24th ANNUAL DRUG THERAPY DECISION MAKING COURSE

An Evidence-Based Thriller

April 12th and 13th, 2013

Fairmont Waterfront Hotel
Vancouver, B.C.

Saturday Syllabus

Sponsored by

The THERAPEUTICS EDUCATION COLLABORATION
In Cooperation with the
DEPARTMENT OF FAMILY MEDICINE and
FACULTY OF PHARMACEUTICAL SCIENCES
UNIVERSITY OF BRITISH COLUMBIA

COURSE DIRECTORS
DRS. ROBERT RANGNO, JAMES MCCORMACK and
MICHAEL ALLAN

The New Therapeutics: Ten Commandments

Thou shalt treat according to level of risk rather than level of risk factor.

Thou shalt exercise caution when adding drugs to existing polypharmacy.

Thou shalt consider benefits of drugs as proven only by hard endpoint studies.

Thou shalt not bow down to surrogate endpoints, for these are but graven images.

Thou shalt not worship Treatment Targets, for these are but the creations of Committees.

Thou shalt apply a pinch of salt to Relative Risk Reductions, regardless of P values, for the population of their provenance may bear little relationship to thy daily clientele.

Thou shalt honour the Numbers Needed to Treat, for therein rest the clues to patient-relevant information and to treatment costs.

Thou shalt not see detailmen, nor covet an Educational Symposium in a luxury setting.

Thou shalt share decisions on treatment options with the patient in the light of estimates of the individual's likely risks and benefits.

Honour the elderly patient, for although this is where the greatest levels of risk reside, so do the greatest hazards of many treatments.

Course Directors

Bob Rangno, Emeritus Prof., Medicine, Pharmacology, UBC & PHC
James McCormack, Prof., Pharmaceutical Sciences, UBC

Guest Faculty

G. Michael Allan, Assoc. Prof., Family Practice, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Asst. Prof., Family Medicine, University of Alberta

Local Faculty

Gillian de Gannes, Clin. Instr., Dermatology, Dept. of Skin Sciences, UBC
Tom Elliott, Clin. Assoc. Prof., Medicine, Endocrinology, VGH
Ken Gin, Clin. Prof., Medicine, Cardiology, UBC & VGH
Barry Koehler, Clin. Prof. Emeritus, Medicine, Rheumatology, UBC
Mark McLean, Public Health Consultant, Adj. Faculty, School of Population and Public Health, UBC
Andrew Merkur, Clin. Asst. Prof., Dept. of Ophthalmology and Visual Sciences, UBC & VGH
Natasha Press, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC
Jeremy Road, Prof., Medicine, Respiratory, UBC & VGH
Kam Shojania, Clin. Prof., Medicine, Head, Rheumatology, UBC & PHC
Adil Virani, Assoc. Prof, Pharmaceutical Sciences, UBC, & Director, LMPS
Pearce Wilcox, Assoc. Prof., Medicine, Respiratory, UBC & PHC

FHA – Fraser Health Authority
PHC – Providence Health Care
PHSA – Provincial Health Services Authority
UBC – University of British Columbia
VCHA – Vancouver Coastal Health Authority
VGH – Vancouver General Hospital
LMPS – Lower Mainland Pharmacy Services, FHA, PHSA, PHC, VCHA

24th Annual

DRUG THERAPY DECISION MAKING COURSE

Saturday, April 13, 2013

07:30 Registration (Coffee & Muffins)

Chairs - Bob Rangno and James McCormack

"THIS WILL TAKE YOUR BREATH AWAY"

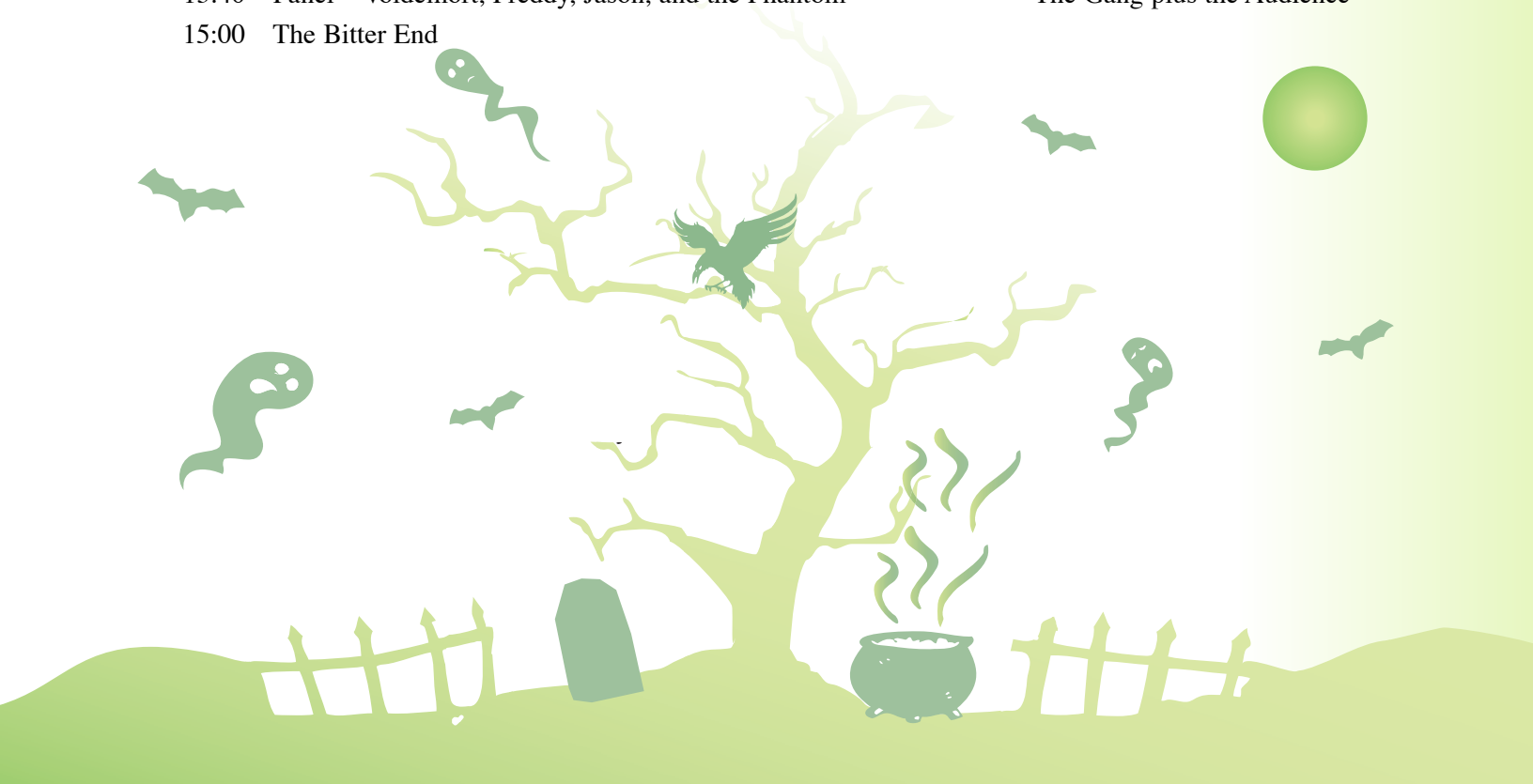
08:30	COPD – preventing the last gasp	Jeremy Road
08:50	Asthma – the wheeze exorcism	Pearce Wilcox
09:10	Croup – the scare of a lifetime and Salt of the Earth – the battle between good and evil	Tina Korownyk
09:30	Questions	
09:50	Refreshment Break	

"SCARED STRAIGHT ON RISKS AND BENEFITS"

10:10	Apocalyptic revelations around risk assessment	James McCormack/Mike Allan
10:30	ASA – A Scary Analysis	Mike Kolber
10:50	Questions	
11:10	These new studies may stop your heart	Ken Gin
11:40	Questions	
12:00	Lunch	

"A DASTARDLY FINALE"

13:00	Keeping an eye out on diabetic retinopathy	Andrew Merkur
13:20	Why regularly repeating BMD, LDL, and SBP is BAD medicine	James McCormack
13:40	Panel – Voldemort, Freddy, Jason, and the Phantom	The Gang plus the Audience
15:00	The Bitter End	



Jeremy Road

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Dr Jeremy Road
- **Relationships with commercial interests:**
  - **Grants/Research Support: N/A**
  - **Speakers Bureau/Honoraria:** GSK,BI,Takeda,Novartis,Grifols,AZ
  - **Consulting Fees:N/A**
  - **Other: N/A**

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has received financial support from** [*organization name*] **in the form of** [describe support here – e.g. an educational grant].N/A
- **This program has received in-kind support from** [*organization name*] **in the form of** [describe support here – e.g. logistical support].N/A
- **Potential for conflict(s) of interest:**
  - Dr Jeremy Road has received honoraria from GSK,BI,Takeda and AZ organizations whose products are being discussed in this program.
  - These supporting organizations produce the following products :Advair (Fluticasone/Salmeterol),Spiriva (Tiotropium),Daxas(Roflumilast) and Symbicort (Pulmicort/Formoterol)

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

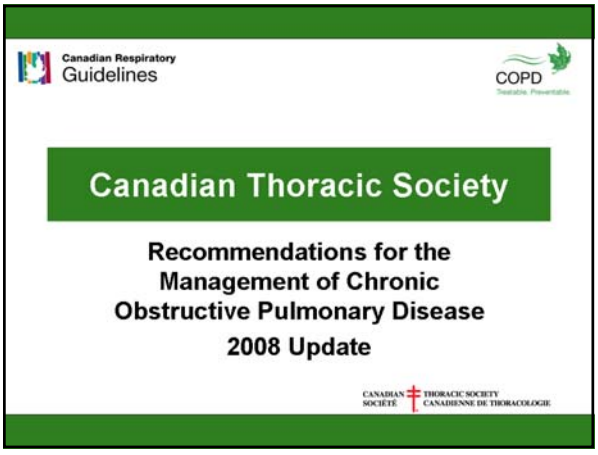
- These potential sources of bias will be dealt with by providing recommendations which are evidenced based.

