLE 6. Ten-Year Absolute Risk of Fragility Fracture in Women, ≥60 yr of Age Among Different Levels of the Risk Score

	*Number of risk factors**			
	0	*1*	*2*	*3 of 4*
60–69 yr	5%	6%	8%	NA
70–79 yr	11%	12%	20%	29%
80+ yr	12%	24%	35%	31%
Corticosteroid use	NA			

Gray area means at high risk.
* Number of the following four risk factors: any prior fracture since age 50, body weight <64 kg, use of a walking aid, and smoking.
NA, not applicable because of too low power.

J Bone Min Res 2009;24;768-74

http://www.shef.ac.uk/FRAX/



Simple is better

"Simple models based on age and BMD alone or age and fracture history alone predicted 10-year risk of hip, major osteoporotic, and clinical fracture as well as more complex FRAX models"

Arch Intern Med 2009;169:2087-94

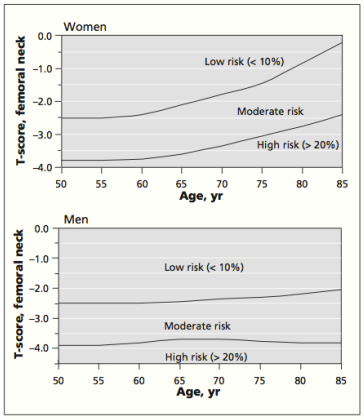
A simple tool for estimating chance of fractures with a BMD

10 year probability of a fracture

(hip, forearm, humerus, clinical vertebral)

SD	1	0	-1	-2	-2.5	-3	-4
Women							
AGE							
50	2	4	6	9	11	14	21
55	3	4	7	11	13	17	26
60	3	5	8	13	16	20	31
65	4	6	10	16	19	24	36
70	4	7	12	18	23	28	42
75	4	7	12	19	25	31	46
80	5	8	13	21	26	32	46
85	5	7	12	19	24	30	43

CMAJ 2002 167: S1-S34, Ost Int 2001 12:989-95



2010 tool of the Canadian Association of Radiologists and Osteoporosis Canada

CMAJ 2010. DOI:10.1503/cmaj.100771

Drugs for osteoporosis/fracture prevention

Nutritional	calcium	Oral daily
	vitamin D	Oral daily
Anabolic agents	teriparatide (Forteo)	Daily SC
Bisphosphonates	alendronate (Fosamax, generics)	Oral daily and weekly
	etidronate (Didrocal, generics)	Oral daily x 14 days Q3months
	risedronate (Actonel, generics)	Oral daily, weekly, monthly
	zoledronic acid (Aclasta)	Yearly IV infusion
RANK Ligand inhibitors	denosumab (Prolia)	Q6M SC
Selective estrogen receptor modulators	raloxifene (Evista, generics)	Oral daily
Calcitonin	calcitonin salmon (Miacalcin, Calcimar, Caltine, generics)	daily intranasal daily or Q2 days SC

A simple table describing the benefits of treating osteoporosis

• Osteoporosis Drugs Benefit - 2-3 years •

RELATIVE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~ 50%	~ 20%	~40%
Raloxifene	~ 40%	NS	NS
Teriparatide	~ 70%	~ 40%	NS
Vitamin D usually with calcium	~15-25%	~15-25%	~15-30%
Denosumab	~ 70%	~ 20%	~40%
Strontium	~40%	~ 15%	NS
ALL DRUGS	~50%	~20%	~25%

ABSOLUTE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~4-8%	~2%	~0.5-1%
Raloxifene	~4%	NS	NS
Teriparatide	~10%	~4%	NS
Vitamin D usually with calcium	1-2%	1-2%	~1%
Denosumab	~5%	~2%	~0.5%
Strontium	~8%	~2%	NS
ALL DRUGS	~5%	~2%	~0.5%

*~ 90% of the studies enrolled patients with a history of fractures with the exception of the VitaminD/calcium studies where this was ~ 50%
** etidronate has only been shown to reduce vertebral fractures in secondary prevention

"There is good evidence from randomized controlled trials (RCTs) that alendronate, etidronate, ibandronate, risedronate, calcitonin, 1-34 PTH, and raloxifene prevent vertebral fractures compared with placebo.

