Newsmakers of 2011

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Disclosure

- I have no conflicts of interest to disclose.

Learning Objectives

- To identify the key therapeutic trials from internal medicine from this past year.
- To review the background information that is relevant to understand these trials.
- To critically evaluate the literature and discuss its impact on patient care.
- To highlight and discuss therapeutic controversies that may be relevant to the specific practice areas.

Outline

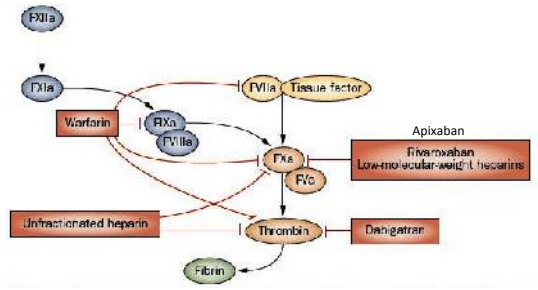
- New Alternatives to Warfarin
- Azithromycin in COPD
- Salmeterol vs Tiotropium
- Steroids in Community-Acquired Pneumonia
- Nitrates for Osteoporosis

Background

- ACCP Guidelines: Antithrombotic & Thrombolytic Therapy 8th Ed[1]
  - Recommendation is for Vitamin K antagonist targeted to an INR between 2 – 3 if the patient:
    - Has atrial fibrillation & has had a prior ischemic stroke, TIA, or systemic embolism or has a $CHADS_2 \geq 2$
- Bleeding[2]
  - Estimates vary – 0.6% for fatal bleeding, 3% for major bleeding, 9.6% for major and minor bleeding
- Barriers to Use[3]
  - Usage pattern of warfarin in pts w/ a fib
  - 86% stratified @ high stroke risk, 55% received tx
  - Perceived bleeding risk negative predictor of warfarin use

1. Chest 2008; 133: 546S-592S; 2. Landefeld Am J Med 1993; 95(3): 315-328.; 3. Arch Intern Med 2003; 163: 1580-1586.

Background



www.medscape.com accessed Nov 4th, 2011

Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY)

- Dabigatran 110mg BID OR Dabigatran 150mg BID (blinded) vs Warfarin (adjusted to INR 2-3)
- Population
  - N=18,113 pts
  - Mean age 71 yrs; 63.6% ♂; mean $CHADS_2$ = 2.1
  - Warfarin within target range 64%
- Results
  - Both dabigatran doses were noninferior to warfarin (p<0.001)
  - Dabigatran 150mg BID was superior
    - RR 0.66; 95% CI 0.53 to 0.82; p<0.001
  - Dabigatran 110mg BID had less bleeding
    - RR 0.80; 95% CI 0.69 to 0.93; p=0.003

NEJM 2009; 361: 1139—51.


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

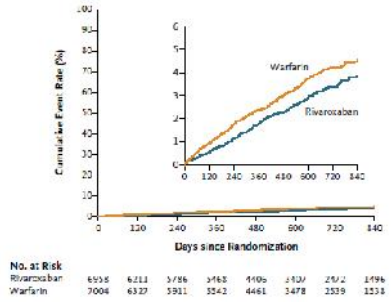
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

R, MC, DB

P Patient	N=14,264 Median age 73 yrs; 39.7% ♀; mean $CHADS_2$ score 3.5
I Intervention	Rivaroxaban 20mg daily (↓ dose to 15mg/d if CrCl 30-49mL/min)
C Comaparator	Adjusted dose Warfarin (target INR 2.0-3.0)
O Outcome	Efficacy – composite of stroke (ischemic or hemorrhagic) & systemic embolism Safety – composite of major and nonmajor bleeding

NEJM 2011; 365: 883-91.

Primary Outcome – Per Protocol Analysis



NEJM 2011; 365: 883-91.

Results

Study Population	Hazard Ratio (95% CI)	P Value	
		Noninferiority	Superiority
Per-protocol, as-treated population	0.79 (0.66-0.96)	<0.001	
Safety, as-treated population	0.79 (0.65-0.95)		0.02
Intention-to-treat population	0.88 (0.75-1.03)	<0.001	0.12

NEJM 2011; 365: 883-91.

