Translating the Evidence: From Publication to Practice

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Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Objectives

1. Compare the benefits and risks of 12 months and 30 months of dual antiplatelet therapy after placement of drug-eluting stents.
2. Review the findings of the HEAT-PPCI trial on heparin versus bivalirudin in percutaneous coronary intervention
3. Describe what effect vitamin D has on fall prevention in elderly women
4. List limitations of the randomized controlled trials reviewed

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Duration of DAPT?

12 OR 30 MONTHS OF DUAL ANTIPLATELET THERAPY AFTER DRUG-ELUTING STENTS

N Engl J Med. 2014;371(23):2155-2166.

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Background

- IHD affects 13 million in the U.S.
- PCI most common revascularization procedure
  - Performed twice as often as CABG
- PCI indicated when
  - IHD unstable
  - Persistent symptoms
  - Severe ischemia or high-risk anatomy
  - Diabetes
  - Impaired LV function
- Efficacy: improves outcomes
  - In UA (>95%)
  - When used early in MI ± cardiogenic shock

Harrison's Principles of Internal Medicine

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Background

- Stents
  - BMS
    - Restenosis in 20% within 6 months
  - DES
    - Restenosis reduced to <10%
- Stent complication: thrombosis
  - Greatest risk within first 30 days
  - Similar between BMS and DES?
  - Everolimus may be safest (reduces MI and stent thrombosis compared to BMS)
  - Everolimus, sirolimus, and zotarolimus most efficacious

Circulation. 2012;125(23):2873-2891.
Harrison's Principles of Internal Medicine

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Background

- DAPT
  - Aspirin + P2Y12 receptor inhibitor
- DAPT benefits
  - Decreases stent thrombosis
  - More intensive antiplatelet therapy helps further reduce thrombosis during time when metal stent is not endothelialized
  - Decreases MI

JAMA. 2005;293(17):2126.

Guidelines

- ACCF/AHA/SCAI 2011 and CHEST 2012
  - For ACS and PCI with stents, 12 months of DAPT:
    - Low-dose aspirin (75 mg to 162 mg)
      and
    - Ticagrelor 90 mg bid
      or
    - Clopidogrel 75 mg daily
      or
    - Prasugrel 10 mg daily
  - Continue low dose aspirin plus P2Y12 inhibitor for 12 months for all stents
  - Continue single antiplatelet therapy indefinitely

Durations vary depending on
- Indication
- Stent type
- Emergent/elective

J Am Coll Cardiol. 2011;58(24):e44-122.
Chest. 2012;141(2 Suppl):e637S-668S.

DAPT Duration Controversy

- Longer duration (>12 months)
  - Benefit
    - Further decrease in risk for events
  - Increased risk for bleeding?
- Evidence
  - Multiple studies on DAPT duration that were not adequately powered
  - ISAR-SAFE
    - 6 months NI to 12 months of DAPT in drug eluting stents

Eur Heart J. 2015;36(20):1252-63.

12 or 30 Months of DAPT?

- Study objective
  - Determine the safety and efficacy of continuing DAPT beyond 1 year in patients with coronary stents
- Methods
  - Multicenter, randomized, placebo-controlled trial
  - Open-label from stent placement through month 12, then randomization to DAPT or aspirin + placebo

12 or 30 Months of DAPT?

Inclusion
- Adults undergoing PCI with stent placement
- Either BMS or DES
- "12 month clear"

Exclusion

At enrollment
- Concomitant anticoagulation
- Planned surgery

At randomization
- Death
- MI or repeat PCI at >6 weeks
- CABG
- Stroke
- Major bleed

Interventions				
Months	Aspirin Dose	Thienopyridine Dose		Placebo
		Clopidogrel	Prasugrel	
0 to 6	75 mg to 325 mg	Loading: 300 to 600 mg Maintenance: 75 mg daily	Loading: 60 mg Maintenance: 10 mg daily	NA
6 to 12	75 mg to 162 mg	75 mg daily	10 mg daily	NA
12 months: Randomization to T or P				
12 to 30	75 mg to 162 mg	75 mg daily	10 mg daily	✓

12 or 30 Months of DAPT?