There is good evidence from RCTs that risedronate and alendronate prevent both nonvertebral and hip fractures compared with placebo.

There is good evidence that zoledronic acid prevents vertebral and nonvertebral fractures, and fair evidence that it prevents hip fractures."

Agency for Healthcare Research and Quality - report #12

December 2007

Benefit of treatments for hip fractures

Meta-analysis - 12 trials, 18,667 patients - over 3 years hip fractures are reduced by 0.5%

J Bone Miner Res 2006;21:340-9

Zoledronic acid after hip fracture

Patients

1,065 patients with a surgical repair of a hip fracture, 91% white, 76% female, mean age 75, T score 2.5 or less - 41%, -2.5 to -1.5 - 35%, more than -1.5 11%

Treatment

Zoledronic acid 5mg IV yearly or placebo

Duration

Median follow up of 1.9 years

Results

Bone density differences (total hip) - drug vs placebo

12 months 2.6% inc vs 1% dec

24 months 4.7% inc vs 0.7% dec

36 months 5.5% inc vs 0.9% dec

N Engl J Med 2007;357

Zoledronic acid results

	Any fracture(%)	Hip fracture (%)	Nonvertebral fracture (%)	Death (%)	Serious A Fib (%)	Any serious adverse event(%)
Zoledronic acid 5 mg	8.6	3.5	7.6	9.6	1.3	38.3
Placebo	13.9	2.0	10.7	13.3	0.5	41.2
Relative risk	38	NSS		35	250	NSS
Absolute risk	5.3		3.1	4.7	0.8	
Number needed to treat/harm	19		29	21	125	

Muscle aches and/or pyrexia increased by 3-6% within 3 days of infusion

Compliance/adherence

"almost three-quarters of all women initiating osteoporosis drug therapy-regardless of the medication received-are no longer adherent with treatment 12 months following therapy initiation, and almost one-half have discontinued such therapy by this time."

"compliance with weekly bisphosphonate therapy appears to be generally no better than that with medications requiring more frequent dosing."

Osteoporos Int 2006;17:1645-52

Bisphosphonates and atrial fib

Meta-analysis of all Merck-conducted placebo controlled trials of alendronate

32 studies - 9,518 alendronate, 7,773 placebo

RR for all AF events

1.16 (CI = 0.87, 1.55) p = 0.33

Osteoporos Int 2010 DOI 10.1007/s00198-011-1546-9

Bisphosphonates and Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women

A population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of women aged 68 years or older from Ontario

52,595 women with at least 5 years of bisphosphonate therapy

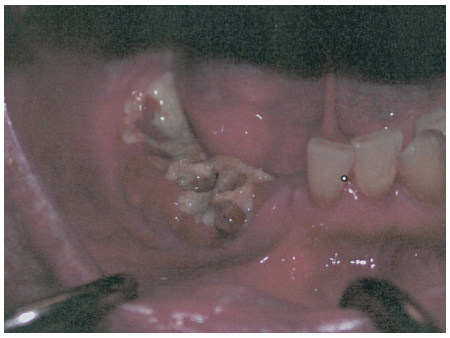
subtrochanteric or femoral shaft fracture 0.13% during the subsequent year - 0.22% within 2 years

JAMA 2011;305:783-9

Jaw osteonecrosis from bisphosphonates

More often occurs after dental procedures reported A minimum and maximum frequency of ONJ in patients receiving oral BPs as one in 2,030 and one in 950, respectively, and a minimum and maximum frequency of patients receiving oral BPs who have undergone extractions as one in 270 and one in 125, respectively

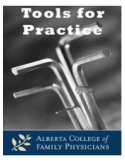
J Oral Maxillofac Surg 2007;65:415-23



Very good review

The American Journal of Medicine 2009;122:S33–S45

February 7, 2011

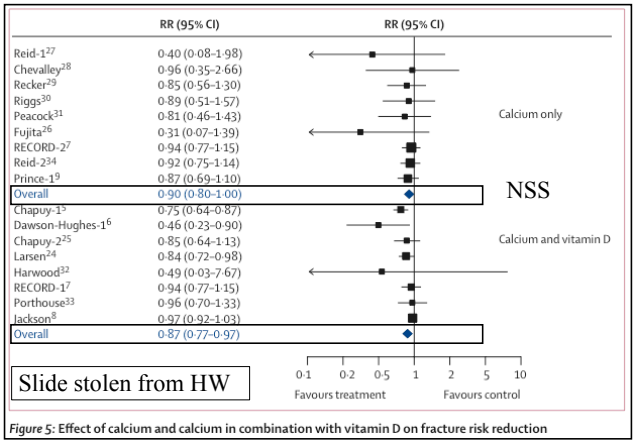


Does Calcium Supplementation Increase the Risk of MI?

