Breaking the cycle of recurrent fracture in patients with osteoporosis

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Disclosures

- 2014-Unrestricted grant in aid Amgen pharmaceuticals \$10,000 (5% total budget)
- 2016- One time Amgen advisory board
- Scientific Advisory Committee Osteoporosis Canada

Disclosures

- Not a geriatrician
- Currently:
 - Hospitalist physician
 - Osteoporosis consultant
 - Research and quality improvement

Osteoporosis services-PAH



Healthy Bones Clinic Physicians, physiotherapist, dietitian Group education classes



Projects in osteoporosis

- Breaking the cycle of recurrent fracture
 - Knowledge Translation research
 - Current project funded by MSFHR
- Improving the patient journey after vertebral fracture
 - Funded through Facility Engagement Specialist
 Services Committee

Learning objectives

- Recognize the breadth of the osteoporosis care gap in Canada
- 2. Interpret the evidence around effective ways to close the care gap
- 3. Apply the evidence in clinical practice to benefit patients

What I am not going to cover

- Primary prevention
- Studies of medication efficacy
- Duration of therapy and drug holidays
- Long term care guidelines

Low trauma / fragility fracture

- Fracture that occurs with very little trauma or force, from standing height or less.
 - Turn around lose balance hip fracture
 - Trip over a loose carpet edge wrist fracture
 - Lifting laundry out of dryer vertebral fracture





Risk Factors

- Age >65 years
- Family history -hip #
- Early menopause
- Low weight (<56kg)

- Medical conditions
 - Malabsorption
 - Rheumatoid arthritis
 - Hx of over-active thyroid, parathyroid
 - Diabetes
 - COPD, emphysema

Risk Factors

- Medications
 - Steroids-prednisone
 - Aromatase inhibitors
 - Anti-Androgen
 - Anti-seizure
 - Acid reflux
 - Diabetes



- Fall risk
- Lifestyle
 - Alcohol,smoking,caffeine
 - Physical activity
 - Diet
 - Calcium
 - Vitamin D
 - Protein