Results – Rate of Bleeding Events

Variable	Hazard Ratio (95% CI)	P value
Principal safety end point: major & nonmajor clinically relevant bleeding	1.03 (0.96 – 1.11)	0.44
Major Bleeding		
Any	1.04 (0.90-1.20)	0.58
Decrease in hemoglobin ≥ 2g/dl	1.22 (1.03-1.44)	0.02
Transfusion	1.25 (1.01-1.55)	0.04
Critical bleeding	0.69 (0.53-0.91)	0.007
Fatal bleeding	0.50 (0.31-0.79)	0.003
Intracranial hemorrhage	0.67 (0.47-0.93)	0.02
Nonmajor clinically relevant bleeding	1.04 (0.96-1.13)	0.35

NEJM 2011; 365: 883-91.

Author's Conclusions

" in patients who were at moderate-to-high risk for stroke, rivaroxaban was noninferior to warfarin in the prevention of subsequent stroke or systemic embolism. There were no significant differences in rates of major and clinically relevant nonmajor bleeding between the two study groups"

NEJM 2011; 365: 883-91.

Limitations

- Higher risk population
- ↓ time in target range of IN -3 for warfarin
- ?once daily dosing – $t_{1/2}$ = 5-9hrs
- ↑ risk of stroke and embolism in days 2-7 after therapy discontinuation
  - Rivaroxaban 31 participants vs warfarin 12 participants


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

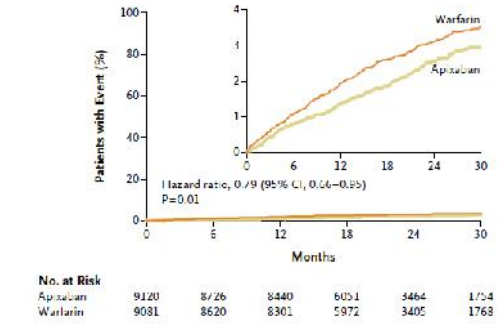
Apixaban versus Warfarin in Patients with Atrial Fibrillation

R, DB, 2 years duration

P Patient	N=18,201 pts Median age = 70yrs; 35.3% ♀; mean $CHADS_2$ score 2.1
I Intervention	Apixaban 5mg BID OR Apixaban 2.5mg BID if the pt had ≥ 2 of the following: age >80yrs; body weight ≤ 60kg or SCr >133 µmol/L
C Comaparator	Warfarin adjusted to an INR between 2-3
O Outcome	Composite - Stroke (ischemic, hemorrhagic, or of uncertain type) or systemic embolism Safety – major bleeding

NEJM 2011; 365: 981-92.

Results – Primary Outcome



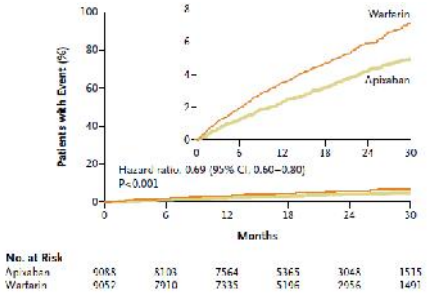
NEJM 2011; 365: 981-92.

Results

Outcome	Hazard Ratio	P value
Primary Outcome	0.79 (0.66-0.95)	0.01
Stroke	0.79 (0.65-0.95)	0.01
Ischemic or uncertain type of stroke	0.92 (0.74-1.13)	0.42
Hemorrhagic stroke	0.51 (0.35-0.75)	<0.001
Systemic embolism	0.87 (0.44-1.75)	0.70

NEJM 2011; 365: 981-92.

Results – Major Bleeding



NEJM 2011; 365: 981-92.

Results

Outcome	Hazard Ratio (95% CI)	P value
Primary Safety Outcome: ISTH major bleeding	0.69 (0.69-0.80)	<0.001
Intracranial	0.42 (0.30-0.58)	<0.001
Other location	0.79 (0.68-0.93)	0.004
Gastrointestinal	0.89 (0.70-1.15)	0.37

NEJM 2011; 365: 981-92.