COPD

Preventing the LAST GASP!

Jeremy Road MD

- COPD and CAD prevalence worldwide
- 2002 2030
- CAD 1 1
- CVD 2 2
- HIV/AIDS 4 3
- COPD 5 4
- Lung CA 9 6
- PLOS MED 2006 Global Burden of disease



Jeremy Road

Canadian Respiratory Guidelines — COPD

Reducing Mortality in COPD

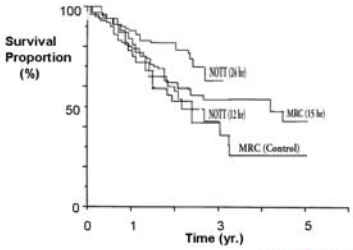
1. Discontinuing cigarette smoking
2. Long-term oxygen therapy in appropriate patients
3. Lung-volume reduction surgery (upper lobe predominance with poor exercise capacity)
4. Non-invasive ventilation for AECOPD associated with acute respiratory failure

Can Respir J 2008;15(Suppl A):1A-8A.

CANADIAN THORACIC SOCIETY / SOCIÉTÉ CANADIENNE DE THORACOLOGIE

Canadian Respiratory Guidelines — COPD

Long-Term Oxygen Therapy: Survival



NOTT *AIM* 1980. MRC *Lancet* 1981.

CANADIAN THORACIC SOCIETY / SOCIÉTÉ CANADIENNE DE THORACOLOGIE

Canadian Respiratory Guidelines — COPD

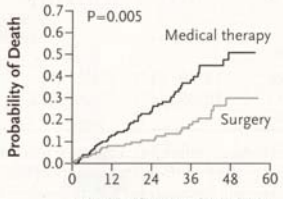
Long Term Oxygen Therapy: Survival

- Domiciliary oxygen (≥15 hrs/day to achieve SaO_2≥ 90%) improves survival in stable COPD patients with severe hypoxemia (PaO_2 ≤ 55 mmHg) or when the PaO_2 ≤ 60 mmHg in the presence of ankle edema, cor pulmonale or hematocrit ≥ 56%.

Can Respir J 2008;15(Suppl A):1A-8A.

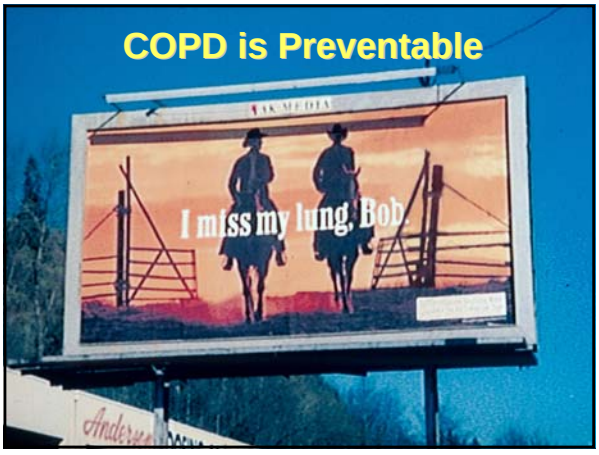
CANADIAN THORACIC SOCIETY / SOCIÉTÉ CANADIENNE DE THORACOLOGIE

D Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)



No. at Risk

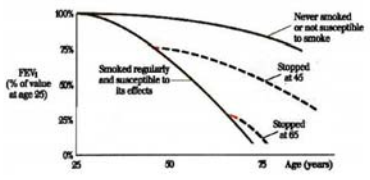
Surgery	139	121	93	61	17
Medical therapy	151	120	85	43	13



Canadian Respiratory Guidelines — COPD

Smoking Cessation

Effects of Smoking and Stopping Smoking on FEV_1



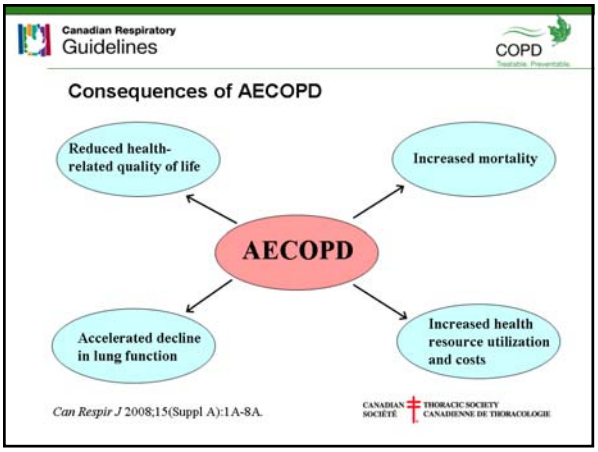
Fletcher C, Peto R. *BMJ* 1977.

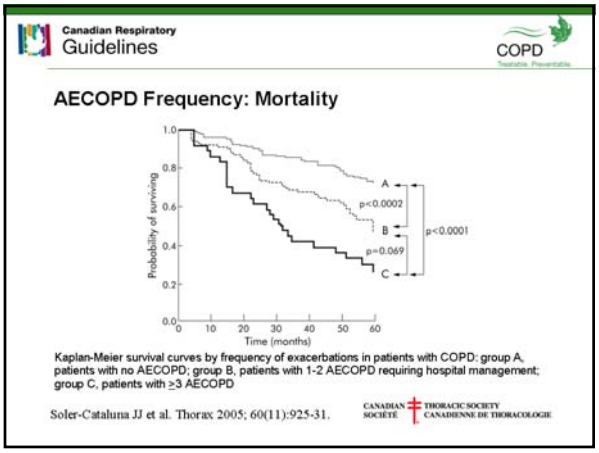
CANADIAN THORACIC SOCIETY / SOCIÉTÉ CANADIENNE DE THORACOLOGIE

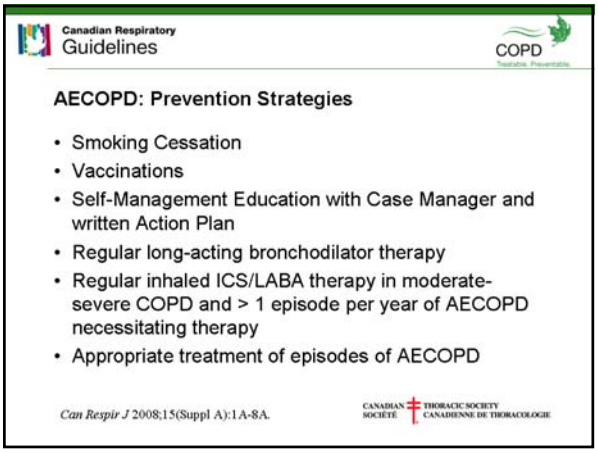
Jeremy Road

- How else can we prevent the last gasp?

- Exacerbations
- =LUNG ATTACKS!



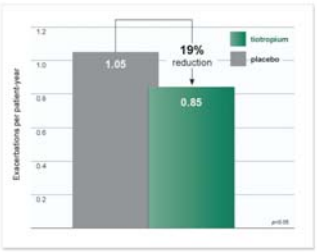




Jeremy Road

Canadian Respiratory Guidelines — COPD

Long-acting Anticholinergic: Exacerbations

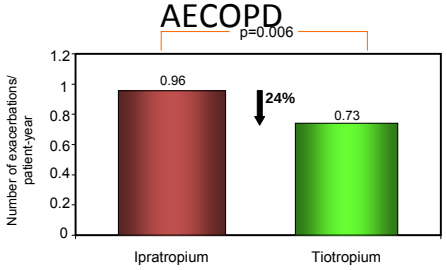


- **19% reduction in mean number AECOPD per pt-year. p<0.05**
- **28% reduction in hospitalizations for AECOPD per pt-year. p< 0.05**

Niewoehner DE, et al. Ann Intern Med 2005; 143(5):317-26.