Most important risk factor for fracture

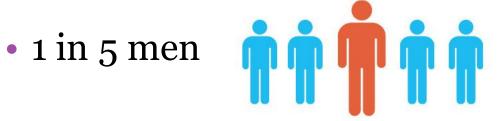


Low trauma fracture

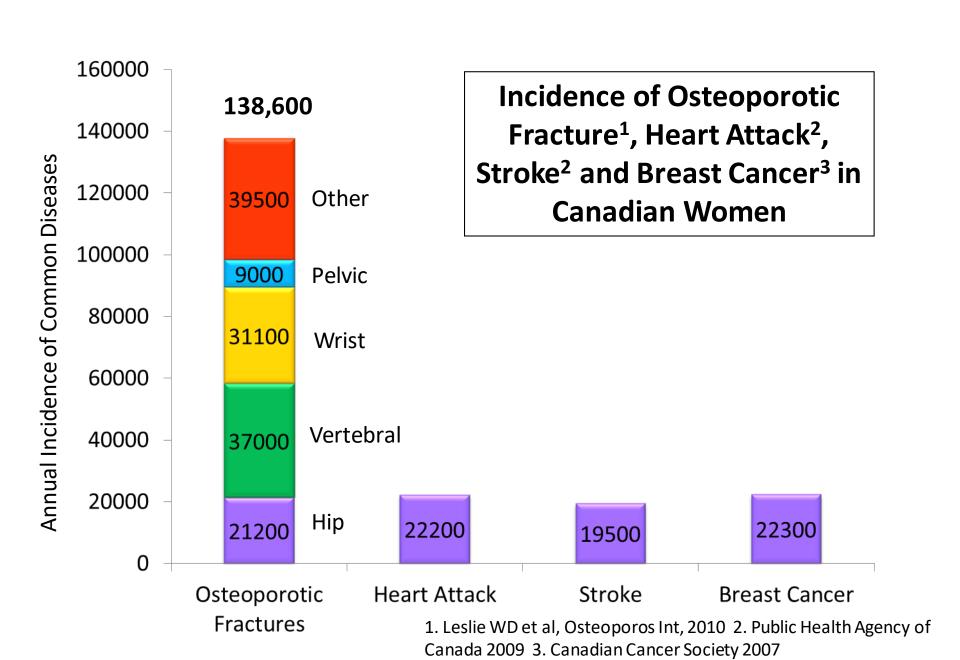
Osteoporosis is common

• 1 in 3 women





 Will suffer an osteoporosis related fracture over their lifetime

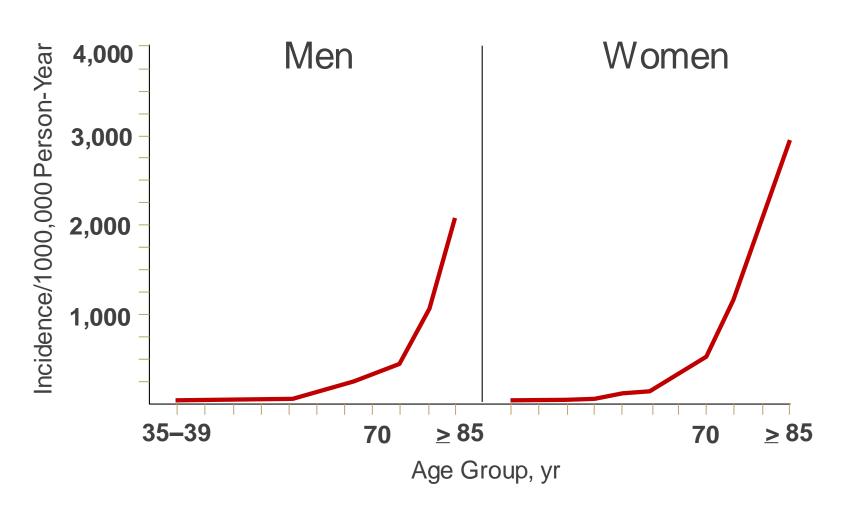


Vertebral Fracture Risk with Age



Adapted from Sambrook et al., Lancet 2006;367:210-8

Hip Fractures by Age



Re-fracturing is common

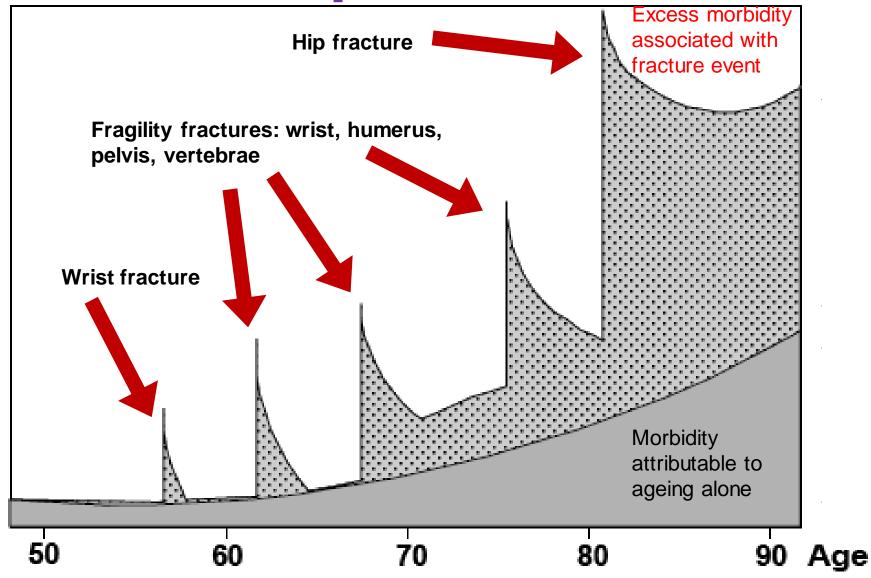
Fracture Type	Risk of New Fracture (within 1 year)	Risk of Fracture (3-5 years)
Wrist ¹		14% any fracture within 3 years
Vertebra ²	20% second vertebral	
Hip ³	9% contra-lateral hip 36% for non-hip	20% contralateral hip 57% non-hip fracture within 5 years

^{1.} Khan SA, Arch Int Med, 2001

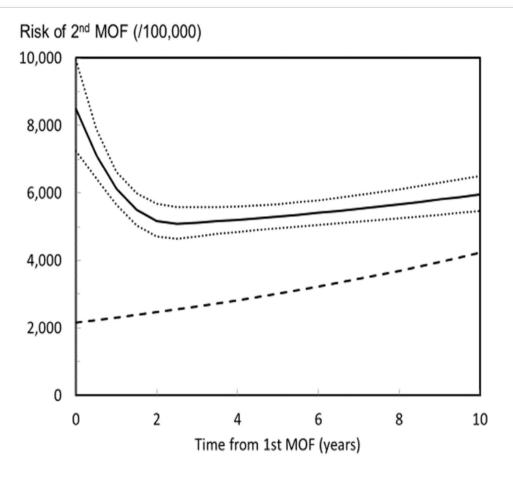
^{2.} Lindsay R et al, JAMA, 2001

^{3.} Ryget al, ASBMR, 2009

The Osteoporosis Career



Imminent fracture



MOF= Major osteoporosis fracture Wrist, humerus,hip,spine

Fig. 1.

Risk per 100 000 (95% CI) of a second major osteoporotic fracture (MOF) after a first MOF for a woman at the age of 75 years at her first fracture. Knots for the spline function are set at 0.5, 2.5 and 15 years of follow up after the first fracture. The dashed line is the risk of first MOF in whole population (n=18,872) for a woman 75 years at baseline.

Johansson H et al, Osteoporos Int. 2017 March; 28(3): 775–780. doi:10.1007/s00198-016-3868-0.

Consequences post hip fracture

Fracture Begets Future Fracture

Deteriorated **Quality of Life**

Long-term Care
Admission

Mortality



In women with hip fracture:

40% had prior fracture¹



In women with hip fracture:

40% need assistance walking²



In women with hip fracture:

18% enter

LTC³



In women with hip fracture:

23% die

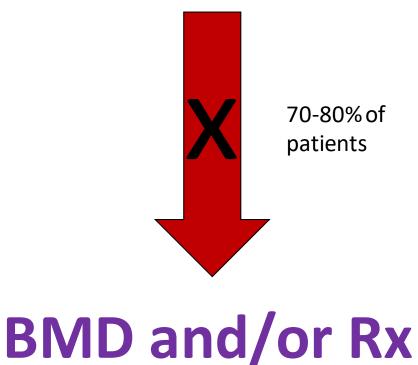
within 1 year4

- 1. Hajcsar EE, et al. CMAJ 2000, 163:819-822.; 2. Cooper C. Am J Med. 1997:103:12S-19S;
- 3. Jean et al. JBMR 2013; 28:360-71. 4. loannidis G, et al. CMAJ 2009;181: 265-271.
- 5. Hopkins et al .Osteo Intl 2012; 23:921-927