Authors' Conclusions

"In conclusion, in patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality."

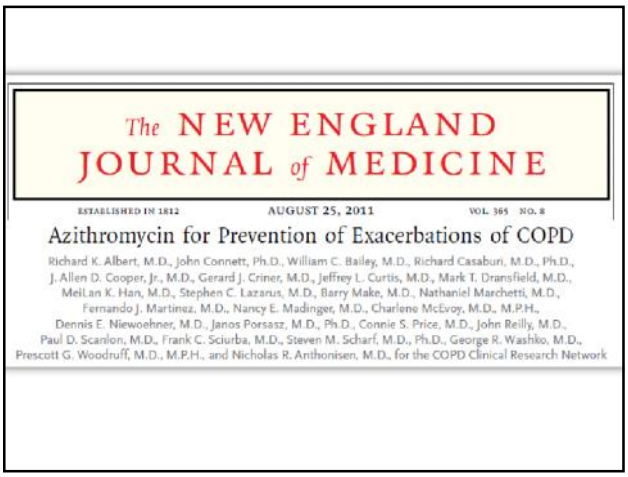
NEJM 2011; 365: 981-92.

Trial Group	Primary Endpoint	Rates of primary outcome	Overall Results	Status/Cost
ARISTOTLE Apixaban Compared 5mg apixaban BID w/ warfarin (target INR 2-3)	Ischemic or hemorrhagic stroke or systemic embolism	1.27%/yr apixaban group vs 1.60%/yr warfarin	Apixaban significantly reduced the risk of stroke or systemic embolism; major bleeding; and death	Not yet approved in Canada
RE-LY Dabigatran Compared dabigatran 110mg OR 150mg BID with warfarin	Stroke or systemic embolism	1.53%/yr dabigatran group vs 1.69%/yr warfarin group	Dabigatran 110mg had similar rates of stroke & systemic embolism with warfarin but lower rates of major hemorrhage. Dabigatran 150mg had lower rates of stroke & systemic embolism but similar rates of hemorrhage	Indicated for stroke/systemic embolism prevention in a fib & for VTE prevention in pts who have undergone THR or TKR $1.60/110mg tab $1.60/150mg tab
ROCKET-AF Rivaroxaban Compared rivaroxaban 20mg daily with adjusted dose warfarin	Per-protocol analysis: rivaroxaban is non-inferior to warfarin for stroke or systemic embolism	Primary analysis: 1.7%/yr rivaroxaban vs warfarin 2.2%/yr Intention-to-treat analysis: 2.1% /yr rivaroxaban vs 2.4%/yr for warfarin	Rivaroxaban was noninferior to warfarin for prevention of stroke or systemic embolism. No significant differences in the risks of major bleeding. Intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.	VTE prevention in pts who have undergone THR or TKR $6.20/10mg tab

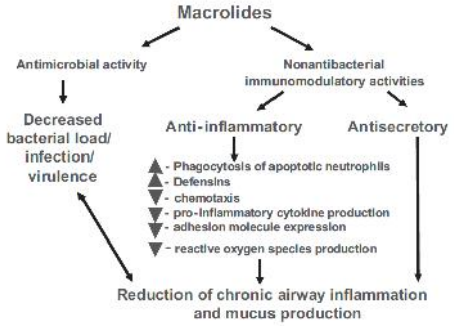
Neurology Today. 11(18):1,13-15, September 15, 2011. DOI: 10.1097/01.NT.0000406547.42622.8f

Limitations of Newer Agents

- Increased expense vs warfarin
- No antidote for newer drugs
- No INR testing required = no ability to test for compliance?



Proposed MOA of Macrolides



International Journal of COPD 2008; 3(3): 331-350.