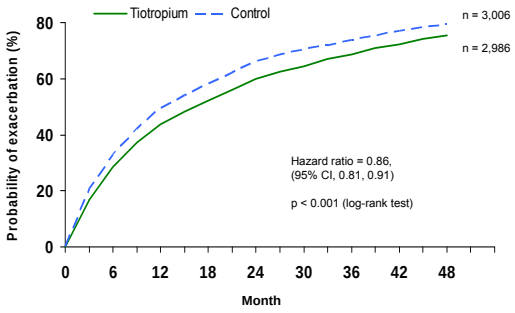
CANADIAN SOCIÉTÉ THORACIC SOCIETY CANADIENNE DE THORACOLOGIE

Long-acting Anticholinergic: AECOPD



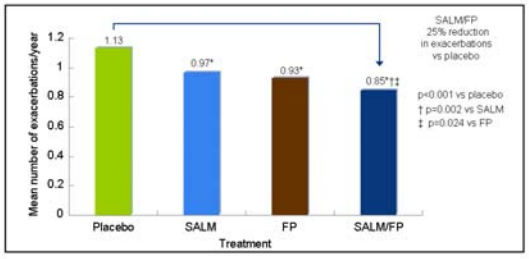
Vincken et al. *Eur Respir J* 2002;19: 209-216.

Probability of COPD Exacerbation (UPLIFT Study)



Canadian Respiratory Guidelines — COPD

TORCH: ICS/LABA Reduced Exacerbation Rate Over 3 Years



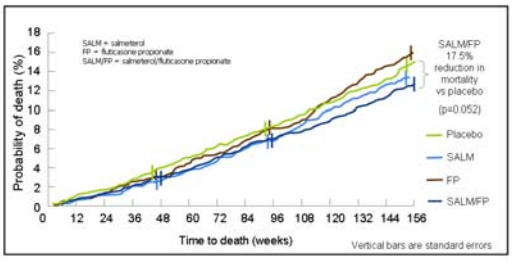
Calverley PMA, et al. N Engl J Med 2007; 356:775-89.

CANADIAN SOCIÉTÉ THORACIC SOCIETY CANADIENNE DE THORACOLOGIE

- Roflumilast and Pulmicort/formoterol have also been shown to reduce exacerbations
- However does this translate to reduced mortality?

Canadian Respiratory Guidelines — COPD

TORCH: All Cause Mortality



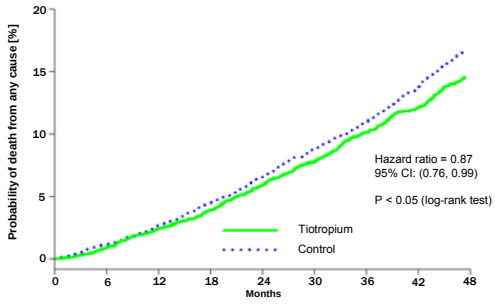
Calverley PMA, et al. N Engl J Med 2007; 356:775-89.

CANADIAN SOCIÉTÉ THORACIC SOCIETY CANADIENNE DE THORACOLOGIE

Jeremy Road

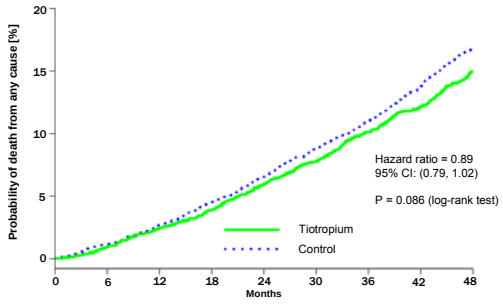
Probability of Death from Any Cause

On-Treatment + Vital Status – Day 1440



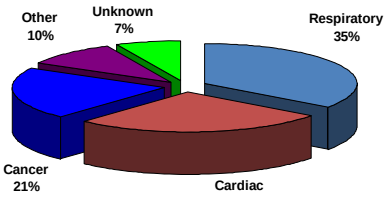
Probability of Death from Any Cause

On-Treatment + Vital Status – Day 1470



- "ALL CAUSE MORTALITY" not REDUCED

Overall Causes of Death in COPD Patients*



*as adjudicated by the TORCH Clinical Endpoint Committee

Calverley et al. NEJM 2007; 356:775-89.

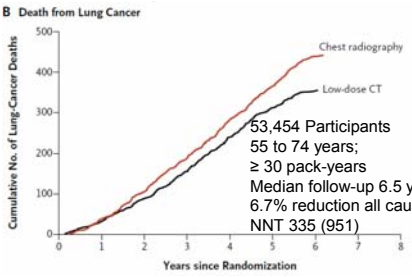
Two important Comorbidities in COPD

Can we reduce mortality due to

- Lung Cancer?
- CAD?

In COPD patients

NLST - 20% Reduction In Lung Cancer Mortality With LDCT



53,454 Participants
55 to 74 years;
≥ 30 pack-years
Median follow-up 6.5 years
6.7% reduction all cause mortality
NNT 335 (951)

NLST. NEJM 2011; 365:395-409

Jeremy Road

Potential Harms Of LDCT Screening

- Overdiagnosis
- Radiation exposure
- Unnecessary biopsy or surgery
- False assurance – encourage smokers continue to smoke?
- Anxiety

BC Cancer Agency

Existing Guidelines

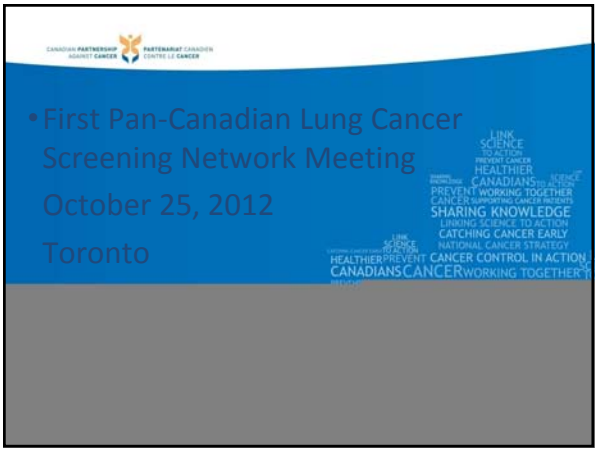
Organization	Type of Statement	NLST Criteria 55-74 y; ≥30 pk-yrs; Ex Smoker ≤15 yrs	Outside of NLST Criteria
ACCP/ ASCO/ ATS endorsed	Guideline	Suggest it be offered	No
ACS	Guideline	Recommended	No
ALA	Guidance	Recommended	No
NCCN	Consensus guidelines	Recommended	≥50 y; ≥20 pack-yrs + one risk factor
AATS	Guideline	Recommended (55-79y; no upper limit for years quit for former smokers)	50-79 y; ≥20 pack years & 5 y cumulative risk of ≥5%; lung cancer survivors

UBC

BC Cancer Agency

Private Lung Cancer Screening in Vancouver

http://www.falsecreekdiagnostics.com/services/ct-scan-cat-scan/ct-lung-cancer-screening



Major Issues

- Define screening population
- Diagnostic, treatment & follow-up pathway
- Frequency & duration of screening
- Resource utilization and cost implication

UBC

BC Cancer Agency

- How significant is the Cardiac Comorbidity??

Jeremy Road

Mechanisms Linking CAD to COPD

- Systemic inflammation
- Oxidative stress
- Hypoxemia

WHO WITH COPD SHOULD BE ON STATINS??

- Those with established CV risk factors as in secondary prevention or primary prevention?
- ATP III criteria for STATINS
- Presence of clinical atherosclerosis.Plus Risk Factors :cigarette smoking,BP,HDL< 40 mg/dl,F.H.,age > 45 .COPD??
- Eg. 2 + risk factors lowers LDL Level

- At least 50% of COPD patients would qualify by ATP III criteria.

- Many patients with COPD should be evaluated for risk factors and should be on statins .

- The Canadian Cardiovascular Society (CCS 2012) recommends lipid screening in those with RA,AS,IBD,SLE and also “COPD”
- Can we apply CV conditioning in COPD successfully?

CV Benefits of Exercise

- Decrease lipids
- Decrease systemic inflammation
- Increase anti inflammatory cytokines
- Decrease oxidative stress

- Leung et al Sports Med 2008

Jeremy Road

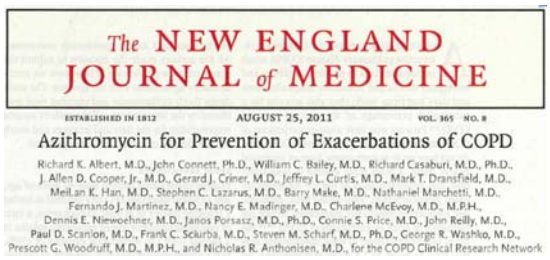
- Treatment of comorbidities should reduce mortality .
- For lung cancer screening the answer may be yes
- For CVD the jury is still out

- At least 50% of patients with moderate to severe COPD have suffer with them and current therapies are only partially effective
- WHAT ELSE CAN WE OFFER IN THE REALM OF THE LUNG ATTACK??