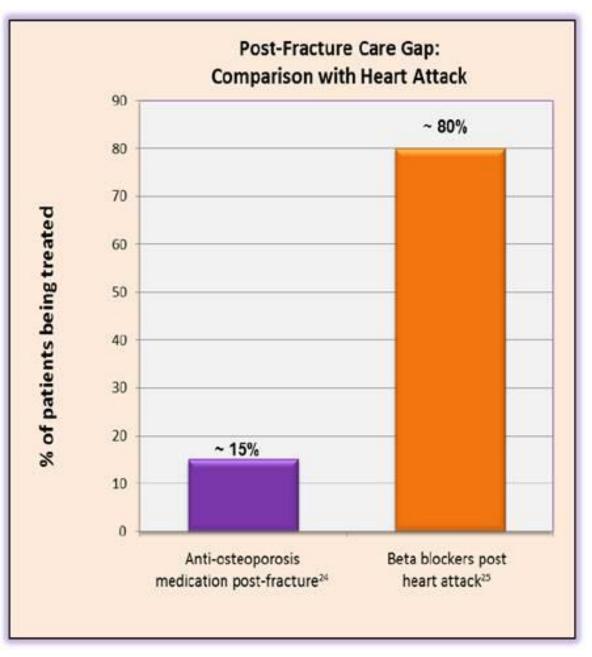
Vertebral Fractures



Fragility fracture



Papaioannou A, et al. *Osteoporos Int* 2008; 19(4):581-587. Giangregorio L, Osteoporos Int 2009; 20(9):1471-8.



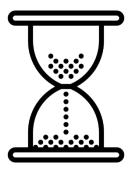
Source: Osteoporosis: Towards a Fracture Free Future.
Osteoporosis Canada, March 2011. Available online:

http://www.osteoporosis.ca/m ultimedia/pdf/White Paper M arch 2011.pdf

- 24. Bessette L, Ste-Marie LG, Jean S et al. The care gap in diagnosis and treatment of women with a fragility fracture. Osteoporos Int 2008;19(1):79-86.
- 25. Austin PC, Tu JV, Ko DT, Alter DA. Factors associated with the use of evidence-based therapies after discharge among elderly patients with myocardial infarction. CMAJ 2008;179(9):901-908.

Why the big care gap?

- Emergency staff: no time for preventative care
- Orthopedics surgeons busy fixing the fracture
- GPs-distracted by other health issues
- Allied health busy with rehabilitation
- Patients focussed on fracture recovery



Interventions to improve osteoporosis investigation and treatment

- Sale et al, systematic review 2011
- 57 studies looking at care provided at 6 months after fragility fracture
- BMD testing and medication starts

Conclusions

- Education-based interventions:
 - improved rates of BMD testing
 - limited success improving rates of treatment
 - patient education alone not impact on treatment
- All outcomes higher for interventions with:
 - dedicated personnel
 - BMD testing and/or treatment

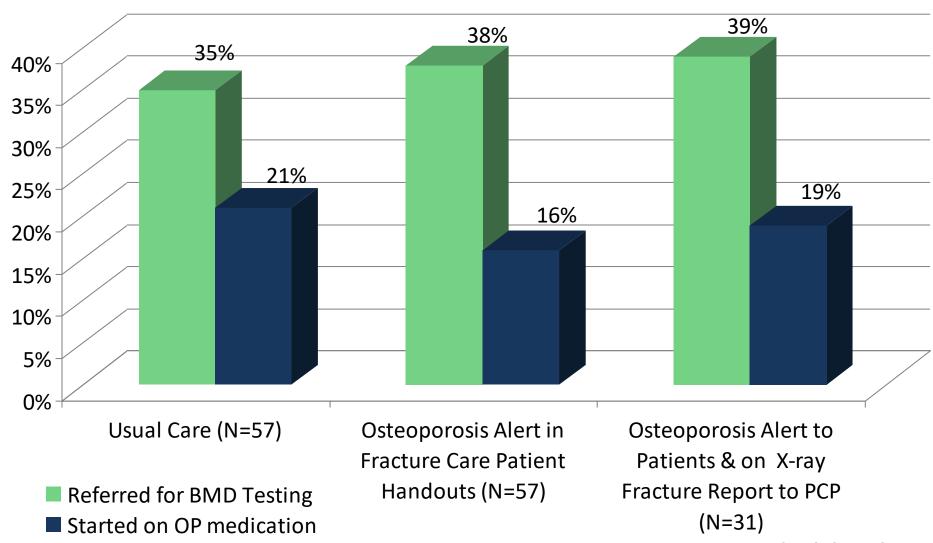
Models of care for secondary fracture prevention

- Systematic review and meta-analysis 2013
- 42 studies
- Types of models
 - 3i- identification, investigation, initiate treatment*
 - 2i-identification, investigation*
 - 1i-identification
 - oi- patient education only

Conclusions

- 3i and 2i models cost effective
- Some 3i models showed significant decreases in re-fracture rates
- Fully coordinated, intensive models were more effective than approaches using alerts or education alone.