- Follow-up
  - 33 months post-procedure
  - 6, 12, 15, 24, 30, and 33 months post-PCI
  - Months 30 to 33 were "off-treatment"
  - Events adjudicated by independent committee

Primary Endpoints

Efficacy

- MACCE
  - Death
  - MI
  - Stroke
- Stent thrombosis

Safety

- Severe/moderate bleeding (GUSTO)
- BARC bleeding (secondary)

Bleeding Classification

GUSTO

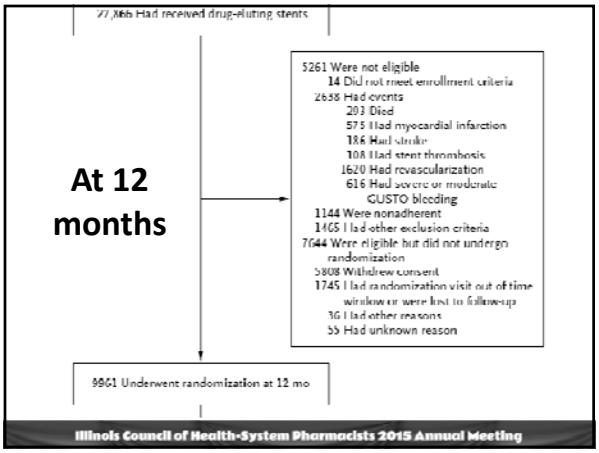
- Severe or life-threatening:
  - ICH or hemodynamic compromise
- Moderate:
  - Transfusion needed but no hemodynamic compromise
- Mild:
  - Bleeding that does not meet above criteria

BARC

- Type 0:
  - No bleeding
- Type 1:
  - Bleeding that is not actionable
- Type 2:
  - Overt bleeding requiring nonsurgical intervention
- Type 3:
  - Overt bleeding plus various Hgb drops defined by subtypes
- Type 4:
  - Related to CABG
- Type 5:
  - Fatal bleeding

12 or 30 Months of DAPT?

- Statistical considerations
  - Hochberg approach
    - Error rate controlled at 0.05
  - Efficacy (ITT)
    - 9,800 DES patients at 12 months = 85% power for superiority
  - Safety (PP)
    - 9960 DES patients if NI margin set at 0.8% = 80% power for noninferiority



Baseline Characteristics

- N=5020 continued thienopyridine
- N=4941 placebo
- Mean age 61 years
- 25% female
- Nonwhites: 8.8%
- Comorbidities
  - DM: 33%
  - HTN: 75%
  - Smokers: 25%
  - Previous stroke: 3%
  - CHF: 5%
  - PAD: 6%
  - Prior PCI: 30%
  - Prior CABG: 11%
  - Prior MI: 21%

12 or 30 Months of DAPT?

- Indication for PCI
  - STEMI: 10%
  - NSTEMI: 15%
  - Angina
    - Unstable: 17%
    - Stable: 38%
  - Other: 20%
- Stent type
  - Everolimus: 47%
  - Paclitaxel: 27%
  - Zotarolimus: 13%
  - Sirolimus: 11%
- Thienopyridine
  - Clopidogrel 65%
  - Prasugrel 35%

Efficacy Outcomes – 12 to 30 months

	T No. of patients (%)	P No. of patients (%)	Hazard ratio T vs. P (95% CI)	P-value	NNT
Stent thrombosis	19 (0.4)	65 (1.4)	0.29 (0.17 to 0.48)	<0.001	100
MACCE	211 (4.3)	285 (5.9)	0.71 (0.59 to 0.85)	<0.001	63
Death (overall)	98 (2.0)	74 (1.5)	1.36 (1.00 to 1.85)	0.05	NA
Death (cardiac)	45 (0.9)	47 (1.0)	1.00 (0.66 to 1.52)	0.98	NA
Death (vascular)	5 (0.1)	5 (0.1)	0.98 (0.28 to 3.39)	0.98	NA
Death (noncardiovascular)	48 (1.0)	22 (0.5)	2.23 (1.32 to 3.78)	0.002	NNH: 200
MI	99 (2.1)	198 (4.1)	0.47 (0.37 to 0.61)	<0.001	50
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51 to 1.25)	0.32	NA