Clinical Question: Does calcium (Ca+) supplementation contribute to increased risk of myocardial infarction (MI) and other cardiovascular disease (CVD)?

Bottom-line: The present evidence suggests that calcium supplementation, particularly ≥1000mg/day, may lead to an increase risk of MI. This evidence is poor and the risk, if present, is likely <1%

Effect of Calcium and Ca + Vitamin D on Fracture Risk Reduction



Slide stolen from HW

Figure 5: Effect of calcium and calcium in combination with vitamin D on fracture risk reduction

Tang, BMP et al. Lancet 2007;370:657-66

Calcium and risk of MI - meta-analysis

Patients

11,921 receiving at least 500mg a day of elemental calcium, >40 y/o, no vitamin D, average age 74, 78% female, 10% smokers, 8% CHD, 97% white - 15 studies

Treatment

placebo or calcium

Duration

4 years

BMJ 2010;341:c3691doi:10.1136/bmj.c3691

Results

	MI (%)	MI, stroke, sudden death (%)	Stroke (%)	Mortality (%)
Calcium	2.7	5.9	3.5	9.1
Placebo	2.2	5.5	3.3	9.2
Relative risk increase	23	NSS	NSS	NSS
Absolute risk increase	0.5			
Number needed to harm	200			

RCT evidence of Vitamin D

Fracture (19 trials) - High dose (>400IU/day)
2-4 years?
reduced Non-vertebral fractures 1.1%
reduced Hip fractures by 0.6%
Arch Intern Med 2009;169:551-61

Falls (5 trials)
Reduced falls by 7%
JAMA 2004;291:1999-2006

Mortality (18 trials) - 6 years
reduced overall mortality by 0.4-0.5%
Arch Intern Med 2007;167:1730-7

BUT!!

BMJ

RESEARCH

Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe

The DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group

"This individual patient data analysis indicates that vitamin D given alone in doses of 400-800 IU is not effective in preventing fractures. By contrast, calcium and vitamin D given together reduce hip fractures and total fractures, and probably vertebral fractures, irrespective of age, sex, or previous fractures"

OVER THREE YEARS
ANY FRACTURE
0.5% REDUCTION
0.9% IF >70 - 0.4% (hip)
1.2% if previous fracture - 0.2% (hip)

BMJ 2010;340:b5463

Calcitonin injections

5 RCTs - 264 patients

"Pain at rest was reduced as early as 1 week into treatment (weighted mean difference [WMD] =3.08; 95% confidence interval [CI]: 2.64, 3.52) and this effect continued weekly to 4 weeks (WMD = 4.03; 95% CI: 3.70, 4.35). A similar pattern was seen for pain scores associated with sitting, standing, and walking."

Osteo Int 2005;16:1281-90

Calcitonin

Meta-analysis of 30 trials and 3993 pts

- 4 RCT vertebral Fracture: RR 0.46 (0.25-0.87)
  - Relative risk reduction = 54%
- 3 RCT non-vertebral Fracture: RR 0.52 (0.22-1.23)
  - Not significant
- Concerns: Lots of heterogeneity and Bigger trials find less benefit

US Agency of Healthcare Research and Quality

- Reduced vertebral fracture: Fair Evidence
- No change in non-vertebral: Good Evidence

Endocr Rev 2002 23: 540-551, Ann Intern Med 2008;148:197-213

PTH

Meta-analysis 13 RCTs (but not all have # data)
7 RCTs (4359 pts) Vertebral Fracture:
RR 0.36 (0.28-0.47), Relative risk reduction 64%
5 RCTs (2377 pts) Non-vertebral Fracture:
RR 0.62 (0.48-0.82), Relative risk reduction 38%
Note: unclear if RR or Odds Ratio, if latter, not interpretable.