One "I" Program - Identify only



* No significant different between interventions and usual care

Singh S et al unpublished

Fracture Liaison Services (FLS)

Dedicated FLS coordinator working with orthopedic staff



- Blood tests
- Bone density
- Assess risk of repeat fractures and falls

Initiate Treatment

- Education
- Osteoporosis medications
- Referrals
 - Fall prevention
 - OP specialist
 - Exercise programs

Identification

- > 50 years
- Low trauma fracture

Communication throughout the process with the primary care providers.

Systematic review FLS programs

- Jan 2000-Feb 2017 with 74 studies included
- When compared to individuals that receive usual care, individuals that go through an FLS program* have been found to have:
 - Higher rates of BMD testing (48%* vs 23.5%; NNT = 4)
 - Greater treatment initiation (38%* vs 17.2%; NNT = 5)
 - Greater adherence to treatment(57%* vs 34.1%; NNT = 5)
 - Decreased re-fracture rates (6.4% * vs 13.4%; NNT = 20)
 - Reduction in mortality (10.4%* vs 15.8%; NNT = 33)

FLS is now the standard of care worldwide to prevent OP fractures





National FLS registry

Canada – 43 FLS programs

- British Columbia 1 (Peace Arch Hospital)
- Alberta 10
- Ontario 26
- Quebec 3
- Nova Scotia 3



First FLS in BC Implemented!

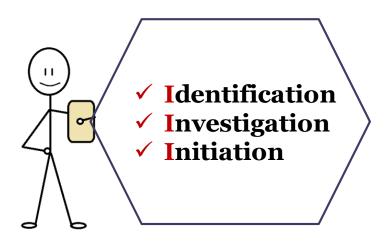


Orthopedic surgeons: Drs Bubbar, Kwee and Yao Cast technician Riz



FLS CARE at PAH since 2015

• FLS coordinator will link up with you while you are at the ortho clinic:



- Talk to you about risk of another fracture
- Order tests: BMD,X-rays of spine, blood tests
- Do an assessment of future fracture risk
- Assess risk of falling

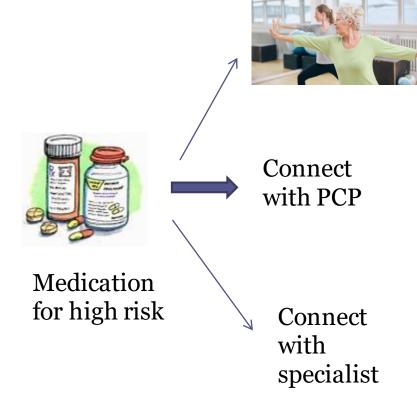
FLS CARE

Referrals and recommendations

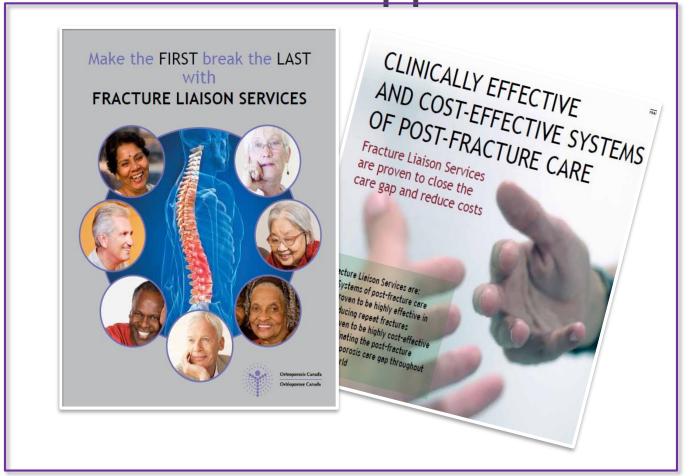




Education classes

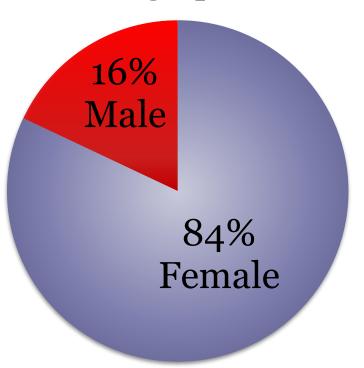


Osteoporosis Canada FLS Toolkit and Appendices



Study: Before and After 195 patients recruited

Demographics



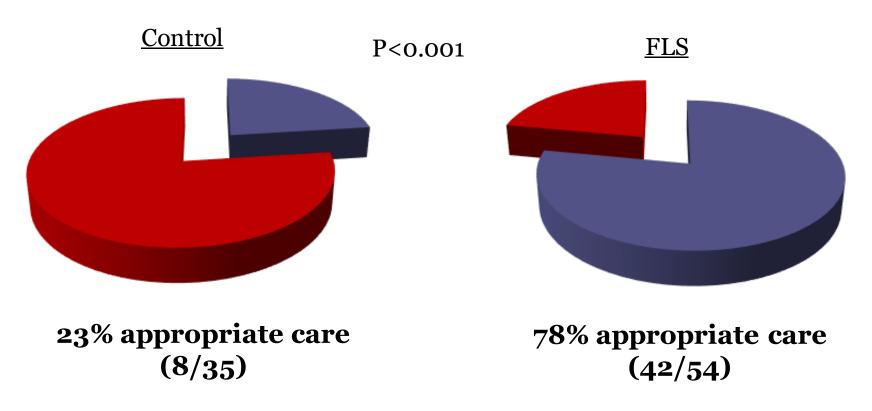
Average Age: 70.5 years (SD 11.5)