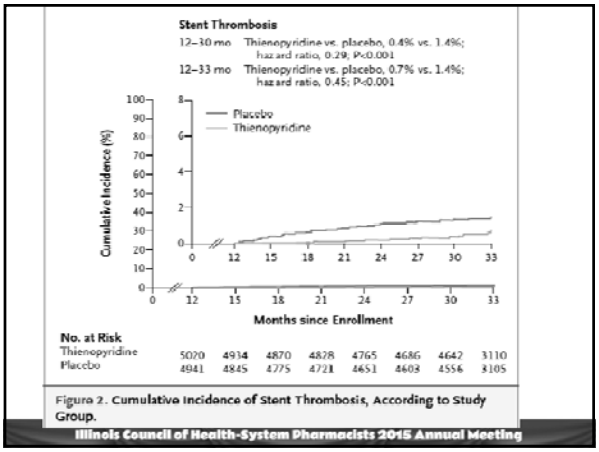


Figure 2. Cumulative Incidence of Stent Thrombosis, According to Study Group.

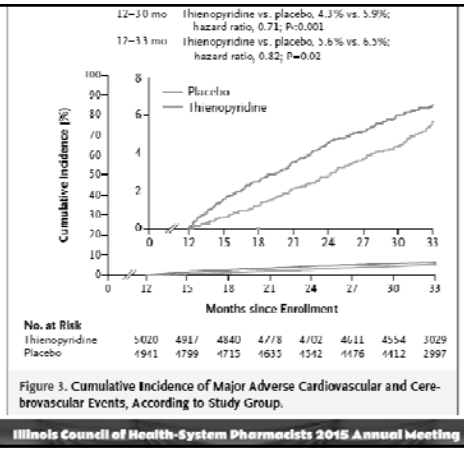


Figure 3. Cumulative Incidence of Major Adverse Cardiovascular and Cerebrovascular Events, According to Study Group.

Safety (Bleeding) Outcomes – 12 to 30 months

	T No. of patients (%)	P No. of patients (%)	Hazard ratio T vs. P (95% CI)	P-value	NNH
GUSTO (severe or moderate)	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001	111
GUSTO (severe)	38 (0.8)	26 (0.6)	0.2 (-0.1 to 0.6)	0.15	NA
GUSTO (moderate)	81 (1.7)			0.004	142
BARC type 2, 3, or 5	263 (5.6)			<0.001	37
BARC Type 2	145 (3.1)			<0.001	62
BARC Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001	90
BARC Type 5	7 (0.1)	4 (0.1)	0.1 (-0.1 to 0.2)	0.38	NA

Noninferiority for bleeding not found (difference not <0.8)

Limitations

Strengths

- Strong design
  - 1st RCT to assess longer duration
- Used appropriate populations for data analysis
  - ITT – superiority
  - PP – noninferiority
- Major undertaking/coordination

Limitations

- Only those who did not have an event in 1st 12 months were randomized
- BMS data analyzed separately
- No data for ticagrelor
- Selection bias
- Pts not randomized to thienopyridine or stent type
- No net clinical benefit analysis done
- Limited external validity for race and gender

12 or 30 months of DAPT?

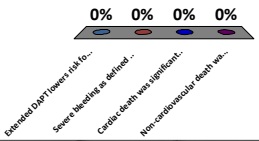
- Conclusion
  - Extension of DAPT beyond 1 year of DES placement
    - Provides additional benefit for reduction of ischemic events
      - Stent thrombosis
      - Myocardial infarction
    - Results in an increase in bleeding events
    - Increase in non-cardiovascular mortality?

12 or 30 months of DAPT?

- From publication to practice:
  - Consider extending DAPT after DES for 30 months total for those who
    - Have lower bleeding risks
    - Are able to adhere to the regimen
    - Are white males

Which of the following was NOT a finding of the DAPT trial?

A. Extended DAPT lowers risk for stent thrombosis
B. Severe bleeding as defined by both GUSTO and BARC criteria was significantly greater with extended DAPT treatment
C. Cardiac death was significantly greater with extended DAPT treatment
D. Non-cardiovascular death was significantly greater with extended DAPT treatment



HEAT-PPCI

UNFRACTIONATED HEPARIN VERSUS BIVALIRUDIN IN PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Lancet. 2014;384(9957):1849-1858.

