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

James McCormack, B.Sc. (Pharm), Pharm.D.
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia

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

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

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero				One				Two			
BMI	35	30	25	20	35	30	25	20	35	30	25	20
Female												
50	2	3	3	3	4	4	5	5	6	6	7	8/1
60	5	6	6	7/2	7	9	10/1	10/4	11/1	13/2	14/2	16/6
70	8/1	9/2	10/2	11/4	11/2	13/3	15/4	17/7	16/4	18/6	21/7	25/12
80	14/4	16/5	19/7	16/11	20/8	23/10	27/13	24/20	28/14	33/18	38/22	35/32
Male												
50	2	2	2	2	3	3	4	4	4	5	6	6
60	3	4	4	4	5	6	6	7/1	7	8	10/1	10/2
70	4	5/1	6/1	6/2	6	7	8/2	9/4	8	10	12/4	13/6
80	6/2	7/3	9/4	9/5	9/4	11/5	13/7	14/10	13/7	16/9	19/12	21/16

Risk factors - Previous fracture "atraumatic", Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

A simple tool for estimating chance of fractures with a BMD

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero			One			Two		
t-score	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5
Female									
50	4	5/1	9/4	6	8/2	14/7	8	12/3	21/11
60	7	10/2	16/6	10/1	14/3	23/9	14/1	20/5	32/14
70	9/1	13/3	21/7	12/1	18/4	30/11	16/2	25/6	41/16
80	13/3	18/6	29/14	17/6	26/12	40/24	24/10	35/20	52/37
Male									
50	4	5/2	11/6	5	8/3	16/10	8/1	12/5	24/16
60	6/1	9/3	15/8	8/1	12/4	21/11	12/2	18/6	29/17
70	6/2	10/4	16/8	9/3	14/6	22/13	12/4	19/10	31/20
80	7/3	11/5	16/9	11/5	16/9	23/16	15/9	22/15	32/25

Risk factors - Previous fracture "atraumatic", Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

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	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

The Vitamin D Society is a Canadian non-profit group

"Optimal vitamin D blood levels are 50 ng/mL (125 nmol/L), according to The Vitamin D Council"

"The ideal 25(OH)D level continues to be debated ... [but] do we wait for science to complete its work .. or is it safer to wait with levels normally achieved by humans in a sun- rich environment" John Cannell

"Research indicates that well adults and adolescents should receive at least 5,000 IU vitamin D3 per day (either from sunlight or supplementation)"

Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes[1–3] AM J CLIN NUTR 2006;84:18–28

Heike A Bischoff-Ferrari, Edward Giovannucci, Walter C Willett, Thomas Dietrich, and Bess Dawson-Hughes

"Summary of all outcomes indicates that a desirable serum 25(OH)D concentration for optimal health begins at 75 nmol/L, and the best concentration is 90 –100 nmol/L"

BMJ RESEARCH

BMJ 2009;339:b3692

Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials

Fracture Prevention With Vitamin D Supplementation: A Meta-analysis of Randomized Controlled Trials

Heike A. Bischoff-Ferrari; Walter C. Willett; John B. Wong; et al.

JAMA. 2005;293(18):2257-2264 (doi:10.1001/jama.293.18.2257)

http://jama.ama-assn.org/cgi/content/full/293/18/2257

Prevention of Nonvertebral Fractures With Oral Vitamin D and Dose Dependency

ARCH INTERN MED 2009;169:551-61

A Meta-analysis of Randomized Controlled Trials

Heike A. Bischoff-Ferrari, DrPH; Walter C. Willett, DrPH; John B. Wong, MD; Andreas E. Stuck, MD; John Orav, PhD; Anna Thoma, MD; Douglas P. Kiel, MD; Jana Henschkowski, MD

Variability in Measurement

"whether an individual is found to have low or normal vitamin D status is a function of the laboratory used"

J Clin Endocrin Metab 2004;89:3152-7

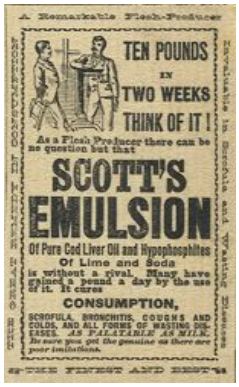
Variability in Measurement

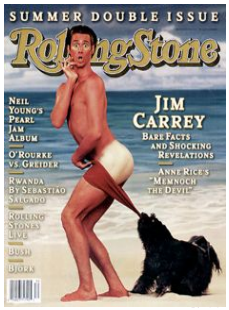
Between lab/Assay variability
"The differences between the mean values for serum 25(OH)D between the laboratories with the highest and lowest values was 38%"
Ost Int 1999;9:394-7