35% had prior fracture

Primary Outcome

- "Appropriate care"=One or more of the following occurred within 6 months after the fracture in patients at high risk to re-fracture
 - Osteoporosis medication started
 - Already on medication, medication review
 - Referral to an osteoporosis specialist

Appropriate care High Risk Patients (6 months follow-up)



Singh, S., Whitehurst, D.G., Funnell, L. et al. Arch Osteoporos (2019) 14: 116. https://doi.org/10.1007/s11657-019-0662-6

FLS is a permanent program at PAH

- No new money
- Leveraged existing positions
- Mind set: FLS is part of providing best practice guideline care for fracture patients

Implementation Science Team Grant (2019-2022)

- Breaking the cycle of recurrent fracture
- Spreading FLS to other sites within Fraser Health
- Developing a plan for FLS implementation province-wide



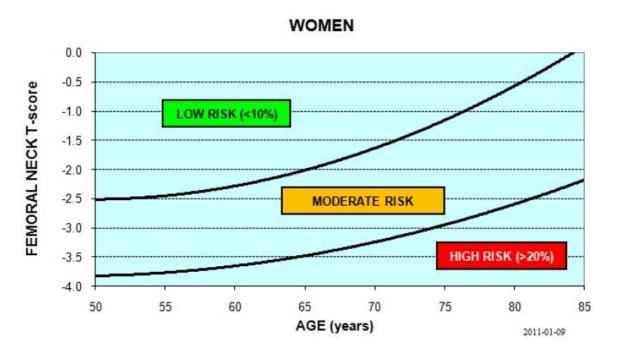
How to apply evidence to your practice?

Apply principles of FLS to your practice Patients with fractures

Assess their risk of repeat fracture
Treatment for those at high risk
These guidelines apply even for the over 75 age
group

Major OP fractures (MOF)

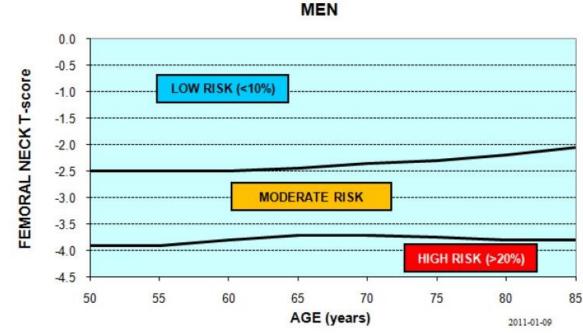
- Hip, vertebral, wrist, humerus, pelvis
- Automatically high risk
 - Hip, vertebral or multiple fractures
 - Fracture on prednisone
- Other fractures
 - BMD and risk scoring
 - Spine X-rays
- OP specialist referral but do not wait to treat
- REMEMBER IMMINENT RISK!





Go up one category of risk if the following are present:

Fragility Fracture
Current use of steroids



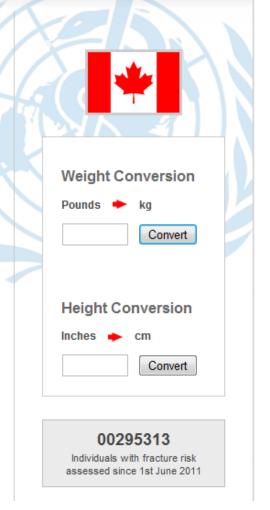
FRAX ® WHO Fracture Risk Assessment Tool

Home Calculation Tool ▼ Paper Charts FAQ References English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Canada	Name/ID:		About the risk factors
Questionnaire: 1. Age (between 40 and 90 years) Age: Date of Birth: Y: M: 2. Sex 3. Weight (kg) 4. Height (cm) 5. Previous Fracture 6. Parent Fractured Hip 7. Current Smoking 8. Glucocorticoids 9. Rheumatoid arthritis	or Date of Birth D: No Pemale No Yes No Yes No Yes No Yes No Yes No Yes No Yes	10. Secondary osteoporosis 11. Alcohol 3 or more units/day 12. Femoral neck BMD (g/cm²) Select BMD Clear Calculate	No ○ YesNo ○ Yes





Osteoporosis Medications

	Antiresorptive Therapy			
Type of Fracture		Bisphosphonates		
Traciale	Alendronate	Risedronate	Zoledronic Acid	Denosumab
Vertebral	✓	✓	✓	✓
Hip	✓	✓	✓	✓
Non-vertebral [†]	✓	✓	✓	✓

Labs

- Rule out secondary causes / safety of meds
- CBC, creatinine/GFR, TSH, Alk phos, Calcium/albumin
- Selectively:
 - SPEP in those with vertebral fractures
 - Vitamin D-malnourished, sarcopenic
 - Celiac serology
 - LFTs
 - B12 addressing fall risk



ORAL BISPHOSPHONATE ADMINISTRATION*

Once a week: Once a month: alendronate 70 mg risedronate 35 mg	
First thing in the morning, on an empty stomach	
DO NOT give with any other morning medications. It will NOT be absorbed or effective if given after eating.	
With a full glass of water	
DO NOT administer with milk, juice, coffee, tea, etc. It will NOT be absorbed or effective if given with anything other than water.	
Resident/patient should wait 30 min	0
(60 min preferred) before eating or drinking,	
including other medications.	(30 _{min})
The medication needs time to be absorbed. Absorption will stop when food or other medications enter the stomach.	
Do NOT crush/allow chewing of medication.	▲ WARNING: Do Not
It will NOT be well absorbed and may damage the esophagus or cause sores in the mouth if not taken whole.	CHEW or Crush
Patient should NOT lie down post-dose.	
Patient can sit or stand or walk.	
Patient can lie down AFTER breakfast- 30 min post dose (60min preferred). DANGER: Lying down after this medication may lead to an esophageal ulcer which may bleed or perforate.	