Background

- Antithrombin agents during PCI
  - Bivalirudin (class I; Level B)
    - Regardless if prior treatment with UFH
    - Possible reduced bleeding compared to UFH?
      - But not with concomitant GP IIb/IIIa inhibitor
    - Increase in ischemic events?
  - UFH (class I; Level C)

Levine, et al. *Circulation*. 2011;124(23):2574-2609

Background

HORIZONS-AMI 2008

- STEMI pts and PPCI
- Bivalirudin had lower "net adverse clinical events" than heparin + GP IIb/IIIa inhibitors
- RR, 0.76; 95% CI, 0.63 to 0.92; P=0.005
  - Lower bleeding with B
  - Higher stent thrombosis within 24 hours with B
  - Lower cardiac and overall death with B

N Engl J Med. 2013;369(23):2207-17

EUROMAX 2013

- STEMI pts and PPCI
- Bivalirudin reduced composite of death or major bleeding compared to UFH/LMWH
- RR, 0.60; 95% CI, 0.43 to 0.82; p=0.001
  - Lower bleeding with B
  - Higher stent thrombosis with B
  - No difference in death or MI

N Engl J Med 2008;358(21):2218–30.

Bivalirudin vs. Heparin

- Study objective
  - To assess the relative safety and efficacy of heparin and bivalirudin during PPCI
- Methods
  - Open-label, single-center, randomized controlled trial
    - Stratified by age and cardiogenic shock
  - Duration: 28 days

Bivalirudin vs. Heparin

Inclusion

- Adults scheduled for PPCI

Exclusion

- Intolerance or C/I to any study drug
- Active bleeding
- Artificial ventilation
- Impaired consciousness

Bivalirudin vs. Heparin

- Interventions
  - Heparin (n=907)
    - 70 U/kg body weight before PCI
    - Add'l doses if ACT <200 seconds
  - Bivalirudin (n=905)
    - 0.75 mg/kg bolus + infusion of 1.75 mg/kg/hour
    - Re-bolus of 0.3 mg/kg if ACT <225 seconds
  - GP IIb/IIIa inhibitor (abciximab) allowed if
    - Massive thrombus
    - Slow or no re-flow
    - Thrombotic complication

Primary Outcomes

Efficacy

- Proportion of patients with ≥1 MACE at 28 days
  - All-cause mortality
  - CVA
  - Reinfarction
  - Add'l revascularization

Safety

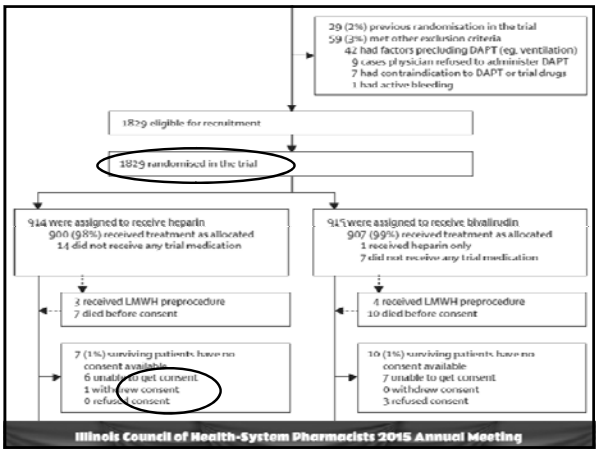
- Proportion of patients who had major bleeding by 28 days per BARC definition (types 3-5)

Bivalirudin vs. Heparin

- Secondary outcomes
  - Stent thrombosis rates
  - Cardiac enzymes
  - Minor bleeding (BARC type 2)
- Subgroup analyses
  - Arterial vascular access route
  - Left ventricular function
  - Age
  - Diabetes
  - Type of P2Y12 inhibitor
  - Whether or not PCI was attempted

Bivalirudin vs. Heparin

- MACE rate estimated to be 7.5% in both groups
- Chi-squared test for primary outcomes
- ITT
- α=0.05



Baseline Characteristics

- 77% STEMI
- Mean age 63 years
- 28% female
- 96% white
- 37% - 45%:
  - DM
  - HTN
  - HL
  - FH of CVD
  - Smoked
- Noteworthy differences
  - Previous MI
    - Bivalirudin: 14%
    - Heparin: 10%
  - Previous PCI
    - Bivalirudin: 8%
    - Heparin: 6%