	Suzuki et al. Chest 2001; 120; 730-733.	Banerjee et al. Respiratory Medicine 2005; 99: 208-215.	Seemungal et al. Am J Respir Crit Care Med 2008; 178: 1139-1147.	He et al. Respiration 2010; 80: 445-452	Blasi et al. Pulmonary Pharmacology & Therapeutics 2010; 200-207.
Design	R, C, not blinded	R, DB, PC	R, DB, PC	R, DB, PC	R, MC, open-label, uncontrolled
Duration	12 months	3 months	12 months	6 months	6 months
Population	N=109 Average age ~70 yrs ~ 45% ♂ FEV1 ~ 1.40 L/s Concomitant theophylline SR and inhaled anticholinergics	N=67 Average age ~ 67 yrs 69% ♂ FEV1 %predicted ~43 Concomitant inhaled corticosteroid use, 18% LABA, 63% inhaled anticholinergics	N=109 Average age 67.2 (8.6) yrs 63% ♂ FEV1 % predicted 50.0(18.0) Concomitant medication use: 77% inhaled steroids, ~63% LABA, ~34% inhaled anticholinergic, ~10% theophylline	N=36 Average age ~ 69 yrs 86% ♂ FEV1 % predicted ~ 43 Concomitant medication use: inhaled steroids ~40%, theophylline ~57%, anticholinergic ~52%, β-adrenergic ~75%	N=22 Average age ~ 72 yrs 86% ♂ Pts had a hx of severe COPD & **tracheostomy**
Intervention	Erythromycin 200 to 400mg/d vs no ACTIVE treatment (received riboflavin 10mg/d)	Clarithromycin 500mg XL once daily vs placebo	Erythromycin stearate 250mg BID vs placebo	Erythromycin 125mg TID vs placebo	Azithromycin 500mg daily M,T,W + standard care vs standard care
Results	Control vs Erythromycin Group: Common cold: RR 9.26 (95% CI 3.92 to 31.74; p = 0.0001) Exacerbations: RR 4.71 (95% CI 1.53 to 14.5; p=0.007)	No SS difference seen in primary outcome of health status	↓ exacerbation rate: rate ratio 0.648 (95% CI 0..489 to 0.859; p=0.003)	↓ neutrophil counts (p=0.005) ↓exacerbation rate RR =0.554, p=0.042 Delayed time to first exacerbation (p=0.032)	↓ exacerbations @ 3 months High rate of deaths ↓ overall sample size → no further statistical analysis carried out

Azithromycin for Prevention of Exacerbations of COPD

R, PC, MC; 12 month duration

P Patient	N=1142 randomized; 1117 included in primary analysis
I Intervention	Azithromycin 250mg daily
C Comaparator	Placebo
O Outcome	Time to first acute exacerbation of COPD

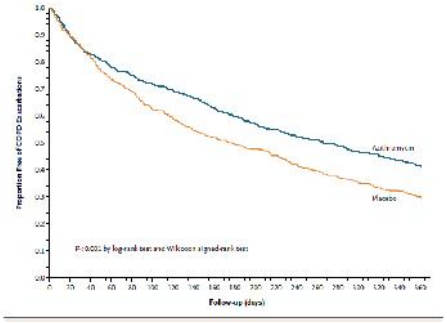
NEJM 2011; 365: 689-98.

Baseline Characteristics

Characteristic	Azithromycin (N=558)	Placebo (N=559)
Age – yr	65 ± 9	66 ± 8
Female sex – no. (%)	229 (41)	227 (41)
Postbronchodilator FEV1 % predicted	39 ± 16	40 ± 16
Gold Stage – no. (%)		
II	144 (26)	148 (26)
III	225 (40)	226 (40)
IV	188 (34)	182 (33)
Medications for COPD – no. (%)		
Inhaled glucocorticoids, LABAs & LAMAs	273 (49)	255 (46)
Inhaled glucocorticoids & LABAs	104 (19)	125 (22)
Inhaled glucocorticoids & LAMAs	23 (4)	28 (5)
LABAs & LAMAs	30 (5)	23 (4)
Inhaled glucocorticoids only OR LAMAs only OR LABAs only	70 (13)	85 (15)
None	58 (10)	43 (8)

NEJM 2011; 365: 689-98.

Proportion of Participants Free from Acute Exacerbations for 1 year



NEJM 2011; 365: 689-98.