STATINS FOR COPD LUNG ATTACKS

- Animal studies in rats and mice showed reductions in lung injury
- Observational study by Mancini et al (A.J.of Cardio,2006)
- Systematic review Surinder Janda et al.9 studies all non interventional ,concluded evidence is compelling but " insufficient"

- STATCOPE, RCT underway


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

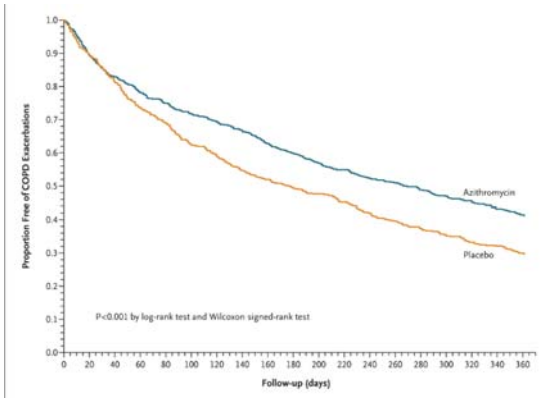
Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

Study Design

- 1142 patients with Hx of at least one" Lung Attack" in previous year or on oxygen therapy.
- Lung Attacks = Rx with steroids or antibiotics
- 80% were on LABAs, LAMAs and or ICS
- RCT for 1 year : standard therapy plus Azithromycin or placebo.
- Primary outcome :exacerbations.

Jeremy Road



Results

- 900 v 741 attacks in treatment group
- HR 0.73 (95% CI 0.63-0.84)
- NNT was 2.86
- Nasopharyngeal swabs 81 v 41% resistance to Macrolides in treatment group

Conclusions

- Similar patients could be prescribed this Rx
- Caveat watch QTc, hearing should be monitored.
- Effect on bacterial resistance requires scrutiny.

Take Home Messages

- We can decrease lung attacks with inhalers but have not been able to demonstrate reduced mortality .
- Interventions such as smoking cessation and long term oxygen therapy have been shown to prolong survival.
- Remember the comorbidites :Lung cancer screening and possibly CAD may reduce mortality.
- New approaches to reduce lung attacks eg macrolides or statins may indeed be effective at reducing Lung Attacks but would they prolong TTLG (Time to Last Gasp)??

Pearce Wilcox

ASTHMA: THE WHEEZE EXORCISM

Dr. Pearce Wilcox
Professor Dept. of Medicine UBC
Respirologist St Paul's Hospital

Faculty/Presenter Disclosure

- **Faculty:** P. Wilcox
- **Relationships with commercial interests:**
  - **Grants/Research Support: Vertex, Actelion, Gilead, Intermune**
  - **Speakers Bureau/Honoraria: Actelion, Novartis, Astra Zeneca, Intermune, Abbott**
  - **Consulting Fees: NA**
  - **Other: NA**

Objectives

- Asthma
  - To discuss potential adverse effects of ICS and ways to minimize them
  - To review the latest recommendations in Asthma for
    - Intermittent vs continuous ICS
    - When to consider adjunct therapies to ICS and what to consider
    - New strategies for achieving and maintaining control
  - Address newer treatment options for asthma

Case 1 SP 13 yr old

- Recurrent symptoms of SOB and wheezing with activity had to give up playing basketball
- Seasonal allergic rhinitis
- Nocturnal awakening once weekly "chest tight"
- Prescribed salbutamol using 3-4 x weekly and prior to exercise
- Spirometry FEV1 85% pred with 15% improvement post bronchodilator

Asthma Pharmacotherapy

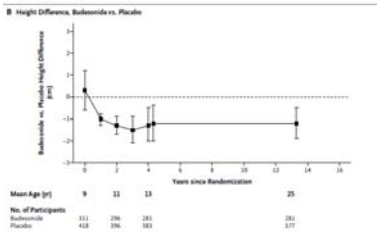
- You recommend an ICS
  - Parents reluctant
    - "Too many side effects"

Pearce Wilcox

ORIGINAL ARTICLE

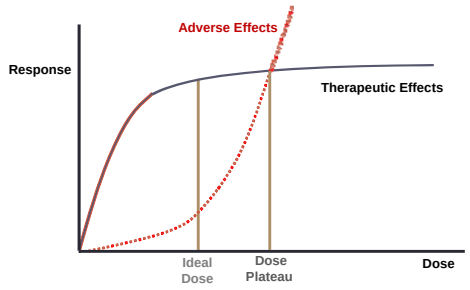
Effect of Inhaled Glucocorticoids in Childhood on Adult Height

H. William Kelly, Pharm.D., Alice L. Sternberg, Sc.M., Rachel Lescher, M.D., Anne L. Fuhlbrigge, M.D., Paul Williams, M.D., Robert S. Zeiger, M.D., Ph.D., Hengameh H. Raissy, Pharm.D., Mark L. Van Natta, M.H.S., James Tonascia, Ph.D., and Robert C. Strunk, M.D., for the CAMP Research Group*



NEJM 2012

ICS: Theoretical Dose-Response Curve



Robinson DS, *et al.*, 1996.

Canadian Respiratory Guidelines — Asthma

Inhaled corticosteroids (ICS) dosing categories in children and adults

	Pediatric Daily ICS Dose (mcg) (Age 6-11 years)			Adult Daily ICS Dose (mcg) (12 years and over)		
PRODUCT (Trade Name)	LOW	MEDIUM	HIGH	LOW	MEDIUM	HIGH
Beclomethasone dipropionate HFA (QVAR®)	≤200	201-400	>400	≤250	251-500	>500
Budesonide * (Pulmicort® Turbuhaler®)	≤400	401-800	>800	≤400	401-800	>800
Ciclesonide * (Alvesco®)	≤200	201-400	>400	≤200	201-400	>400
Fluticasone (Flovent® MDI and spacer; Flovent® Diskus®)	≤200	201-400	>400	≤250	251-500	>500
Mometasone (Asmanex® Twisthaler®)				200	≥400-800	≥800

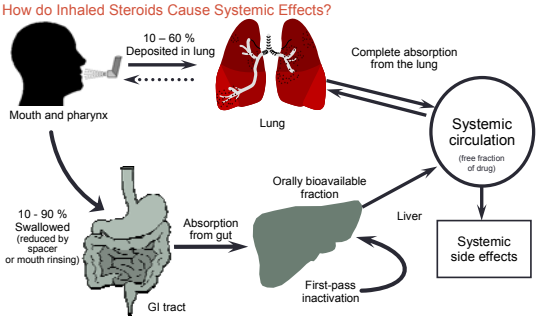
*Note: Dosing categories are approximate, based upon a combination of approximate dose equivalency as well as safety and efficacy data rather than available product formulations. *Licensed for once daily dosing in Canada. Highlighting indicates doses which are not approved in Canada.*

Canadian Respiratory Journal 2012;19(2): 127-64.

CANADIAN THORACIC SOCIETY / SOCIÉTÉ CANADIENNE DE THORACOLOGIE

The Fate of Inhaled Steroids:

How do Inhaled Steroids Cause Systemic Effects?



Barnes NC, 2007; Gulliver T, *et al.*, 2007; Salvatoni A, *et al.*, 2003.

- Can I take my inhaled steroid only when my asthma flares?

Canadian Respiratory Guidelines — Asthma

Written Action Plan – Intermittent ICS

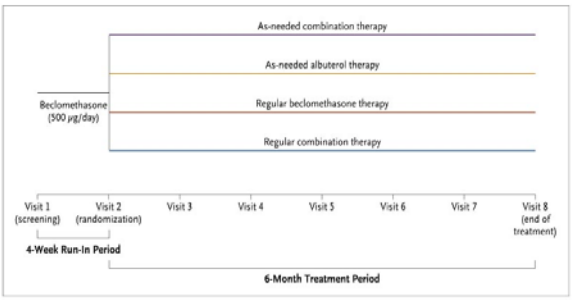
- Evidence does not support the use of intermittent ICS started only at the onset of an episode of loss of asthma control in children or adults, which underlines the importance of prescribing and ensuring adherence to daily controller therapy.

Canadian Respiratory Journal 2012;19(2): 127-64.

CANADIAN THORACIC SOCIETY / SOCIÉTÉ CANADIENNE DE THORACOLOGIE

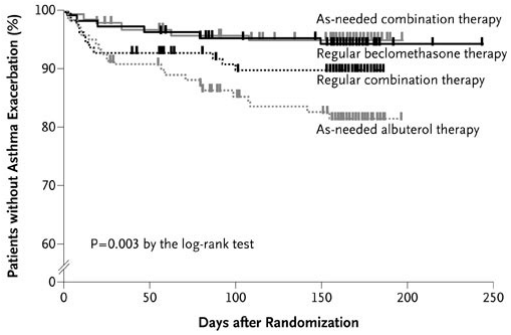
Pearce Wilcox

Study Design: Multinational, randomized, double blind, double dummy – *"1 puff of the blue b.i.d and one or more puffs PRN of the green MDI" (no action plan)*



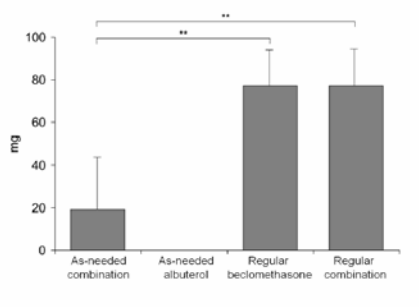
Papi NEJM 2007

Time to First Asthma Exacerbation



Papi A, N Engl J Med 2007

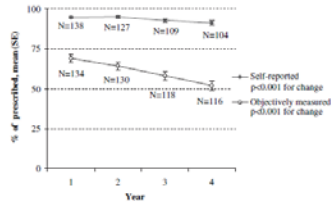
BEST:Total ICS use over 6 months



Papi A, N Engl J Med 2007

Adherence to inhaled corticosteroids: An ancillary study of the Childhood Asthma Management Program clinical trial