Baseline Characteristics

- P2Y12 inhibitor
  - Ticagrelor (62%)
  - Prasugrel (27%)
  - Clopidogrel (11%)
- 82% managed with PCI
  - 90% of these had stent
    - 80% had DES
- GP IIb/IIIa inhibitor use
  - Bivalirudin: 13%
  - Heparin: 15%
- Aspirin use in all
- 80% had radial access site
- 45% had normal EF after event
- Approximately 80% - 90% had meds at d/c:
  - ACE or ARB
  - Aspirin
  - Beta blocker
  - P2Y12 inhibitor
  - Statin

Efficacy Outcomes

	Bivalirudin No. of patients (%)	Heparin No. of patients (%)	Relative risk (95% CI)	P-value	NNT
Primary efficacy outcome	79 (8.7)	52 (5.7)	1.52 (1.09 to 2.13)	0.01	34
Death	46 (5.1)	39 (4.3)	1.18 (0.78 to 1.79)	0.43	NA
CVA	15 (1.6)	11 (1.2)	1.37 (0.63 to 2.96)	0.43	NA
MI or re-infarct	24 (2.7)	8 (0.9)	3.01 (1.36 to 6.66)	0.004	56
Revascularization	24 (2.7)	6 (0.7)	4.01 (1.65 to 9.76)	0.001	50

Safety (Bleeding) Outcomes

	Bivalirudin No. of patients (%)	Heparin No. of patients (%)	Relative risk (95% CI)	P-value	NNH
Major bleed (primary safety)	32 (3.5)	28 (3.1)	1.15 (0.70 to 1.89)	0.59	NA
Minor bleed	83 (9.2)	98 (10.8)	0.85 (0.64 to 1.12)	0.25	NA
Any bleed	113 (12.5)	122 (13.5)	0.93 (0.73 to 1.18)	0.54	NA

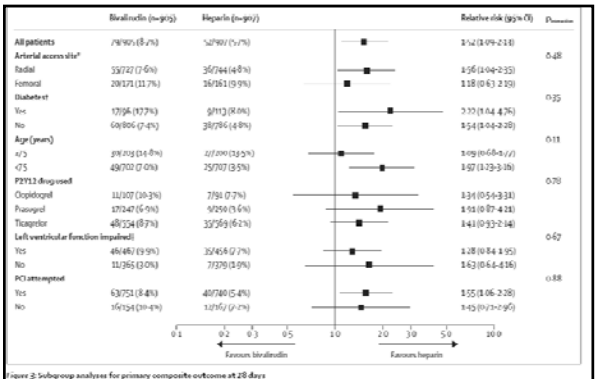


Figure 3: Subgroup analyses for primary composite outcome at 28 days
*Procedures completed exclusively via radial access (radial group) versus all other cases (femoral group). †Patients receiving oral hypoglycaemic or insulin therapy. ‡Left ventricular ejection fraction <55% in surviving patients after index event.

Limitations

Strengths

- Delayed consent
  - Allowed for sicker patients
- First RCT to compare bivalirudin and heparin with GP IIb/IIIA use in both groups
- Free from manufacturer bias

Limitations

- Delayed consent?
  - Ethical?
- Single-center study
- Homogeneous population in terms of race
- Lower heparin doses than in clinical practice?
- Higher rates of previous PCI and MI in bivalirudin

Bivalirudin vs. Heparin

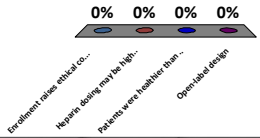
- Conclusions
  - Heparin provides a benefit over bivalirudin during PPCI for
    - Acute stent thrombosis
    - Reinfarction
  - Heparin does not increase the risk for bleeding as compared to bivalirudin

Bivalirudin vs. Heparin

- From publication to practice
  - Heparin may be preferred to bivalirudin during PPCI without increased safety concerns
    - When used in combination with newer P2Y12 inhibitors
  - Can't be as confident about this in females, non-whites
  - Both bivalirudin and heparin may be used per guidelines – evidence may increase strength of recommendation for heparin

Which is NOT a criticism of the HEAT-PPCI trial?