US Agency of Healthcare Research and Quality
Reduced vertebral fracture: Good Evidence
Reduced non-vertebral: Fair Evidence

Osteoporos Int 200718:45–47, Ann Intern Med2008;148:197

Bottom-Line PTH and Calcitonin

The evidence for PTH and Calcitonin is not as robust as bisphosphonates.

Calcitonin reduces vertebral fracture rates (and the degree is likely < 50%) but does not improve non-vertebral fracture rate.

PTH reduces vertebral & non-vertebral fracture rates but the reliability of the data is somewhat uncertain.

Strontium

"pooled data from SOTI and TROPOS indicate that strontium ranelate therapy is associated with a significant reduction in the risk of vertebral fracture [relative risk (RR) compared with placebo 0.60, 95% confidence intervals (CI) 0.53 to 0.69, p < 0.001] and non-vertebral fracture (RR 0.84, 95% CI 0.73 to 0.97, p = 0.01). The studies were not powered to identify a statistically significant difference in the incidence of fracture at any specific peripheral fracture site"

Thromboses were "found to be significantly higher in patients receiving strontium ranelate compared with placebo (RR 1.42, 95% CI 1.02 to 1.98, p = 0.036)"

Health Technology Assessment 2007;Vol 11:number 4

Densoumab

- Sample: 7868 women
  - mean age 72, BMD 26, 80% European, mean T-score = -2.8 spine, -1.9 total hip, & -2.16 femoral neck, 23.5% vertebral fractures
- Outcomes at 36 months mean

Outcome	Denosumab	Placebo	Diff (NNT)	Relative Risk Reduction	P-value
Vertebral	2.3%	7.2%	4.8% (21)	68%	<0.001
Non-vertebral	6.5%	8%	1.5% (67)	20%	0.01
Hip	0.7%	1.2%	0.3% (333)	40%	0.04
Clinical Vertebral	0.8%	2.6%	1.7% (59)	69%	<0.001

Notes: The clinical vertebral NNT much higher than overall. Hip AR reported in trial worse than my calculation (Diff = 0.44%, NTT 228). Still not very impressive

Hormone replacement issues

Hormone replacement therapy (HRT) helps with the symptoms of menopause

The best designed trials to date have shown that HRT does more harm than good on average

Likely "safe" for 3-4 years

Use the lowest dose to decrease symptoms

JAMA 2002;288:321-33

Lower doses of estrogen

2,673 postmenopausal women

1 year of placebo, 0.625, 0.45, 0.3 mg/d or 0.625/2.5, 0.45/2.5, 0.45/1.5, 0.3/1.5mg/d

Benefits

Number and severity of hot flushes were reduced to a similar degree in all groups compared to placebo

Fertil Steril 2001;75:1065-79

Lower doses of estrogen

Harm

Breast pain – 26% in 0.625/2.5 group, 7% in 0.3 group

Vaginal hemorrhage – 14% in 0.625 group, 6% in 0.625/2.5 group, 2% in 0.3 group

Breast enlargement, vaginal moniliasis, leg cramps, dysmenorrhea and vaginitis also more common in higher dose groups

Fertil Steril 2001;75:1065-79

Harms from hormone replacement

	CHD (%)	Stroke (%)	DVT (%)	PE (%)	Total CVD (%)	Breast CA (%)	Global Index (%)
Estr/prog	1.9	1.5	1.4	0.8	8.2	2.0	8.8
Placebo	1.5	1.0	0.6	0.4	6.7	1.5	7.7
RRI	27	50	133	100	22	25	14
ARI	0.4	0.5	0.8	0.4	1.5	0.5	1.1
NNH	250	200	125	250	67	200	91

JAMA 2002;288:321-33

Benefits from hormone replacement

	Colorectal CA (%)	Hip fractures (%)	All fractures (%)	Deaths (%)
Estr/prog	0.5	0.5	7.6	2.7
Placebo	0.8	0.8	9.7	2.7
RRR	38	38	22	NSS
ARR	0.3	0.3	2.1	
NNT	333	333	48	

JAMA 2002;288:321-33

Outcomes per 10,000 woman-years

	Estrogen PLUS progestin	Estrogen alone
Fractures	46 less	56 less
Invasive breast cancer	8 more	8 less
Stroke	9 more	11 more
Death	-	2 fewer
DVT	12 more	7 more
PE	9 more	-
Lung cancer death	5 more	-
Gallbladder disease	20 more	33 more
Dementia	22 more	-
Urinary incontinence	872 more	1271 more