Results

- Median time to first acute exacerbation
  - 266 days vs 174 days (p<0.001)
- Hazard ratio of having an acute exacerbation of COPD per patient-year
  - 0.73 (95% CI 0.63 to 0.84; p<0.001)
    - Differences remained significant after adjustment for differences in sex, FEV_1, age, smoking status & study centre
- NNT to prevent one acute exacerbation of COPD was 2.86
- No difference in rate of adherence
  - 67.3% vs 66.9% (p=0.84)

NEJM 2011; 365: 689-98.

Results

- Audiogram-confirmed hearing decrement occurred in 142 of the azithromycin group vs 110 of the placebo group (p=0.04)
- Azithromycin group had more pronounced hearing deficits at 3 months
- 66 (12%) azithromycin vs 172 (31%) placebo group became colonized (nasopharyngeal) (p<0.001)
- No statistically significant difference between the prevalence of macrolide resistance between the two groups (52% vs 57%; 0=0.64)

NEJM 2011; 365: 689-98.

Limitations

- ↑ incidence of hearing deficits with treatment
- Variation in exacerbation rates due to time of year
- Less frequent dosing regimen possible?
- Unclear where in hierarchy of therapies it falls

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ESTABLISHED IN 1812 MARCH 24, 2011 VOL. 364 NO. 12

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

Claus Vogelmeier, M.D., Bettina Hederer, M.D., Thomas Glaab, M.D., Hendrik Schmidt, Ph.D., Maureen P.M.H. Rutten-van Mölken, Ph.D., Kai M. Beeh, M.D., Klaus F. Rabe, M.D., and Leonardo M. Fabbri, M.D., for the POET-COPD Investigators*

LABA vs Tiotropium

	LABA	Tiotropium
MOA	Relax airway smooth muscle by stimulation of β2-adrenergic receptors, which cAMP and produce functional antagonism to bronchoconstriction.	Blockage of acetylcholine's effect on M3 and M1 receptors
Duration of Action	12hrs	24hrs
Dosing	Formoterol 12 µg bid Salmeterol 25-50 µg bid	18 µg inhaled daily
Delivery Device	Formoterol – caps, turbuhaler Salmeterol – MDI, diskus	Caps
Adverse Effects	Tachycardia, palpitations, irritability, insomnia, muscle cramps, tremors	Dryness of the mouth More rare: prostatic symptoms, glaucoma (if local administration),
Cost	Formoterol - $59 Salmeterol - $69	Tiotropium - $82

LABA vs Tiotropium

	Donohue 2002 Chest. 2002; 122(1): 47-55.	Brusasco 2003 Thorax 2003; 58:399-404.	van Noord 2005 Eur Respir J 2005; 26:214-222.	Briggs 2005 Pulm Pharmacol Ther 2005; 18: 397-404.
Design	R, PC, MC, DB	R, PC, MC, DB	R, DB, crossover	R, PC, MC, DB
Duration	6 months	6 months (x 2 studies)	3 x 6 weeks	12 weeks
Population	N=623 Mean Age = 65±8yrs; FEV1 40.2±12.1%	N=1207 Mean Age = 63.8-64.6 yrs FEV1 37.7-39.2%	N=71 Mean Age = 64.9±9.4 yrs FEV1 37.2±8.6%	N=653 Mean Age = 64yrs; FEV1 37.7%
Intervention	Tiotropium 18µg/d vs Salmeterol 50µg/d	Tiotropium 18µg/d vs Salmeterol 50µg/d	Tiotropium 18µg/d vs formoterol 12µg bid, Tiotropium 18µg + formoterol 12µg daily	Tiotropium 18µg/d vs Salmeterol 50µg/d
Results	Tiotropium > Salmeterol for FEV1, FVC, TDI score	Tiotropium > salmeterol for spirometry	Tiotropium > formoterol for spirometry	Tiotropium > salmeterol for FEV1, FVC

LABA vs Tiotropium

	LABA	Tiotropium
prevent disease progression	X	X
↓ frequency & severity of exacerbations	√	√
↓ symptoms	√	√
exercise tolerance/daily activities	?	√
health status	√	√
↓ mortality	X	?

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

R, DB, PC, MC; 1 year duration

P Patient	N=7376
I Intervention	Tiotropium 18µg daily
C Comaparator	Salmeterol 50 µg twice daily
O Outcome	Primary endpoint time to first exacerbation of COPD

NEJM 2011; 364: 1093-103.