A. Enrollment raises ethical concerns
B. Heparin dosing may be higher than usual clinical practice
C. Patients were healthier than in other similar trials
D. Open-label design



Taking care of our elderly:

EXERCISE AND VITAMIN D IN FALL PREVENTION AMONG OLDER WOMEN

JAMA Intern Med. 2015;175(5):703-711.

Background

- Falls in the elderly
  - Leading cause of injury and injury-related death
  - 20% of falls require medical attention
  - <1/10 results in fracture

N Engl J Med. 2003;348(1):42-49.

Background

- Exercise
  - Individualized training and group exercise effective in preventing falls
  - Strength and balance training my reduce noninjurious and injurious falls by 15% to 50%

BMC Geriatrics. 2012;12;12.

Background

- Vitamin D deficiency
  - <25 nmol/L
  - Decreased muscle function, performance
  - Increased disability
  - Associated with frail phenotypes
  - Inversely associated with falls
- Evidence conflicting for benefits of supplementation

Ann Intern Med. 2013;158:691-696.
Biomed Res Int. 2015;2015:953241.

Background

- USPSTF Recommendations for home-dwelling postmenopausal women and primary prevention of fractures
  - **Inconclusive:** whether or not vitamin D >400 IU/day + calcium >1000 mg/day
  - **Recommends against** vitamin D ≤400 IU/day + calcium ≤1000 mg/day

Ann Intern Med. 2013;158:691-696.

Exercise and Vitamin D

- Study objective
  - Assess exercise training and vitamin D supplementation in reducing falls and improving bone density in older women at risk of falls
- Methods
  - Double-blind, placebo-controlled (vitamin D), and open exercise intervention trial with 4 arms; 2 year duration

Exercise and Vitamin D

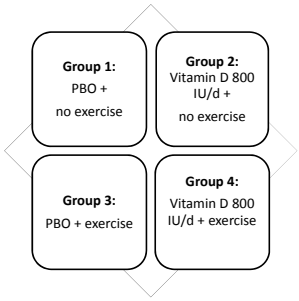
Inclusion

- Women 70 to 80 yrs in Finland
- Living at home independently
- History of ≥1 fall in past year
- No regular vitamin D supplements intake

Exclusion

- Exercise >2 hrs/wk
- Fx in previous 12 mo.
- Inability to exercise
- Marked decline in ADL
- Cognitive impairment
- Primary hyperthyroidism
- Degenerative dz

Interventions



Exercise Description

- Supervised, progressive group training
- 2x/wk for 12 months
- 1x/wk for remaining 12 months
- Balance challenging
- Weight bearing
- Strengthening
- Agility
- Weight machines
- Pulleys
- Free weights
- Home training

Endpoints

- Primary
  - Monthly reported falls
- Secondary
  - Injurious falls
    - Bruises, abrasions, contusions, sprains, fractures, head injuries
  - Number of fallers and injured fallers
  - Bone density
  - Physical functioning

Statistics

- Power calculation
- 260 pts provided 80% power to detect 30% between-group difference at 2 years (α=0.05)
  - Wanted to enroll more in order to eliminate type I error for interaction between vitamin D and exercise
- ITT

Exercise and Vitamin D

Baseline Characteristics

- Well-balanced groups
- Serum 25-hydroxyvitamin D level approx. 26-27 ng/mL
- Mean age 74 years
- Average # of meds: 2.5
- Sufficient calcium intake at baseline and 24 months
- Low alcohol consumption
- Relatively healthy

Results

- Exercise well-tolerated
- 98% pill compliance
- Vitamin D levels increased in Vitamin D groups compared to placebo
  - 25.1 ng/mL → 37.0 ng/mL
- Total of
  - 928 falls
  - 281 fallers
  - 190 multiple fallers
  - 117 multiple injured fallers