Annals of Internal Medicine - 29/05/2012

• Osteoporosis Drugs Benefit - 2-3 years •

RELATIVE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~ 50%	~ 20%	~40%
Raloxifene	~ 40%	NS	NS
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Denosumab	~ 70%	~ 20%	~40%
Strontium	~40%	~ 15%	NS
ALL DRUGS	~50%	~20%	~25%

ABSOLUTE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~4-8%	~2%	~0.5-1%
Raloxifene	~4%	NS	NS
Teriparatide	~10%	~4%	NS
Vitamin D usually with calcium	1-2%	1-2%	~1%
Denosumab	~5%	~2%	~0.5%
Strontium	~8%	~2%	NS
ALL DRUGS	~5%	~2%	~0.5%

*~ 90% of the studies enrolled patients with a history of fractures with the exception of the VitaminD/calcium studies where this was ~ 50%
** etidronate has only been shown to reduce vertebral fractures in secondary prevention

How long do we treat?

Fracture Intervention Trial (FIT)

Women who had taken alendronate for 4.5 yr - randomly given alendronate or placebo for 5 years

No difference in the number of clinical fractures or morphometric vertebral fractures between the two groups

J Bone Mineral Res 2004;10(Suppl 1):S45

Two other alendronate trials showed similar results

N Engl J Med 2004;350:1189–1199

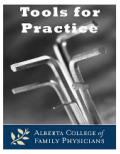
How long do we treat?

Fracture Intervention Trial (FIT) - second report

Women who had taken alendronate for 4.5 yr - randomly given alendronate or placebo for 5 years

No difference in overall clinical fractures but a 3% reduction in clinical vertebral fractures

JAMA 2006;296:2927-38



Bisphosphonates: Forever or Five Years and stop?

Clinical Question: Can patients with osteoporosis who have been on bisphosphonates for 5 years discontinue treatment without increasing future fracture risk?

"Available evidence suggests that after 5 years of treatment, discontinuation of bisphosphonates carries little to no increased future fracture risk. Choosing appropriate patients to continue therapy beyond 5 years and determining when or if to reinitiate therapy in those discontinued, remains uncertain."

An example of what should be told to patients

Your risk of NOT having a hip fracture in the next 3-5 years is 97%

The non-Rx measures are exercise, calcium, Vitamin D, preventing falls, stopping drugs (benzo's antihypertensives)

If you take this drug for the next 3-5 years your risk of NOT having a fracture will be approximately 98.5%

The side effects are not much different than placebo – approximately 1% chance of esophageal side effects (JAW OSTEONECROSIS)

Take a pill every day – glass of water, can't lie down etc

Costs

American Family Physician letter

May 15, 2001

Physicians don't talk to their patients with these conditions in the terms proposed by Dr. McCormack

We tell our patients, "Your blood pressure is too high; you should be on medication to reduce it;" or "Your cholesterol level remains elevated despite diet and exercise; we need to add medication to bring it down."

If …Dr. McCormack takes the approach he advocates for patients … I doubt that many of his patients opt for therapy

NELSON B. WATTS, M.D.
Emory University School of Medicine
Atlanta, Georgia

American Family Physician letter

May 15, 2001

I agree with the request for including more complete information about the results of clinical trials

I strongly disagree with his proposal for using this information in clinical practice

I tell patients who have low bone density or a fragility fracture that they have osteoporosis … I tell them that patients who have osteoporosis should be treated

Most patients want my advice, not a lesson in data analysis

NELSON B. WATTS, M.D.
Emory University School of Medicine
Atlanta, Georgia

CMAJ REVIEW

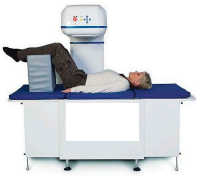
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary

"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"