Baseline Characteristics

Characteristic	Tiotropium (N=3707)	Salmeterol (N=3669)
Age – yr	62±9	62.8±9
Male sex – (%)	74.4	74.9
Postbronchodilator FEV1 % predicted	49.2±13.3	49.4±13.1
Gold Stage – (%)		
II	47.8	49.6
III	43.1	42.1
IV	8.9	7.9

NEJM 2011; 364: 1093-103.

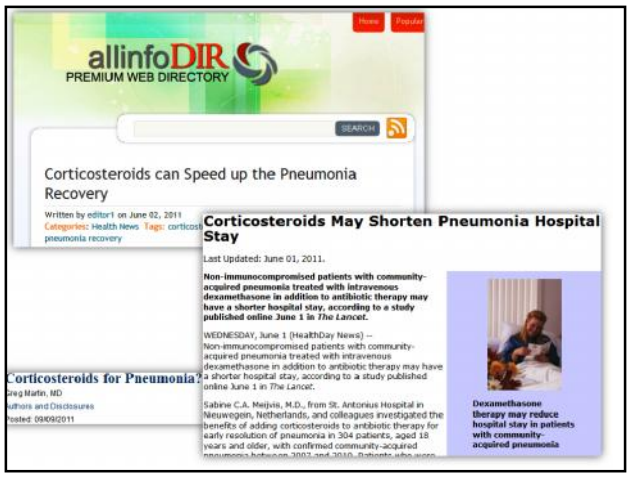
Results

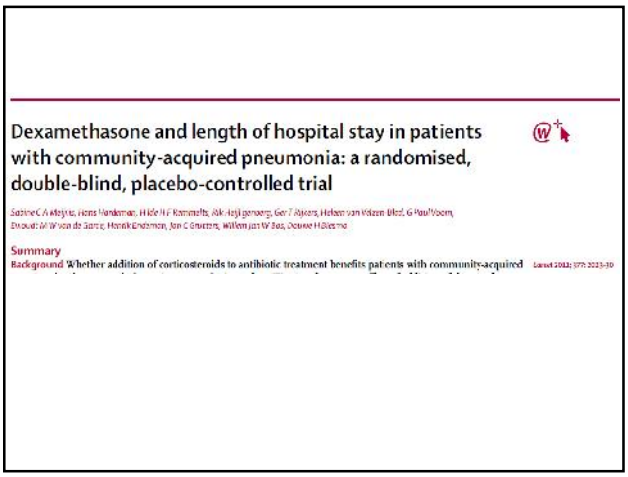
- Time to first exacerbation increased by 42 days with tiotropium vs salmeterol
  - 17% risk reduction with tiotropium
  - HR 0.83 (95% CI 0.77 to 0.90; p<0.001)
- ↓ risk of moderate exacerbations by 14% ;
  ↓ risk of severe exacerbations by 2

NEJM 2011; 364: 1093-103.

Limitations

- Adherence not assessed
- Concomitant medication allowed w/ >50% on inhaled glucocorticoids
- Patient population was more severe




Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial

Summary

Background

- Efficacy of Corticosteroids in the Treatment of Community Acquired Pneumonia Requiring Hospitalization[1]
  - Open-label, randomized, single centre
  - N=31 pts; prednisolone 40mg IV x 3 days
  - Primary Endpoint: length of hospital stay – NSS
- Efficacy of Corticosteroids in Community-acquired Pneumonia[2]
  - Randomized, double-blind, placebo controlled, single centre
  - N=213 pts; prednisolone 40mg IV daily x 7 days vs placebo
  - Primary Endpoint: clinical cure - NSS

1. Lung 2007; 185: 249-255.
2. Am J Respir Crit Care Med 2010; 181: 975-982.

Dexamethasone & length of hospital stay in patients with community-acquired pneumonia: a raondomised, double-blind, placebo-controlled trial.

R, DB, PC, SS

P Patient	N=304
I Intervention	Dexamethasone 5mg IV once daily x 4 days
C Comaparator	Placebo
O Outcome	Length of hospital stay

Lancet 2011; 377: 2023-30.