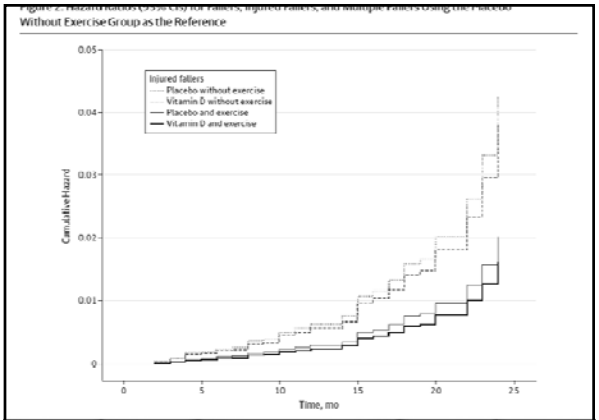
Rate of falls per 100 person-years

	Placebo without Exercise	Vitamin D without Exercise	Placebo and Exercise	Vitamin D and Exercise
All falls	118.2	132.1	120.7	113.1
Injurious falls	13.2	12.9	6.5	5.0
All falls IRR (95% CI)	Reference	1.08 (0.78 to 1.52)	1.07 (0.77 to 1.45)	0.99 (0.72 to 1.39)
Injurious falls IRR (95% CI)	Reference	0.84 (0.45 to 1.57)	0.46 (0.22 to 0.95)	0.38 (0.17 to 0.81)

Hazard ratios for falls

	Vitamin D Without Exercise	Placebo and Exercise	Vitamin D and Exercise
Fallers	0.77 (0.54-1.11)	0.93 (0.66-1.31)	0.91 (0.64-1.28)
Injured fallers	0.89 (0.47-1.69)	0.47 (0.23-0.99)[a]	0.38 (0.17-0.83)[a]
Multiple fallers	1.07 (0.71-1.62)	1.14 (0.76-1.71)	1.14 (0.77-1.71)

Exercise ± vitamin D reduces only injurious falls



Results - secondary

	Change at 24 mo	*P* Value[a]
Femoral neck BMD, g/cm^2		
Placebo without exercise	−1.22 (−4.75 to 2.45)	NA
Vitamin D without exercise	−0.87 (−4.47 to 2.86)	.02
Placebo and exercise	−0.98 (−4.55 to 2.73)	.01
Vitamin D and exercise	−1.24 (−4.72 to 2.38)	.04
Distal tibia trabecular density, mg/cm^3		
Placebo without exercise	−0.49 (−3.77 to 2.80)	NA
Vitamin D without exercise	0.03 (−3.36 to 3.42)	.12
Placebo and exercise	−0.16 (−3.43 to 3.11)	.41
Vitamin D and exercise	0.19 (−3.04 to 3.42)	.02

Results - secondary

Outcome	Change at 24 mo	*P* Value[a]
Backward walking, proportion of those able to do 6.1 min, %		
Placebo without exercise	7.76 (−2.87 to 18.47)	NA
Vitamin D without exercise	9.48 (−0.66 to 20.08)	.68
Placebo and exercise	26.27 (15.71 to 35.13)	.001
Vitamin D and exercise	25.47 (15.30 to 33.39)	.03
Muscle strength, N/kg		
Placebo without exercise	1.8 (−4.8 to 8.4)	NA
Vitamin D without exercise	1.5 (−5.0 to 8.1)	.10
Placebo and exercise	14.0 (7.8 to 20.2)	<.001
Vitamin D and exercise	15.6 (9.1 to 22.2)	<.001

Exercise and Vitamin D

Strengths

- Strong design, long duration
- High adherence
- Low withdrawal
- Recruited patients at risk for falls

Limitations

- No reporting of fractures
- Baseline levels of vitamin D high
- Relatively good health/physical condition
- Limited external validity

Conclusion

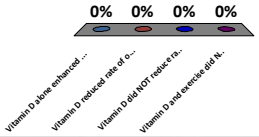
- Exercise ± vitamin D reduces the risk for injurious falls among elderly women
- Interventions alone and in combo do not decrease overall falls

Exercise and Vitamin D

- From publication to practice
  - Exercise ± vitamin D did not reduce risk for all fall types
  - Important to consider fall prevention strategies with osteoporosis prevention strategies, but this trial does not support
  - Justifies USPSTF recommendations
  - Don't prescribe vitamin D + exercise for purposes of preventing falls in elderly women

Based on this trial, which of the following statements is TRUE?

A. Vitamin D alone enhanced muscle strength and balance
B. Vitamin D reduced rate of overall falls
C. Vitamin D did NOT reduce rate of injurious falls
D. Vitamin D and exercise did NOT reduce the rate of multiple falls



Which of the following is a limitation common to ALL the trials discussed?

A. Selection bias
B. Single-center study
C. Manufacturer bias
D. Limited external validity

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