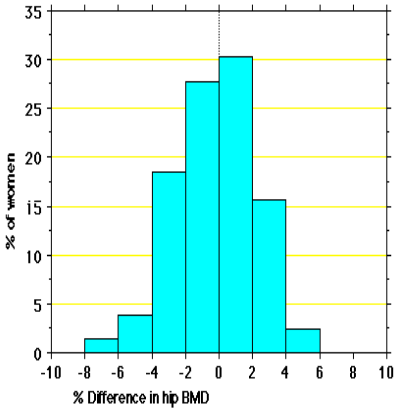
"For individuals with low risk of fracture and without additional risk factors for rapid loss of bone mineral density, a testing interval of 5–10 years may be sufficient"

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



Follow-up bone density measurements after treatment



Stolen from

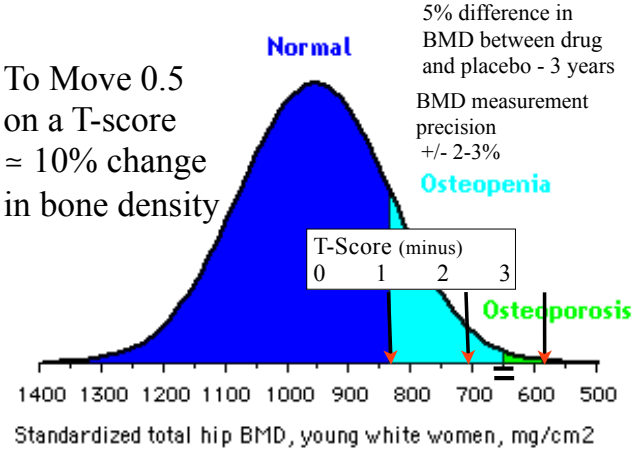
Susan Ott, MD
Associate Professor
Department of Medicine
University of Wash

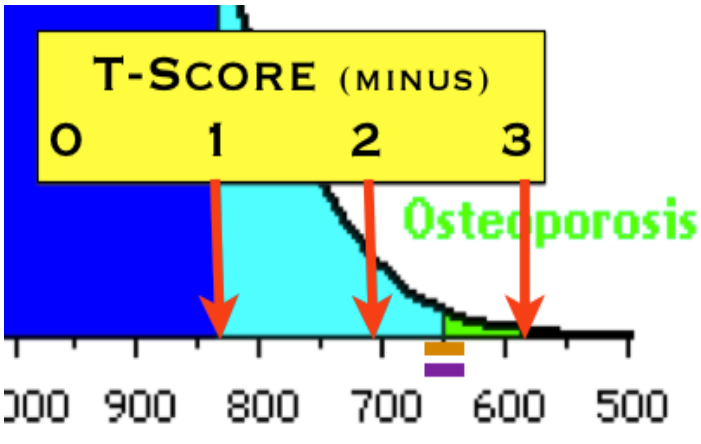
Bone density reports that state a change in bone density has been seen

"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

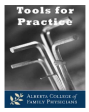
Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data

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"

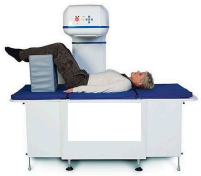
BMJ 2009;338;b2266



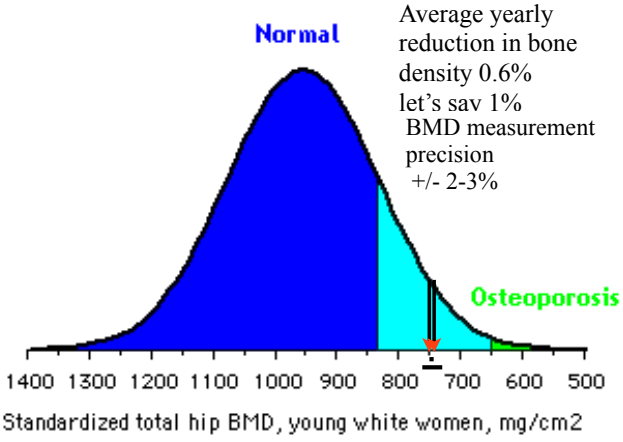
Bone Mineral Density – Too much of a good thing?