Not suitable

Dementia Patients

- forgotten
- taken with food
- put in their morning blister
- Dysphagia
- Significant reflux
- CKD with GFR <30.

^{*}Actonel DR MUST be given WITH breakfast.

Zoledronic Acid (Aclasta®)

- For patients who cannot tolerate oral bisphosphonates
- 5mg by IV infusion every 12-18 months
- Cost: about \$700/year
 - Generic \$350/year



Side effects

- Achy muscles and joints
- Stomach irritation, acid reflux
- With Zoledronic acid
 - flu like illness 3-4 days after infusion

Denusomab (Prolia®)

- Every 6 months SQ injection
- Can be used in setting of renal failure GFR <30.
- Hypocalcemia can be an issue with severe CKD. Check before and 2 weeks after in at risk patients.
- Side effects: Muscle pain in arms, back, rash, slight increase risk of infection



Cost: ~\$700 per year

Key take home message

- Check serum calcium and GFR
- No Bisphosphonates with GFR<30
- Denosumab can cause hypocalcemia
- Denosumab discontinuation (>7 months) can lead to increased risk of vertebral fracture
 - Ensure given every 6 months
 - If stopping, give one year of bisphosphonate

Are these medications effective in >75 years?

Alendronate

- Cochrane systematic review of 11 trials, with over 12,000 participants
- 40% reduction in hip fractures, <u>independent of</u> <u>age group</u>

Large Swedish cohort

- Falls prevention screening program (2008-2014)
- All over 80 (433,195)
- Screened for patients(52,685)
 - Any prior fracture within preceding 4 yrs
 - Alendronate naïve
 - No prior OP meds

Large Swedish cohort

- 1961 started on Alendronate
- Control group of 7844 (matched 4 to 1)
- Sex, age, wt, ht, RA, DM, Prednisone, fall injury, fracture type, # of fractures, dementia, EtOH

188 1 Bussline characteristics

Description	No alendronate	Alendronate	P-value
Number of petients	7844	1961	
Female sex – no. (%)	6871 (87.6)	1719 (87.7)	0.97
Age, years - mean (SD)	85.7 (4.4)	857 (3.9)	0.63
Weight, kg - mean (SD)	62.1 (13.9)	62.3 (13.0)	0.52
Height, cm - mean (SD)	160.8 (8.4)	160.8 (8.1)	0.85
Alcohol-related diseases – no. (%)	32 (0.4)	7 (0.4)	0.84
Rheamstoid arthritis - no. (%)	367 (4.7)	110 (5.6)	0.09
Previous Intense' glucocorticoid - no. (%)	1909 (24.3)	515 (26.3)	0.08
Time since fracture, years - mean (SD)	5.7 (4.2)	59 (3.6)	0.20
Provious full injury – no. (%)	5569 (71.0)	1366 (69.7)	0.24
Previous hip fracture - no. (%)	1806 (23.0)	436 (22.2)	0.47
Previous hip replacement - no. (%)	1271 (16.2)	331 (16.9)	0.47
Previous vertebral fracture - no. (%)	1949 (24.8)	506 (25.8)	0.38
Number of provious fractures - no. (%)			0.28*
1	5728 (73.0)	1423 (72.6)	
2	1426 (18.2)	395 (20.1)	
≥3	690 (8.8)	143 (7.3)	
Ostropomais – no. (%)	2125 (27.1)	632 (32.2)	+0.001
Secondary ostroporosis – no. (%)	337 (4.3)	94 (4.8)	0.36
In stalin-dependent dials tes - no. (%)	215 (2.7)	55 (2.8)	0.88
Hyputhyroidism – no. (%)	165 (2.1)	46 (2.3)	0.49
Hypngonadism - no. (%)	0 (0)	0 (0)	_
Mahutriton - no. (%)	33 (0.4)	8 (0.4)	1.00
Osteogenesis imperfects – no. (%)	0 (0)	0 (0)	_
Chronic liver disease - no. (%)	37 (0.5)	1 (0.1)	0.86
Charlson modeldity index			0.67*
0	2842 (36.2)	722 (36.8)	
1-2	2739 (34.9)	656 (33.5)	
≥3	2263 (28.9)	583 (29.7)	
Charlson modeldity components:			
la chae mic he art diseases – no. (%)	1596 (20.3)	419 (21.4)	0.32
Congestive heart failum - no. (%)	1413 (18.0)	365 (18.7)	0.51
Cerebrova scalar diseases - no. (%)	1530 (19.5)	376 (19.2)	0.75
Diseases of arterioles and capillaries - no. (%)	666 (8.5)	170 (8.7)	0.79
Diabetes – no. (%)	829 (10.6)	211 (10.8)	0.81
Dementia - no. (%)	840 (10.7)	202 (10.3)	0.62
Chronic pulmonary disease - no. (%)	935 (11.9)	245 (12.5)	0.49
Chronic liver disease - no. (%)	37 (0.5)	10 (0.5)	0.86
Renal failure, mild - no. (%)	256 (3.3)	64 (3.3)	1.00
Renal failure, moderate - no. (%)	33 (0.4)	11 (0.6)	0.45
Peptir ulcer disease - no. (%)	287 (3.7)	73 (3.7)	0.89
Hemiplegia – no. (%)	150 (1.9)	33 (1.7)	0.58