"the mean relative uncertainties...were 19.4%, 16.0%, and 11.3%"
Ost Int 2009 - 9 September 2009 -Online

Within patient variability - 15-20%
"The results of our analyses do not support the view that vitamin D supplements should be given on the basis of measurements of individual 25-OH-vitamin D levels. Conversely, our results indicate that subjects classified as having a sufficient vitamin D status may be diagnosed with vitamin D insufficiency in a **subsequent** measurement"
Ost Int 1998 8:222–30

Historically 400 IU of vitamin D was recommended for better health because it closely approximated the amount of vitamin D in a teaspoonful of cod liver oil





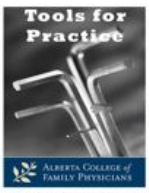
Variability VS Change from Treatment

800 IU raises vitamin D levels by ~ 20 nmol/L
Scand J Clin Lab Invest 2006;66:227–38

This increase is only slightly more than the variability (15-20%) in the measurement

Adrienne J Lindblad BSP ACPR PharmD, Scott Garrison MD PhD, James McCormack BScPharm PharmD

February 3, 2014



Vitamin D Levels: Vitamin Do or Vitamin Don't

Clinical Question: In adults, what is the evidence to test serum vitamin D levels?

Bottom Line: Routine testing of vitamin D levels is unnecessary. Laboratories often report serum levels between 50 and 75–80 nmol/L as insufficient but this is not supported by consistent or reliable evidence. Additionally, large variability in the test limits interpretation of repeat measurements.

>75 nmol/L "are not consistently associated with increased benefit."

Above 50 nmol/L are "practically sufficient for all persons."

Between 30–50 nmol/L "places some, but not all, persons at risk for inadequacy."

<30 nmol/L places one "at risk relative to bone health."

An EXTENSIVE systematic review
IOM(Institute of Medicine) 2011 - Dietary Reference Intakes for Calcium and Vitamin DWashington, DC: The National Academies Press

The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis

Mark J Bolland, Andrew Grey, Greg D Gamble, Ian R Reid Lancet January 2014

Trial sequential meta-analysis

- model the changing precision in estimates of effects as trials are reported

Futility analysis

- analogous to the termination of a clinical trial when an interim analysis indicates that the collection of further data is highly unlikely to alter the interim result

January 24, 2014 http://dx.doi.org/10.1016/ S2213-8587(13)7(

The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis

Mark J Bolland, Andrew Grey, Greg D Gamble, Ian R Reid Lancet January 2014

MI or ischaemic heart disease - 9 studies, 48,647 patients

Stroke or cerebrovascular disease - 8 studies, 46,431 patients

Cancer - 7 studies, 48,167 patients

Total fracture - 22 studies, 76,497 patients

"For our analyses, we chose to calculate thresholds using a 15% risk reduction for all events, except for mortality for which we used a 5% risk reduction"

January 24, 2014 http://dx.doi.org/10.1016/ S2213-8587(13)70212-2

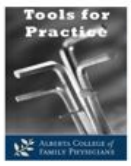
Effect of Vitamin D on clinically important outcomes

	Vitamin D alone	Ca/Vit D	ALL
MI or ischemic heart disease	0.99 (0.86-1.13)	1.18 (0.86-1.63)	1.02 (0.93-1.13)
Stroke or CVD	1.09 (0.92-1.30)	0.99 (0.87-1.13)	1.01 (0.90-1.13)
Cancer	0.98 (0.83-1.17)	0.89 (0.67-1.18)	0.99 (0.93-1.05)
Total fracture	0.97 (0.88-1.08)	0.92 (0.85-0.99)	0.95 (0.88-1.02)
Hip fracture	1.11 (0.97-1.27)	0.84 (0.74-0.96)	0.97 (0.86-1.08)
Mortality	0.97 (0.92-1.01)	0.96 (0.89-1.02)	0.96 (0.93-1.00)

Their Conclusion

"there is little justification for prescribing vitamin D supplements to prevent myocardial infarction or ischaemic heart disease, stroke or cerebrovascular disease, cancer, or fractures, or to reduce the risk of death in unselected community-dwelling individuals."