Jerry A. Krishnan, MD, PhD,[a] Bruce G. Bender, PhD,[b] Frederick S. Wamboldt, MD,[b] Stanley J. Szefler, MD,[b] N. Franklin Adkinson, Jr, MD,[c] Robert S. Zeiger, MD, PhD,[d] Robert A. Wise, MD,[e] Andrew L. Bilderback, MS,[e] and Cynthia S. Rand, PhD,[e] on behalf of the Adherence Ancillary Study Group* *Chicago, Ill, Denver, Colo, Baltimore, Md, and San Diego, Calif*

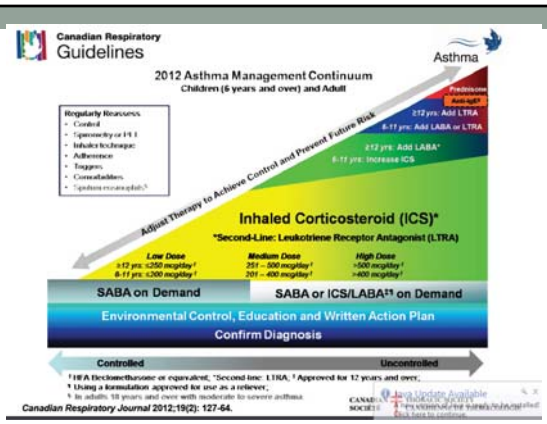


J Allerg Clin Immunol 2012

Case 2 BQ 26 yr old asthmatic

- Taking regular dose of Budesonide 200ug bid for last 6 months
- Missed 4 days of work for worsening respiratory symptoms after a "cold" last month
- Taking salbutamol daily 1-2 x

- What to do next?



Pearce Wilcox

Canadian Respiratory Guidelines — Asthma

Recommendations:

- In adults with asthma not achieving control despite adherence to a low dose of ICS, we recommend the addition of a LABA.(GRADE 1A) Alternative third-line options include adding an LTRA or increasing to a medium dose of ICS. (Consensus)
- In children with asthma not achieving control despite adherence to a low dose of ICS, we recommend increasing to a medium dose of ICS. (GRADE 1A)
- In children not achieving asthma control on a medium dose of ICS, we suggest the addition of a LABA or LTRA. (GRADE 2B)
- Children who fail to achieve control on a medium dose of ICS should be referred to a specialist. (Consensus)

Canadian Respiratory Journal 2012;19(2): 127-64.

- Is there anything better than asthma control evaluation to modify asthma therapy?

Canadian Respiratory Guidelines — Asthma

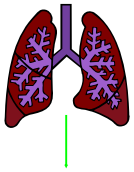
Asthma Control

Characteristic	Frequency or Value
Daytime symptoms	< 4 days/week
Night-time symptoms	<1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school due to asthma	None
Need for a fast-acting beta$_2$-agnonist	<4 doses/week
FEV_1 or PEF	≥90% personal best
PEF diurnal variation*	<10-15%
Sputum eosinophils †	<2-3%

FEV_1 = forced expiratory volume in 1s; PEF = peak expiratory flow.
* Diurnal variation is calculated as the highest PEF minus the lowest divided by the highest PEF multiplied by 100 for morning and night (determined over a 1 - 2 week period).
† Consider in individuals 18 years and over with moderate to severe asthma who are assessed in specialized centres.

Canadian Respiratory Journal 2012;19(2): 127-64.

Hypothesis: additional biomarkers increase the precision of the asthma diagnosis and facilitate tailoring of treatment



Additional biomarkers

AHR, blood, urine

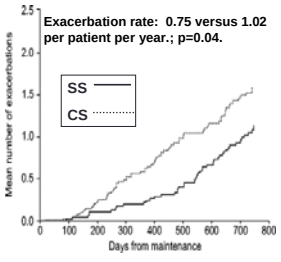
Breath: FeNO / condensate

Sputum: eosinophils / cytokines

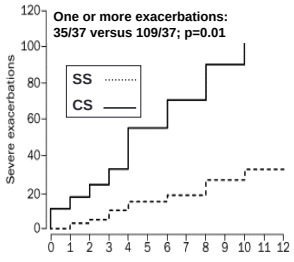
Usual care

↑ Symptoms
↓Lung function
Exacerbations

Management – using "sputum inflammometry"



Jayaram, ERJ 2006; 27: 483-494



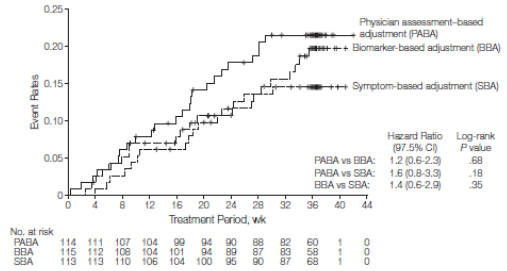
Green, Lancet 2002; 360: 1715-21

Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma

The BASALT Randomized Controlled Trial

Pearce Wilcox

Figure 2. Time to First Treatment Failure



Canadian Respiratory Guidelines — Asthma

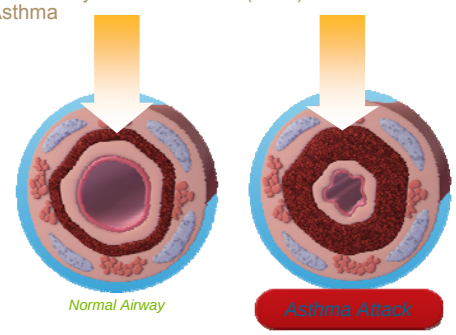
Recommendations:

- We recommend the monitoring of sputum eosinophil counts, in addition to standard measures of asthma control, to adjust anti-inflammatory therapy of individuals 18 years of age and over with moderate to severe asthma in tertiary care or specialized centres. (GRADE 1B)
- We do not suggest the routine use of FeNO, either in addition to or instead of standard measures of asthma control, to adjust anti-inflammatory therapy in children or adults with asthma. (GRADE 2B)

Canadian Respiratory Journal 2012;19(2): 127-64.

Canadian Thoracic Society / Société canadienne de thoracologie

Role of Airway Smooth Muscle (ASM) on Asthma



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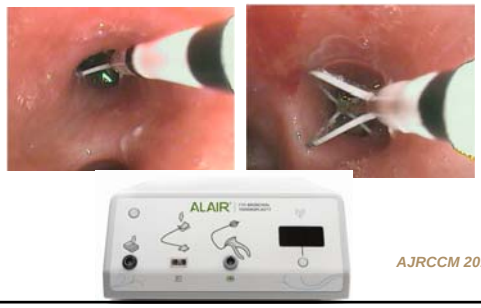
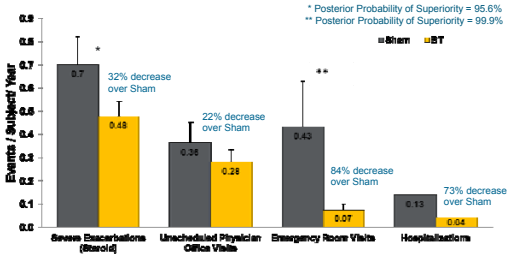
Catheter placement and activation



AJRCCM 2012

Health Care Utilization for Respiratory Symptoms During Post-Treatment Period[1]

- 6 weeks after the last bronchoscopy procedure to 12 month follow-up



1. Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

20

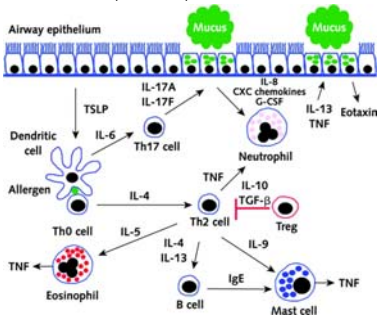
30

Long-Term Safety

- ≥ 3 year follow-up in 3 different studies
  (Feasibility, AIR, RISA):
  - Stable pulmonary function based on spirometry
  - Absence of clinical complications related to the device
- Annual HRCT scans for 5 years (Feasibility Study):
  - No radiographic evidence of structural changes
- Stability over years 1 - 5
- Safety experience from AIR and RISA informed patient selection for AIR2 trial

Pearce Wilcox

Modulating Th2 immune pathways for the treatment of asthma.An early step in the initiation of allergic airway inflammation is the activation and maturation of antigen-presenting dendritic cells in response to TSLP, an IL-7–like cytokine that is produced by airway epithelial cells, fibroblasts, and mast cells.