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

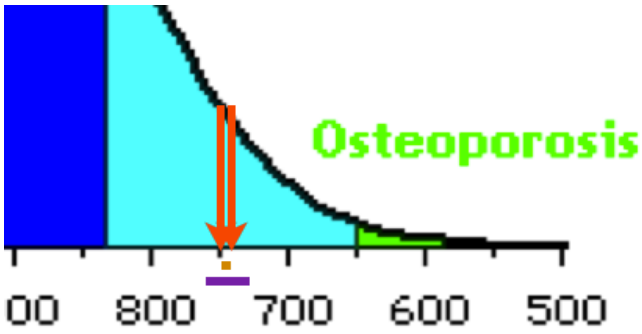
Christina Korownyk & Michael R. Kolber



Follow-up bone density measurements for assessment of "risk"



Average yearly reduction in bone density 0.6%
let's sav 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;167:155-6(

DXA measurements of +/- 2%

What does a measurement error/precision error/ coefficient of variation of +/- 2% really mean?

Changes in BMD from previous measurement

What you can say with reasonable confidence (whatever that means)

+/- 2.0%

impossible to know if this is random variation or a change in bone density

+/- 2.0% to 4%

if you saw this difference in 100 patients 5-32% of the time this difference would be due to chance

+/- > 4%

if you saw this difference in 100 patients less than 5% of the time this difference would be due to chance

in other words you can say the change is likely real and unlikely to be due to machine error but you can't be all that certain as to the amount of change

What should we recommend

PROBABLY BUT NOT FOR EVERYONE?

1. Calcium - 1500 mg daily elemental calcium
2. Vitamin D - 800 units per day

A recent meta-analysis suggests you need to use Vitamin D with calcium
J Clin Endocrinol Metab 2007;92:1415-23

SOUNDS REASONABLE

3. Weight bearing exercise she enjoys
4. Discuss the risks and benefits of bisphosphonates, raloxifene and other drugs for osteoporosis

The Hierarchy of Evidence for Therapy Studies

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
"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

Adverse events associated with testosterone administration

6 months - blinded

Baseline		Placebo 103 subjects	Testosterone gel 100 mg once daily 106 subjects	Add group	Labs		
Average Age	74 yr				A1c	6.2 %	
Black	8 %				Avg DBP	76 mmHg	
Caucasian	90 %				Avg SBP	137 mmHg	
HTN	82 %				BMI	30	
Prev CVD	52 %				HDL	47 mg/dL	
Previous Smokers	69 %				Hyperlipidemia	57 %	
Smokers	9 %				LDL	91 mg/dL	
Type 2 diabetics	26 %				Total chol	168 mg/dL	
					Total testosterone	243 ng/dL	
					Triglycerides	151 mg/dL	
		edit delete	edit delete		ARR (%)	RRR (%)	NNT/NNH
Comparator		○	●				
Control		●	○				
Adverse cardiac events		1.0 n = 1	9.4 n = 10		-8.5	-872	-12
Atherosclerosis-related events		1.0 n = 1	6.6 n = 7		-5.6	-580	-18
Overall CVD		4.9 n = 5	21.7 n = 23		-16.8	-347	-6
Skin reactions at gel application site, itching, erythema, psoriasis, foot ulcers, and increased hair growth		7.8 n = 8	17.9 n = 19		-10.2	-131	-10

Hormone replacement and heart disease

Observational data – heart disease is reduced by 35-50% by estrogen use - Nurses Health Study

Healthy woman selection bias?

Arch Intern Med 2000;160:2263-72

Lowers LDL, raises HDL, increases bone density

Symptom control

Estrogen plus progestin for secondary prevention of CHD in postmenopausal women- the HERS trial

Patients

2763 women with coronary heart disease, postmenopausal with an intact uterus - mean age 66.7

Treatment

0.625 mg of CEE plus 2.5 mg of medroxyprogesterone daily

Duration

4.1 years

JAMA 1998;280;605-13

Estrogen plus progestin for secondary prevention of CHD in postmenopausal women- the HERS trial

Results

11% decrease in LDL, 10% increase in HDL

No difference in:

CHD, CHD death, cancer, fractures, all cause mortality

but a 1.6% increase in both DVT/PE and gallbladder disease

Risk and benefits of estrogen plus progestin in healthy postmenopausal women

Patients

16,608 women mean age 63 – treated for diabetes (4%), treated for hypertension (36%), treated for elevated cholesterol (13%), smoker (11%)