Mean age 85.7 vs 85.7

Previous hip fracture 23% vs 22.2%

Previous vert fracture 24.8% vs 25.8%

Dementia 10.7% vs 10.3%

Dx of OP

27.1% vs 32.2%

Large Swedish cohort

- Watched until death or emigrate or Dec 31 2014
 - □ Hip #
 - □ MOF
 - Any fracture
 - Death
 - Adverse events

Large Swedish cohort

At 3 yrs	ALN	PLB	1	NNT
Hip fractures	4.1%	6.2%	38%	26
MOF	6.0%	8.2%	32%	23
Any fracture	10.9%	13%	22%	20

Safety and Efficacy of Risedronate in reducing fracture risk in OP Women aged 80 and older

- ■Pooled data 3 trials total of ~1400 patients
- BMD T-score -2.5 or a previous vertebral fracture
- 81% decreased risk of new vertebral fracture after one year
- NNT of 12

Pivotal 3 year RCT: Denosumab

- Post hoc analysis: >75 years
- Hip fractures: 2.3% PLB vs 0.9% DEN (p<0.01)
- New vertebral #

At 3 years	PLB	DEN	P-value	NNT
Previous vert #	16.6%	7.5%	<0.001	11
T-score FN -2.5 or less	9.9%	3.1%	<0.001	15
Both	20.1%	8.1%	0.001	9

What about adverse drug events?

Large Swedish cohort

- Mild UGI symptoms more common
 - PLB 1.4% vs ALN 2.3% (p < 0.01)
- Peptic ulcer NS
- Deaths NS (PLB 43.6% vs ALN 40.4%)

Safety and Efficacy of Risedronate in reducing fracture risk in OP Women aged 80 and older

- The incidences of:
 - esophagitis
 - (placebo 1.3%; risedronate 1.7%)
 - stomach ulcer
 - (placebo 1.0%; risedronate 1.4%)
 - duodenal ulcer
 - (placebo 0.6%; risedronate 0.4%)
- Similar between the two treatment groups

Osteoporosis Medications

	Antiresorptive Therapy			
Type of Fracture	Bisphosphonates			
Tractare	Alendronate	Risedronate	Zoledronic Acid	Denosumab
Vertebral	✓	✓	✓	✓
Hip	✓	✓	✓	✓
Non-vertebral [†]	✓	✓	✓	✓

No evidence that any of these drugs:

- Are any less effective in the elderly
- Have more side effects in the elderly

Unlikely to benefit from OP meds

- Life expectancy < 12 months
- Most medications don't begin to see benefits until 6 months
- Need to have 80% adherence to see benefits
- Patient / family preference, cost issues
- You know your patients
 - Dementia, neurologic, cardiac / pulmonary diseases shorten life span

Dementia

- 4 year follow up Sweden community dwellers
 - > 65 yo:
 - with dementia: 25% had a fracture
 - without dementia: 7% had a fracture
- Survey of current use of osteoporosis medication:
 - Dementia 5%
 - Without dementia 12%

Fall Prevention / Hip protectors

- Important and likely high priority on most geriatric services
- Keep in mind that vertebral fractures can occur with no fall
 - Leads to delayed diagnosis
 - OP meds have best efficacy in preventing repeat fractures of vertebra

Controversies

- "Osteonecrosis of the Jaw"-ONJ
 - Vancouver Sun- "Class-action suit launched against Merck Frosst over 'jaw death' warning
- "Atypical Fractures" -AFF
 - Vancouver Sun- "Drugs used mainly to prevent bone fractures or treat osteoarthritis, often in postmenopausal women, may cause bone tissue to crumble and die in rare situations, according to a B.C.-led study"

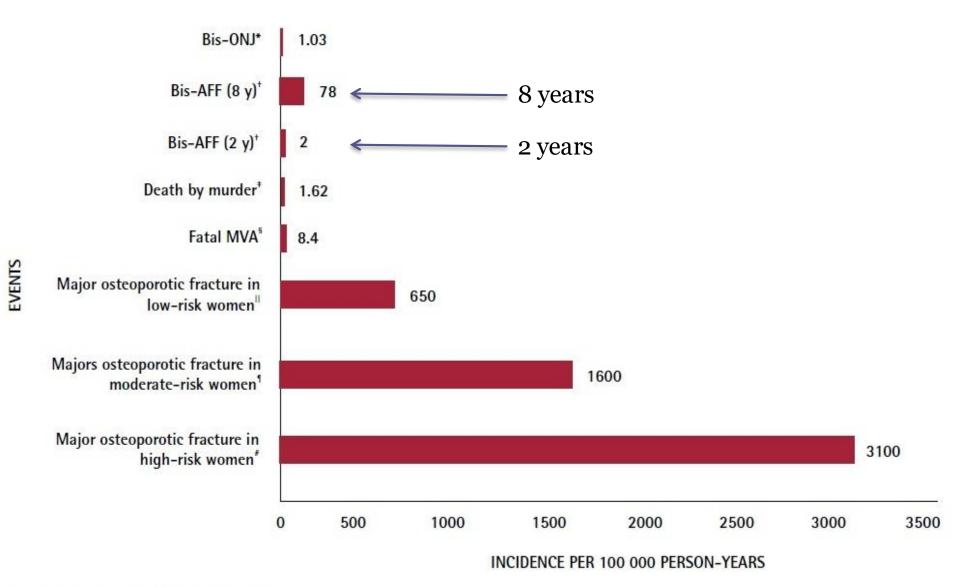
ONJ- what is it

- Delay in dental healing >8 weeks
- 3% to 5% in oncology patients on oncology doses ZOL, Denosumab
- In OP treatment: 1/100,000 patients
- Interruption of therapy not beneficial
- Can time surgery to 6 mo after Denosumab