Annals of Internal Medicine

Levine S J , Wenzel S E Ann Intern Med 2010;152:232-237

Summary

- ICS at current standard dosing are safe and effective in asthma
- Medication adherence in asthma is wanting
- Intermittent dosing of ICS or ICS/LABA may be effective for some mild asthmatics
- Biomarkers (sputum eosinophils, NO) may have a role for adjusting asthma pharmacotherapy
- New approaches (bronchial thermoplasty and biologics) will have an impact (limited)

Croup & Salt

2 scary topics with frighteningly little in common

Tina Korownyk
University of Alberta

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Tina Korownyk
- **Relationships with commercial interests:**
  - **Not applicable**
  - **I like salt**

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

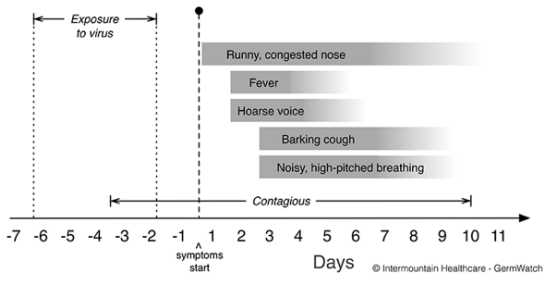
- **No commercial support**
- **Potential for conflict(s) of interest:**
  - Not applicable

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- Not applicable
- I am trying to not like salty foods for this talk

Parainfluenza Virus Infection Timeline



Glucocorticoid Treatment for Croup

Treatment compared	Time (hours)	No of studies/ No of patients	Effect size (95% CI)
Budesonide *v* placebo	6	5/327	-0.9 (-1.4 to -0.4)
	12	2/142	-0.7 (-1.1 to -0.3)
Dexamethasone *v* placebo	6	8/739	-1.1 (-1.8 to -0.5)
	12	5/339	-1.2 (-2.1 to -0.3)
	24	4/189	-1.1 (-2.6 to 0.4)
Budesonide or dexamethasone *v* placebo	6	13/1066	-1.0 (-1.5 to -0.6)
	12	7/481	-1.0 (-1.5 to -0.6)
	24	5/256	-1.0 (-2.0 to 0.1)

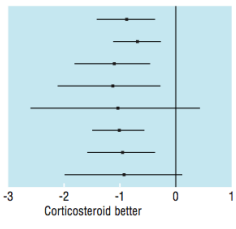


Fig 1 Pooled effect sizes (95% confidence intervals) of glucocorticoid treatment for croup versus placebo. All estimates had significant heterogeneity among trials

BMJ 1999;319:595

Treatment of Mild Croup in the Office

- 720 children, ER, mild croup, 0.6mg/kg dexamethasone po vs placebo
- Dexamethasone demonstrated significant benefit in
  - 1° outcome: return to medical care provider
    - 7.3% vs 15.3%, NNT = 13
  - 2° outcome: presence of ongoing sx
  - Other outcomes: hours of sleep lost by child, stress on part of parent ($p<0.001$)
  - Cost

N Engl J Med. 2004 Sep 23;351(13):1306-13

Calming the Croupy Cough

Mrs. Paraflu brings in her 12 mo old daughter who has been barking like a seal for the past 24hrs. Based on a diagnosis of croup, what will you recommend?

1) Humidified air AT HOME
2) Dexamethasone 0.6mg/kg
3) Dexamethasone 0.15mg/kg
4) A trip to the zoo

N Engl J Med. 2004 Sep 23;351(13):1306-13

Calming the Croupy Cough

- 99 children (6-79mo), ER, Mild to Mod Croup
- Prednisolone 1mg/kg, dexamethasone 0.6mg/kg or dexamethasone 0.15mg/kg
- No signficant difference in any outcome between the three treatment groups:
  - Primary outcome: croup score at 4 hrs, return to medical care or further treatment w/in the week

Emergency Medicine Australasia 2007;19:51-58

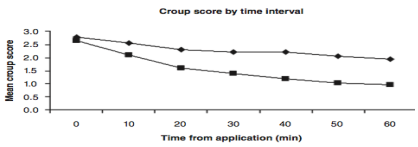
Calming the Croupy Cough

Mrs.Paraflu is thankful for your assistance, and while she would like to see her daughter improve, she also has an important function this evening. She wonders how long it will take to see an effect? You tell her…

1) Minimum 4-6 hrs
2) 30-60 mins
3) About 3-4 days

Time for Healing?

- Double blind RCT, 70 children, mild-mod croup
- 0.15mg/kg dexamethasone vs placebo
- Primary outcome: croup score at 30 mins
- Findings: Trend to lower score at 10mins, statistically significant by 30 mins
- Statistical difference (1 vs 1.9) at 60 mins

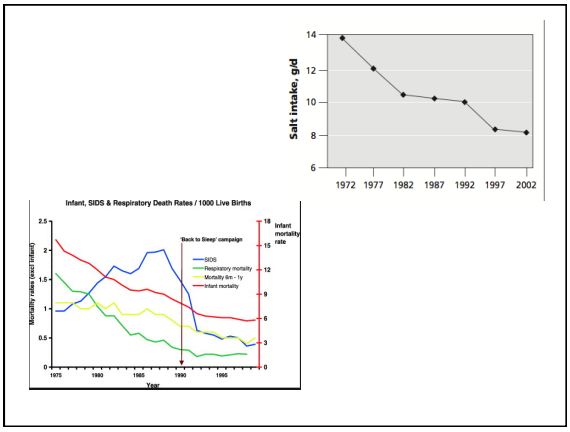


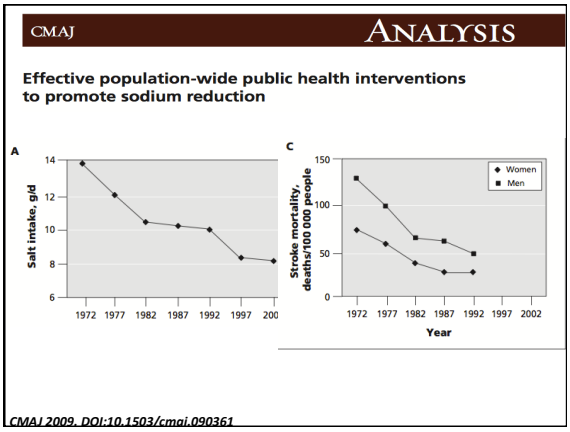
Emergency Medicine Australiasia 2012;24;79-85.

Croup Bottom Line

0.15mg/kg equivalent to 0.6mg/kg for mild – moderate croup

Benefit of steroids seen within 30 mins





Sodium and Blood Pressure

- Low sodium diets reduce BP[1]
  - 1.27mmHg Normotensive, 5.48mmHg HTN
  - this effect appears to attenuate over time[2]
    - 1.1mgHg at 13-60 mo
    - related to compliance? homeostasis?
  - a surrogate marker for CVD
- Atenolol[3] and Aliskiren[4] are interventions that lower BP but do not improve mortality.

1) Cochrane Database Syst Rev. 2011;(11):CD004022. 2) BMJ. 2002;325(7365):628. 3) Lancet. 2004;364(9446):1684-9. 4) N Engl J Med. 2012;367(23):2204-13.

↓ Sodium = ↓ Mortality?

- Two analyses of a large American cohort study (NHANES III) came to opposite conclusions:
- Every 1000 mg / day increase in sodium intake resulted in a trend towards:
  - Decreased all-cause mortality[1]
    - HR = 0.94 (0.88-1.01)
  - Increased all-cause mortality[2]
    - HR = 1.20 (1.03-1.41)

1) J Gen Intern Med. 2008; 23(9):1297-302. 2)Arch Intern Med. 2011; 171(13):1183-91.

Dedicated to advancing the many benefits of salt, particularly to ensure winter roadway safety, quality water and healthy nutrition

A voluntary non-profit activist organization whose primary goal is worldwide salt reduction.

↓ Sodium = ↓ Mortality?

- Systematic review of 13 cohort studies (177,000 patients) reported increased stroke with higher salt intake, RR = 1.23 (1.06-1.43).[1]
- Trend towards increased CVD
  - Actual sodium values not reported

1) BMJ. 2009;339:b4567.

↓ Sodium = ↓ Mortality?

- Systematic review, 7 RCTs, ≥ 6 mo, 6489 pts, ↓ dietary sodium vs control
- From ~ 3900mg to 3000mg/d[1]
- No difference in:
  - All cause mortality:
    - RR 0.90 (0.58-1.40) normotensive
    - RR 0.96 (0.83-1.11) hypertensive
  - CVD events:
    - RR 0.71 (0.42-1.20) – normotensive
    - RR 0.84 (0.57-1.23) – hypertensive

1) Cochrane Database Syst Rev. 2011;(7):CD009217

↓ Sodium = ↓ Mortality?

- Systematic review, 7 RCTs, ≥ 6 mo, 6489 pts, ↓ dietary sodium vs control (from ~ 3900mg to 3000mg/d).[1]
- No difference in:
  - All cause mortality:
    - RR 0.90 (0.58-1.40) normotensive
    - RR 0.96 (0.83-1.11) hypertensive
  - CVD events:
    - RR 0.71 (0.42-1.20) – normotensive
    - RR 0.84 (0.57-1.23) – hypertensive

Reanalysis combining normotensive and hypertensives:

↓ CVD events: RR = 0.80 (0.64-0.99) NNT = 48.[2]

No difference in mortality – Numbers not reported

1) Cochrane Database Syst Rev. 2011;(7):CD009217. 2) Lancet. 2011;378(9789):380-2.