"Investigators and funding bodies should consider the probable futility of undertaking similar trials of vitamin D to investigate any of these endpoints."



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%

RCT of Vitamin D in Pregnancy

600? mothers at 12 weeks' gestation
400 IU daily, 2,000 IU daily or 4,000 IU daily
continued throughout pregnancy

1. 4000 IUs increased vitamin D level by about 50%--to a level of 100 nmol/L
2. Premature births and premature labor - reduced by 50% at both 32 and 37 weeks in those taking 4000 IUs
3. Fewer babies were born "small for dates"
4. Women in the 2000 & 4000 IU groups reduced their number of infections by 50%
5. gestational diabetes, increased blood pressure, and pre-eclampsia were reduced by 30%
6. babies born to moms getting the highest vitamin D levels had fewer colds and less eczema

ABSTRACT - Dec 2009

Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: A combined analysis☆

Carol L. Wagner[a,*], Rebecca B. McNeil[b], Donna D. Johnson[c], Thomas C. Hulsey[a], Myla Ebeling[a], Christopher Robinson[c], Stuart A. Hamilton[d], Bruce W. Hollis[d]

Table 4
Association between neonatal growth and comorbidities of pregnancy by supplementation dose group, adjusted for study and race.

	Control	2000 IU	4000 IU	p-Value (overall)	p-Value (2000 vs. control)	p-Value (4000 vs. control)	NNT/H (2000 IU vs. control)	NNT/H (4000 IU vs. control)
Neonatal birth weight, grams (SD)	3233 (668)	3382 (759)	3231 (632)	0.029	>0.05	>0.05	–	–
Hypertensive Disorders of Pregnancy (N, %)	9/110 (8.2)	9/201 (4.5)	4/193 (2.1)	0.15	0.43	0.052	NNT 27	NNT 17
Gestational Diabetes (N, %)	8/110 (7.3)	16/200 (8.0)	10/191 (5.2)	0.39	0.45	0.18	NNH 138	NNT 50
Infection, any (N, %)	45/110 (40.9)	96/201 (47.8)	75/193 (38.9)	0.30	0.33	0.78	NNH 15	NNT 49
Bacterial Vaginosis (N, %)	12/110 (10.9)	15/201 (7.5)	9/193 (4.7)	0.61	0.75	0.34	NNT 23	NNT 14
Preterm Birth without Preeclampsia (N, %)	14/107 (13.1)	23/198 (11.6)	26/192 (13.5)	0.42	0.20	0.55	NNT 69	NNH 219
Combined comorbidities (N, %)	67/110 (60.9)	125/201 (62.2)	106/193 (54.9)	0.43	0.97	0.30	NNH 79	NNT 17

Journal of Steroid Biochemistry & Molecular Biology 2013;136:313–20

Calcitonin injections (nasal spray removed)

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

Teriparatide

Reduced risk of back pain
Three trials compared drug to placebo and 2 compared to a bisphosphonate
Over roughly one year
Any back pain P = 19% T = 12%
Moderate or severe back pain P = 13% T= 8%
Severe back pain P = 4% T = 2%

Osteoporos Int 2006;17: 273–80

18 month study - teriparatide vs risedronate - 710 patients with Hx of back pain
No difference in back pain

Osteoporos Int DOI 10.1007/s00198-011-1856-y

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

Denosumab

- 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

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	8.8
Placebo	1.5	1	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

Danish HRT study

1006 menopausal, un-blinded, age 50, 43% smokers, 0.6 yrs since menopause, BMI 25, duration 10 years

Given - 2 mg synthetic 17-β-estradiol for 12 days, 2 mg 17-β-estradiol plus 1 mg norethisterone acetate for 10 days, and 1 mg 17-β-estradiol for six days OR Control

BMJ 2012;345:e6409 doi: 10.1136/ bmj.e6409 (Published 9 October 2012)

Danish HRT study

	Death, admission to hospital for MI or HF	CVD mortality	Mortality	Cancer	Breast cancer
HRT	3.2	1	3	1	2
Control	6.5	3.6	5.2	3.6	3.4
NNT	30	39	NSS	NSS	NSS

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

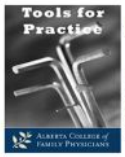
How long do we treat?