Treatment

CEE 0.625 mg CEE PO daily PLUS medroxyprogesterone 2.5 mg PO daily or placebo

Duration

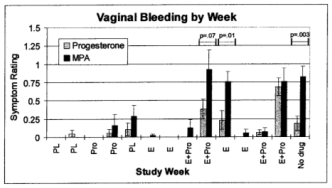
5.2 years (study stopped early due to health risks exceeding benefits)

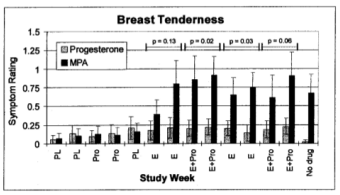
JAMA 2002;288:321-33

The Bioidentical Hormone Debate: Are Bioi Hormones (Estradiol, Estriol, and Progesterone or More Efficacious than Commonly Used Syn Versions in Hormone Replacement Therapy?

"With respect to the risk for breast cancer, heart disease, heart attack, and stroke, substantial scientific and medical evidence demonstrates that bioidentical hormones are safer and more efficacious forms of HRT than commonly used synthetic versions"

	Synthetic progestins vs progesterone
Symptoms	2 RCT's showing no difference
Tolerability	1) Cross sectional survey of 176 women who were currently being treated with HRT including micronized progesterone for a period of 1–6 months and had been treated previously with MPA - advantage to progesterone 2) RCT of 23 women - no differences in symptom control - ? differences in tolerability 3) RCT - CEE + MPA cyclical vs CEE +MP cyclical # of women who had episodes of excess bleeding for each 6 month interval (total 3 years)
Breast CA	"Synthetic progestins clearly associated ... with breast CA" - WHI (RCT), NHS (cohort) etc 1) Lots of surrogate data - cell proliferation and level association 2) Two cohort trials - same one presented twice (one was an update) - cases of invasive breast CA Estrogen +progesterone/dydrogesterone 129/40,537PY = .32% Estrogen and other progestagens = 527/104,243PY = 0.51% 3) "no randomized, controlled trials were identified that directly compared the risks for breast cancer between progesterone and synthetic progestins"
CVD	"MPA.. substantial increas in risk of heart attack and stroke - WHI (RCT) 1) Lots of lipid/surrogate data /animal data 2) One RCT cross over Estrogen and progesterone vs MPA on exercise induced MI ischemia exercise time significantly increased in the progesterone group 3) One case control - progesterone no risk of VTE but there was with synthetic
	Estrogen vs estriol
Breast CA	1) Population based cased cohort trial - 30,000 women Similar rates of endometrial cancer Estrogen but not estriol increased risk of breast CA compared to non-users - BUT no ss difference between estrogen and estriol 2) Case control study - 3,345 women Estrogen increased breast CA but low potency estrogens (oral estriol or topical) did not 3) "Large-scale randomized control trials are needed to quantify the effects of estriol in the risk of breast cancer"





0 = none
1 = slight/a little
2 = some
3 = extreme

23 non-depressed early postmenopausal women

Overall symptom control/ Mood - no difference

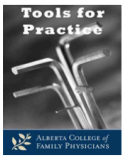
Side effects
1) mpa vs progesterone - no difference
2) When combo was used there was a difference - 0.5 on a 3 point scale
3) Breast tenderness - difference was there when just CEE was used
4) PEPI study - showed no difference in breast tenderness

Menopause 2002;9:253-63

Bioidentical vs synthetic - the evidence

	Symptom control		Tolerability		Breast Ca		CVD	
	P	E	P	E	P	E	P	E
RCT	2 no diff	0	2 ? 1 diff 11% vs 4% - 1 to 1.5 episodes of exc bleeding	0	0	0	1 surrogate end point	0
Cohort/case control	0	0	0	0	1 0.2%/yr diff	2 Topical Head to head?	1 VTE	0
Case series/ case reports	0	0	0	0	0	0	0	0
Expert opinion	+++	+++	+++	+++	+++	+++	+++	+++

March 5, 2012



Bioidentical Hormone Replacement: Are We Missing The Boat?

Clinical Question: Does "bioidentical hormone" micronized progesterone (MP) instead of "synthetic hormone" medroxyprogesterone acetate (MPA) result in improved menopausal symptom control and/or reduction in harm?

Bottom-line: "The theory behind bioidentical hormone use is appealing; however its clinical advantage is not supported by reliable evidence. Long-term safety is largely unknown"