How much sodium should we eat?

- Canadian & US adults eat ~3500 mg/d.[1]
- Canada recommends 1500 mg/d
  - (upper limit 2300 mg) for 14 to 50 y/o.[3]
- American Heart Association also recommends 1500mg/d.[4]

1) Am J Clin Nutr. 2010;92(5):1172-80. 2) Lancet 2011;377:1438-47. 3) http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/food-aliment/sodium-eng.php 4) *Circulation.*

How did we get to 1500mg/d?

- Because of the dearth of large, dose-response studies with clinically relevant biological outcomes carried out in normal … individuals, an Estimated Average Requirement could not be established…[1]
- Hence, an Adequate Intake is provided.
- The Adequate intake for sodium is set at 1500 mg/day to
  - Ensure the overall diet provides adequate intake of other important nutrients
    - Two diets tested in the (DASH)-Sodium trial (Sacks et al., 2001)
  - cover sodium sweat losses in unacclimatized individuals who are exposed to high temperatures or who become physically active

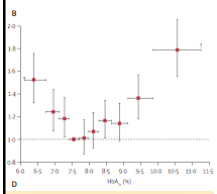
1) Institute of Medicine 2004 (Craddick et al., 2003;Karanja et al., J Am Diet Assoc. 1999;99 (suppl):S19-S27

A Final Thought

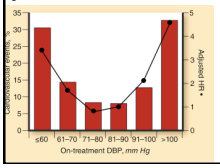
- Some observational data suggests that sodium intake follows a J-curve, with daily intake <2000mg and >4000mg being harmful[6]

You can't be too rich or too low: How many J-curves are enough?

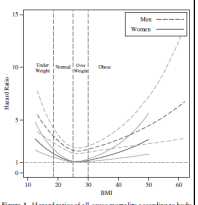
A1C[1]



Diastolic BP[2]



BMI[3] over 65



1) Lancet 2010; 375: 481–89
2) Curr Hypertens Rep (2010) 12:290–295
3) J Am Geriatr Soc 2010; 58:234–241. jjj

Courtesy Mike Allan

Bottom Line:

- Moderate sodium reduction (3900mg to 3000mg) can reduce CVD events
- Effect on mortality is unclear.
- Optimal levels unknown.

James McCormack and G. Michael Allan

Describing Benefits

Apocalyptic revelations around risk assessment

James McCormack
Mike Allan

The chance WITH NO TREATMENT

The chance WITH TREATMENT

Risk Assessment

First Challenge Picking the Right One

Many types:

Framingham (US & Canadian very similar)

UK

New Zealand

Many regions individualize

A Multitude of Cell phone Application (and desktop tools), and Reynolds Risk Score.

Some without Chol & just obesity (Lancet 2008;371:923–31)

Risk of what and over how long

WHAT

CVD is cardiovascular disease

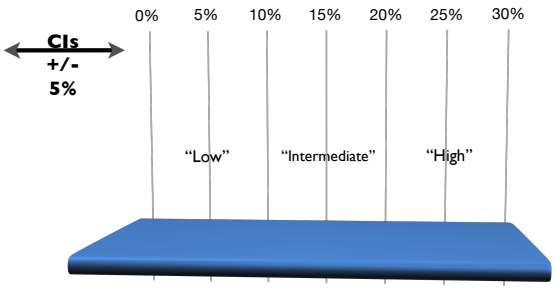
Typically = CHD + cerebrovascular

CHD = coronary heart disease = fatal and non-fatal MIs and sometimes angina

Cerebrovascular disease = fatal and non-fatal strokes - and sometimes TIAs

CVD sometimes includes other conditions - heart failure, peripheral vascular disease

HOW LONG - 5 or 10 years



J Cardiovasc Risk 2002;9:183-90

Variability in Calculating

95% Confidence Intervals (CI) around 10-year predictions of CHD

Framingham[1]	Baseline	<10%	10-20%		30-40%
	CI (+/-)	1.5%	3%		15%
Reynolds[2]	Baseline	10%	15%	20%	30%
	CI (+/-)	4%	5%	6%	7%

1. Am Heart J 1991; 121: 293-98. 2. J Cardiovasc Risk 2002; 9: 183-190.

James McCormack and G. Michael Allan

Are Risk Assessment Tools Similar?

Many use the same data set, so generally yes

Compare BNF and Framingham

Patient: BP (systolic) 130mmHg, Total Cholesterol 232, HDL 35, Non-smoker, Not Diabetic

	Male 60	Female 60	Male 40	Female 40
Framingham	23.7%	15.7%	7%	5.3%
BNF	21.8%	14.4%	7.7%	4.2%

How Accurate are Risk Tools

Looking at variability (95% CI) within models:

Framingham +/- 15% if estimated risk >30% (but only 3% when between 10-20%)[1]

Reynolds risk +/- 5-6% at 15 or 20%. [2]

	<5%	5-10%	10-15%	15-20%	≥20%
No CVD (32 K pts)[3]	2.5%	5.4%	9.5%	11%	20%
Hx CVD (3728 pts)	22%	25%	31%	38%	49%

1. Am Heart J 1991; 121: 293-98. 2. J Cardiovasc Risk 2002; 9: 183-190. 3. Heart 2009;95:125–9.

Primary vs Secondary

35 760 primary care patients 30–74 years of age (mean age 54 y, 57% men, 10% Hx CVD)

Applied PREDICT from Framingham (5 year risk)

Calculated and real

90% primary, and 53% of those <5%, 81% <10%.

	<5%	5-10%	10-15%	15-20%	≥20%
No CVD (32 K pts)	2.5%	5.4%	9.5%	11%	20%
Hx CVD (3728 pts)	22%	25%	31%	38%	49%

Heart 2009;95:125–9

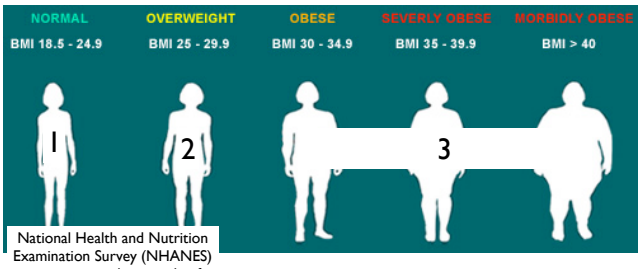
Primary vs Secondary Prevention

How do the outcomes (over approx 5 years) with statins compare between primary and secondary?

	Primary	Diabetes	Secondary
Statin	4.8%	3.6%	10.9%
Placebo	6.1%	5.5%	14.6%
RRR	21%	35%	25%
ARR	1.3%	1.9%	3.7%
NNT	77	53	27

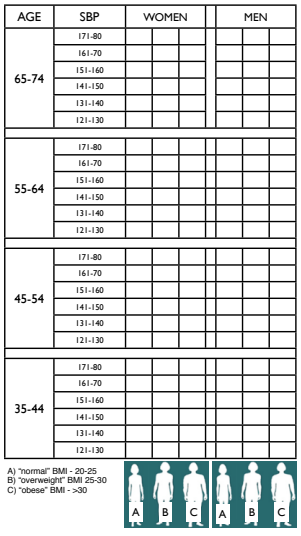
Br J Clin Pharm 2004; 57:640-51 Lancet 2004; 364: 685-96

Lancet 2008;371:923–31



National Health and Nutrition Examination Survey (NHANES) prospective cohort study of 14,407 US participants

ıon-laboratory-based risk factors predicted cardiovascular events as accurately as one that relied on laboratory-based values



≃ 5-year CVD[1] risk (%)[2]
>30
20-30
10-20
5-10
<5%

Smoking or diabetes approx. doubles the risk

1.CVD = death, MI, stroke, CHF, and coronary revascularisation including CABG and PTCA 2.1/2-2/3 are hard endpoints - fatal/nonfatal MI or stroke

Lancet 2008;371:923–31

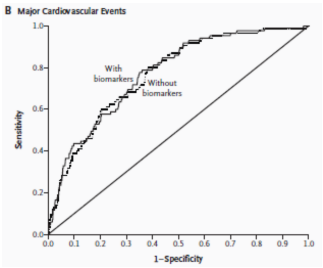
James McCormack and G. Michael Allan

Studies of hsCRP & Biomarkers

CRP (& other biomarkers) provide little additional predictive value.[1-4]

hsCRP (HR ratio 1.19, $p < 0.001$) vs

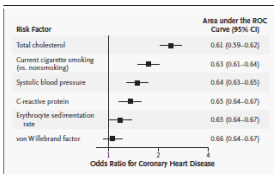
D-dimer (1.36), interleukin-6 (1.28), lipoprotein-A2 (1.17).[3]



0.76 without vs 0.77 with Biomarkers[2]

1) N Engl J Med 2004;350:1387-97. 2) N Engl J Med 2006; 355: 2631-39 3) Arch Intern Med 2006; 166: 1368-73. 4) Int J Epidemiol 2009; 38: 217-31.