Baseline Characteristics

Characteristic	Dexamethasone (n=151)	Placebo (n=153)
Male sex – (%)	84 (56%)	87 (57%)
Age (years)	64.5 ± 18.7	62.8 ± 18.2
Comorbidities – diabetes mellitus	22 (15%)	21 (14%)
Pneumonia severity index score	100.2 ± 33.4	95.8 ± 32.5
Pneumonia severity index risk class		
Class 1	18 (12%)	22 (14%)
Class 2	30 (20%)	34 (22%)
Class 3	24 (16%)	33 (22%)
Class 4	54 (36%)	43 (28%)
Class 5	25 (17%)	21 (14%)

Lancet 2011; 377: 2023-30.

Results

	Dexamethasone group (n=151)	Placebo group (n=153)	p value
Length of stay (days)	6·5 (5·0–9·0)	7·5 (5·3–11·5)	0·0480
In-hospital mortality	8 (5%)	8 (5%)	0·98
Time to death (days)	5·5 (2·6–18·9)	8·8 (3·8–12·8)	0·64
30-day mortality	9 (6%)	11 (7%)	0·68
ICU admission	7 (5%)	10 (7%)	0·47
Time to ICU admission (days)	2·5 (1·5–6·5)	1·8 (1·5–2·6)	0·34
Length of stay in ICU (days)	21·5 (14·5–28·5)	15·5 (10·1–28·5)	0·23
Empyema or pleural effusion	7 (5%)	5 (3%)	0·54
Readmission within 30 days from hospital discharge	7 (5%)	7 (5%)	0·98

Data are median (IQR) or n (%), unless otherwise stated. ICU=intensive-care unit.

Table 2: Outcomes for all enrolled patients

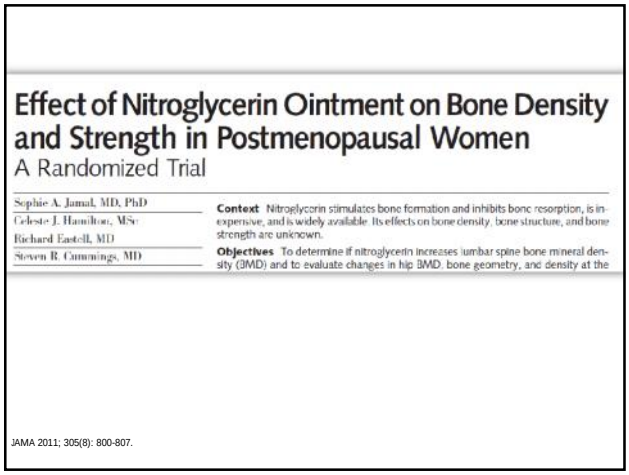
Lancet 2011; 377: 2023-30.

Safety

- Hyperglycemia (non-fasting glucose >11mmol/L) **>** in dexamethasone group
  - 67 (44%) dexamethasone group vs 35 (23%) control group (p<0.0001)
  - 7 (5%) dexamethasone group vs 5 (3%) in placebo group required intervention (NSS)

Limitations

- Single centre; differences in antibiotic use
  - Low level of antibiotic resistance at the site
- Included COPD pts who may have an indication for steroids
- ?longer duration of steroid treatment
- More severe CAP in treatment group
  - ?underestimation of the effect


Effect of Nitroglycerin Ointment on Bone Density and Strength in Postmenopausal Women
A Randomized Trial

Sophie A. Jamal, MD, PhD
Celeste J. Hamilton, MSc
Richard Eastell, MD
Steven R. Cummings, MD

Context Nitroglycerin stimulates bone formation and inhibits bone resorption, is inexpensive, and is widely available. Its effects on bone density, bone structure, and bone strength are unknown.

Objectives To determine if nitroglycerin increases lumbar spine bone mineral density (BMD) and to evaluate changes in hip BMD, bone geometry, and density at the

JAMA 2011; 305(8): 800-807.