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."

CMAJ REVIEW

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

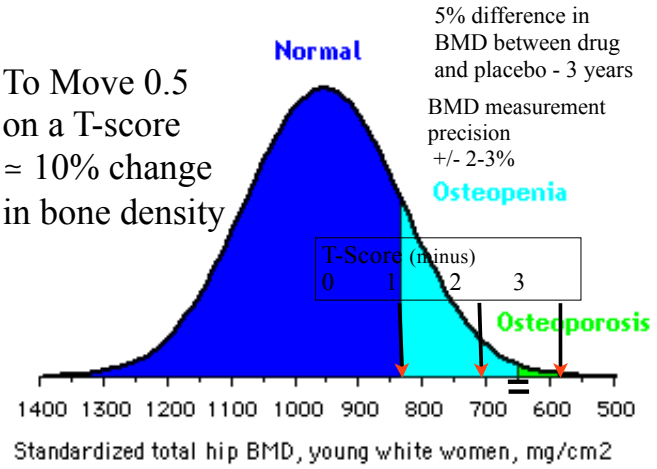
"For patients who are undergoing treatment, repeat measurement of bone mineral density should initially be performed after one to three years; the testing interval can be increased once therapy is shown to be effective"

"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

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



Other Smarter People

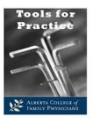
Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data

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"

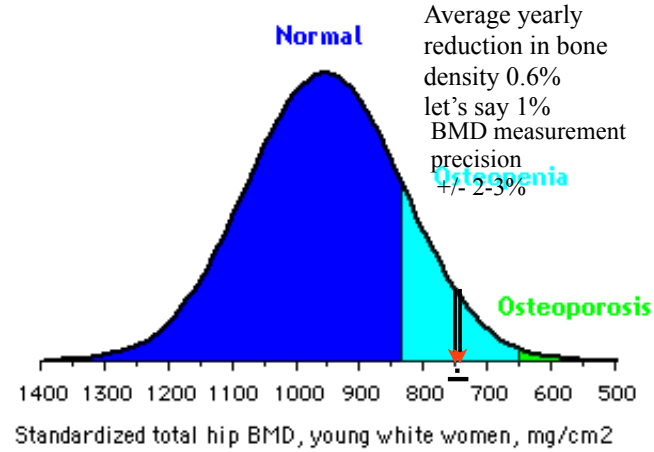
BMJ 2009;338;b2266



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



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

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero				One				Two			
BMI	35	30	25	20	35	30	25	20	35	30	25	20
Female												
50	2	3	3	3	4	4	5	5	6	6	7	8/1
60	5	6	6	7/2	7	9	10/1	10/4	11/1	13/2	14/2	16/6
70	8/1	9/2	10/2	11/4	11/2	13/3	15/4	17/7	16/4	18/6	21/7	25/12
80	14/4	16/5	19/7	16/11	20/8	23/10	27/13	24/20	28/14	33/18	38/22	35/32
Male												
50	2	2	2	2	3	3	4	4	4	5	6	6
60	3	4	4	4	5	6	6	7/1	7	8	10/1	10/2
70	4	5/1	6/1	6/2	6	7	8/2	9/4	8	10	12/4	13/6
80	6/2	7/3	9/4	9/5	9/4	11/5	13/7	14/10	13/7	16/9	19/12	21/16

Risk factors - Previous fracture “atraumatic”, Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero			One			Two		
t-score	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5
Female									
50	4	5/1	9/4	6	8/2	14/7	8	12/3	21/11
60	7	10/2	16/6	10/1	14/3	23/9	14/1	20/5	32/14
70	9/1	13/3	21/7	12/1	18/4	30/11	16/2	25/6	41/16
80	13/3	18/6	29/14	17/6	26/12	40/24	24/10	35/20	52/37
Male									
50	4	5/2	11/6	5	8/3	16/10	8/1	12/5	24/16
60	6/1	9/3	15/8	8/1	12/4	21/11	12/2	18/6	29/17
70	6/2	10/4	16/8	9/3	14/6	22/13	12/4	19/10	31/20
80	7/3	11/5	16/9	11/5	16/9	23/16	15/9	22/15	32/25

Risk factors - Previous fracture “atraumatic”, Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

• 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%

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