Atypical femoral fractures: AFF

- Subtrochanteric, transverse
- Lateral cortical beaking, medial cortical spike
 - 50% bilateral, prodrome groin or thigh pain
 - 20% of AFF's in patients not on OP

Figure 1. Risks of major osteoporotic fracture and other rare events



Key take home message

- Patients on any of these drugs
 - Make sure dentist aware if going for major dental surgery
 - Alert GP if complaining of new mid-thigh pain
 - Re-evaluate after 3-5 years of treatment

Diet

- Older adults often do not get enough protein
- Sarcopenia big contributor to fracture risk
- Post-hip fracture- 25% lost 10lbs or more
- Lose weight = Lose bone

Calcium controversy-2010

- Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis
 - 15 studies, all RCTs, all taking more than 500mg calcium supplement.
- Increased risk of MI (~30%) 166 cases in calcium, 130 placebo

Calcium controversy-2015

- Calcium intake and risk of fracture: systematic review of literature
 - Dietary calcium not associated with risk of fracture
 - Evidence that calcium supplementation prevents fractures is weak

Key take home message

- Calcium 1200 mg per day
 - Most need no more than 500 mg supplement
 - Take as much in diet as possible
 - Space out through day

Osteoporosis Canada online calcium calculator



Vitamin D controversy

- Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis and trial sequential analysis
- Pooled findings of 81 randomized control trials, collectively >50,000 participants.

Conclusion

- Vitamin D supplementation did not have an effect on the risk of fractures or falls, and no meaningful effect on BMD
- No justification for recommending vitamin D supplementation to maintain or improve musculoskeletal health.

My concerns

- Did not address use of vitamin D in deficient populations or in osteoporosis diagnosis population
 - too few studies with low vit D levels (<50 nmol/L)
 - most studies done with adequate vitamin D at baseline
 - Study length of too short to look at fracture reduction (one year)

My recommendation

- Continue to administer Vitamin D supplements to patients with OP and fractures
 - 800 IU-2000 IU
 - 1000 if they are on combined supp with calcium
 - 2000 if not on any calcium
- Frail patients-consider doing a vitamin D test
- Unclear what the optimum Vitamin D level is
 - Above 50 nmol/L
 - Aim for 75 nmol/L

Key take home message

- Adequate vitamin D and Calcium important
- NOT sufficient to prevent fractures in high risk patients
- Patients at high risk for repeat fractures will benefit from OP meds

Exercise / physical activity

- Aerobic
- Resistance training
- Core stability exercises vertebral fractures
- Balance exercises (Tai Chi) at risk of falls

Get to know what resources available in your community

- Choose to move
- Osteofit
- Move for Life

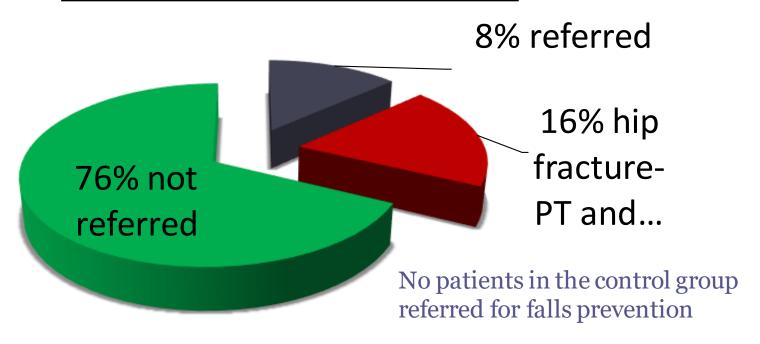
Summary

- History of low trauma fracture best predictor of a future fracture
 - Treat with medication in those at high risk for repeat fracture
- Vitamin D, Calcium, Protein
- Exercise: weight bearing, strength / balance
- Falls prevention strategies/Hip protectors

Questions

FLS Program Patients

Referred for Falls Assessment



Return on Investment at PAH

Costs:	nurse annual salary	assistant	stipend		Total annual costs of the FLS	Savings:	nip fractures	care bed days	•	Net cost avoidance over 8 years
Year 1:	\$94,510	\$11,859	\$6,720	\$8,000	\$121, 088				N/A	
Over 8 years:	\$756,077	\$94,870	\$53,760	\$64,000	\$968, 708	Over 8 years:	38	646	\$2,338,520	\$1,369,812

Osteoporosis Canada Model

^{1.} McLellan AR, Wolow acz SE, Zimovetz EA, et al. Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: A cost-effectiveness evaluation based on data collected over 8 years of service provision. Osteoporos Int. 2011;22(7):2083-2098. doi:10.1007/s00198-011-1534-0