First Line Therapies for Postmenopausal Women

Type of Fracture	Antiresorptive Therapy						Bone Formation Therapy
	Bisphosphonates						
	Alendronate	Risedronate	Zoledronic Acid	Denosumab	Raloxifene	Hormone Therapy (Estrogen)**	Teriparatide
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓		✓	
Non vertebral*	✓	✓	✓	✓		✓	✓

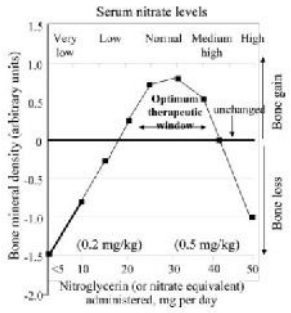
Appendix. CMAJ 2010. DOI 10.1503/cmaj.100771.

Background

- Isosorbide Mononitrate Increases Bone Formation & Decreases Bone Resorption in Postmenopausal Women: A Randomized Trial[1]
  - 12 week, R, DB, PC, sample size = 144
  - Isosorbide mononitrate 5 or 20mg/d vs placebo
  - Primary Outcome:
    - % change in urine N-telopeptide (marker of bone resorption) & serum bone-specific alkaline phosphatase (marker of bone formation)
    - SS difference seen
- Transdermal Nitroglycerin Therapy May Not Prevent Early Postmenopausal Bone Loss [2]
  - 3 yr, DB, SC, PC, sample size = 186 ♀
  - Ntroglycerin 2% ointment 22.5mg/d vs placebo
  - Primary Outcome:
    - Percent change in lumber BMD – no SS difference
  - <70% compliance

1. J Bone Miner Res 2004; 19: 1512-1517.
2. J Clin Endocrinol Metab 2009; 94(9): 3356-3364.

Predicted BMD Response to Nitroglycerin Dose



J Clin Endocrinol Metab 2009; 94(9): 3356-3364.

Effect of Nitroglycerin Ointment on Bone Density & Strength in Postmenopausal Women

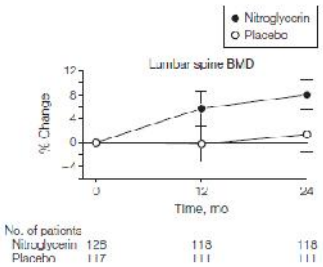
SC, DB, PC, R, 2 years

P Patient	243 ♀; mean age = 61.6 ± 6.9 yrs; T score femoral neck -0.9(0.6) vs -0.8(0.7)
I Intervention	15mg nitroglycerin 2% ointment
C Comaparator	placebo
O Outcome	Lumbar spine density

All participants were supplemented to receive Ca 1200-1500mg/d & Vitamin D 800 IU/d

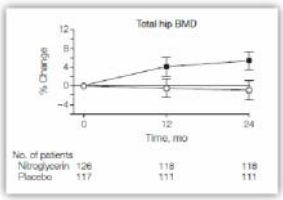
JAMA 2011; 305(8): 800-807.

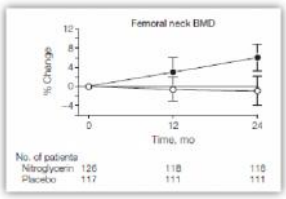
Primary Outcome: Percentage Change in Lumbar Spine



JAMA 2011; 305(8): 800-807.

Results





Adverse Effects:

- Headaches
  - •104/157 ♀ in run-in phase d/c'd secondary to headaches and//or nausea
  - •1st year: 5.6% in the nitroglycerin group vs 1.7% in the placebo group d/c'd secondary to headaches
  - •In 1st month of treatment 35% nitroglycerin group vs 5.4% placebo group reported headaches

JAMA 2011; 305(8): 800-807.

Limitations

- High rate of adverse effects
- Excluded women with osteoporosis
- Too small to assess fracture risk

- Chocolate consumption & cardiometabolic disorders: systematic review & meta-analysis.
  - "levels of chocolate consumption seemed to be associated with a substantial reduction in the risk of cardiometabolic disorders."
- Coffee, Caffeine, & Risk of Depression Among Women.
  - "depression risk decreases with increasing caffeinated coffee consumption."

1. BMJ 2011; 343: dd4488 doi: 10.1136/bmj.d4488
2. Arch Intern Med 2011; 171(17): 1571-1578.