Studies of hsCRP & Biomarkers



"C-reactive protein concentration (and the other inflammatory markers that were assessed) provided comparatively little additional predictive value over that provided by assessment of major established risk factors" (N Engl J Med 2004;350:1387-97)

10 year risk (%)

JNC 6	JNC 7	Systolic mm Hg	Non diabetic		Diabetic	
			CHD	Stroke	CHD	Stroke
Optimal	Normal	110	7	1	9	1
Normal	Prehtn	120	8	1	11	2
Borderline	Prehtn	130	9	2	12	3
Stage 1	Stage 1	140	10	2	13	3
Stage 1	Stage 1	150	11	3	15	4
Stage 2	Stage 2	160	12	4	16	6
Stage 2	Stage 2	180	15	5	19	9

Evidence for CVD benefit - typically over 5 years

	Mortality	Total stroke	Total CHD	Total CVD	Withdrawal due to adverse effects
BASELINE (%)	7	3-4	3-4	8-9	3
Thiazide	0.89 (0.83,0.96)	0.63 (0.57,0.71)	0.84 (0.75,0.95)	0.70 (0.66,0.76)	3.22 (2.90,3.57)
BB	0.96 (0.86,1.07)	0.83 (0.72-0.97)	0.90 (0.78,1.03)	0.89 (0.81,0.98)	4.59 (4.11,5.13)
CCB	0.86 (0.68,1.09)	0.58 (0.41,0.84)	0.77 (0.55,1.09)	0.71 (0.57,0.87)	NR
BASELINE (%)	14	6	14	20	
ACEI	0.83 (0.72,0.95)	0.65 (0.52,0.82)	0.81 (0.70,0.94)	0.76 (0.67,0.85)	

Treatment of Hypertension in the Elderly

typically over 5 years - 2-3 years for the over 80

	Mortality	CV mortality and morbidity	Withdrawal due to adverse effects
BASELINE (%)	12	15	7
60 years or older	0.9 (0.84,0.97)	0.72 (0.68,0.77)	1.71 (1.45,2.00)
BASELINE (%)	14	11	NR
80 years or older	0.98 (0.87,1.10)	0.75 (0.65,0.87)	

Cochrane Library

Absolute benefit of statins over approx. 5 years

	Major coronary events (%)*	Death (%)	Strokes (%)	FROM WHAT CVD TO WHAT CVD (%)
Primary	1-1.5*	-	-	8-9 to 7
Diabetes	2	-	1-1.5	10 to 7
Secondary	4	2	1	20 to 15

* just in males and NO difference in overall serious adverse events

James McCormack and G. Michael Allan

Relative risk reductions with different interventions in DM2

	Treat BP	Treat Lipid	Treat Sugar
CVD events	~ 50%	~20-25%	~ 12.5%
Mortality	16%	8%	NSS

Diabetes Care 2010;33(1): S11-61, Ann Intern Med 2008;148:846-54, Lancet 2009;373:1765–72, Lancet 2008; 371:117–25, Ann Intern Med 2003;138:587-92

10 year CHD risk (%) - UKPDS risk engine

A1c	50f, diabetes 3 years (1%Δ)	50m, diabetes 3 years (2%Δ)	65f, diabetes 10 years (3%Δ)	65m, diabetes 10 years (4%Δ)
7	9	16	21	36
8	10	18	24	40
9	11	20	27	44

BP 140, chol 6, hdl 1, non smoker

A simple A fib table

	Patient's ANNUAL risk (%) of ischemic stroke			Difference in benefit between ASA and OAC
$CHADS_2$ Score	No therapy	ASA	OAC	
0	1.9	1.5	0.6	0.9
1	2.8	2.2	0.9	1.3
2	4	3.1	1.3	1.8
3	5.9	4.6	1.9	2.7
4	8.5	6.6	2.8	3.8
5	18	14	6	8

Risk of Having Osteoporosis

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

5 year chance of fractures - WITHOUT knowing BMD

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

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

Osteoporos Int 2001;12:519–28

10 year probability of a fracture
(hip, forearm, humerus, clinical vertebral)

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

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

James McCormack and G. Michael Allan

Relative and absolute benefits from using alendronate for 2-3 years

	Vertebral fractures		Non-vertebral fractures	
	Prim	Sec	Prim	Sec
Relative	45	45	?	20
Absolute	2	6	?	2

Cochrane Library

Table 2: Odds Ratio for Fracture, Indirect Treatment Comparison Results of Drug versus Placebo (Classical and Bayesian analysis)

Classical analysis

	Non-vertebral fracture		Vertebral fracture		Hip fracture		Wrist fracture	
Drug vs placebo	OR (95% Cr I)	Placebo rate	OR (95% Cr I)	Placebo rate	OR (95% Cr I)	Placebo rate	OR (95% Cr I)	Placebo rate
Alendronate	0.80 (0.68, 0.95)	11.1%	0.51 (0.40, 0.63)	6.7%	0.62 (0.40, 0.96)	1.1%	0.44 (0.30, 0.67)	3.0%
Denosumab	0.80 (0.67, 0.96)	7.5%	0.31 (0.24, 0.40)	7.2%	0.60 (0.37, 0.98)	1.1%	NR	NR
Etidronate	0.64 (0.31, 1.32)	11.5%	0.59 (0.32, 1.10)	9.7%	0.60 (0.14, 2.66)	2.1%	1.19 (0.37, 3.80)	2.2%
Ibandronate	0.88 (0.71, 1.10)	7.5%	0.49 (0.32, 0.73)	7.5%	NR	NR	NR	NR
Raloxifene	0.91 (0.77, 1.07)	9.3%	0.63 (0.50, 0.78)	10.1%	1.12 (0.64, 1.95)	0.7%	0.88 (0.67, 1.15)	3.3%
Risedronate	0.79 (0.69, 0.89)	10.1%	0.59 (0.47, 0.75)	13.3%	0.74 (0.58, 0.94)	2.8%	0.71 (0.56, 0.89)	3.4%
Strontium	0.85 (0.74 (0.98)	14.7%	0.58 (0.50, 0.67)	21.7%	0.66 (1.19)	4.0%	1.59 (1.12, 2.27)	3.2%
Teriparatide	0.62 (0.40, 0.97)	9.7%	0.31 (0.19, 0.52)	14.3%	0.50 (0.09, 2.75)	0.7%	0.50 (0.09, 2.75)	2.4%
Zoledronic Acid	0.74 (0.63, 0.86)	10.0%	0.28 (0.22, 0.35)	10.9%	0.59 (0.83)	2.3%	NR	NR
All drugs vs placebo	0.81 (0.77, 0.86)	10.5%	0.49 (0.41, 0.58)	11.0%	0.73 (0.63, 0.84)	1.9%	0.82 (0.71, 0.94)	3.1%

BMC Musculoskeletal Disorders 2011, 12:209

Mike Kolber

Aspirin in Primary Care
DTC 2013

Mike Kolber BSc, MD, CCFP, MSc
EBM Team, University of Alberta
Department of Family Medicine
Family Physician, Peace River, Alberta

Conflict of Interest

- Academic Family Physician with clinical work in Peace River, Alberta
- No funding from industry
- Supported by University of Alberta department of Family Medicine and Alberta College of Family Physicians

On Tap

- How many of your patients are using ASA?
- Are the right people taking ASA?
- Risks of ASA?
- Benefits and cases
- Post VTE, colorectal cancer, general cancers

Which of the following statements are true about ASA use in primary care today?

- ~40% of all patients ≥ 50 years old take ASA
- ASA use for 1' CV prevention > 2' CV prevention
- ~40% of patients with CVD are NOT taking ASA
- Many patients take ASA for primary CV prevention upon their FP's advise
- **All are true!**

Am J Prev Med 2006;30(1):74, Am J Prev Med 2007;32(5):403
Can Fam Phys 2013;59:55, Lancet 2011; 378: 1231

Risks and Benefits of ASA therapy

- Determine risks of ASA therapy
- Determine baseline CVD risk
- Determine potential benefit of ASA
- Make a decision with your patient's input

Risks: Medication Adverse Events and ER visits / Hospitalizations

- 1/15 UK admissions med AE[2]
  - Aspirin, diuretics, NSAIDs, warfarin
  - 28 deaths (15 GI bleeds, 2 perf DU, 5 ICH):
    - 22 deaths associated with ASA , NSAID or warfarin
- US[3]: estimated 99,000 admissions in 2 years
  - 67% from 4 meds: warfarin (33%), insulin~anti-platelets (13%) hypoglycemics (10%)

[2]BMJ 2004;329:15 [3]NEJM 2011;365:2002

Mike Kolber

Risks: Bleeding with ASA

- All bleeds[1]
  - Baseline risk 1.4% → 2.5% / 2.5 years
    → NNH ≈ 100 / 2.5 years or 250 / year
- Major Bleeds (admit, transfuse or death)[2]
  - 0.6–3.6/1000[3,4] ≈1/1000 →2/1000 → NNH ≈ 1000 / yr
- ICH ≈ 1/1000 ARI in 3-6 years[5,6]
- Bleed RFs: previous bleed, men, ↑age, other anti-platelets or anti-coagulants, or steroids[4]

[1]BMJ 2000; 321;1183 [2]Alim Pharm Ther 2006; 24; 897
[3]Denmark AM J Gastro 2000;95:2218, [4] Italy JAMA 2012;307(21):2286
[5]JAMA 2006;295:306 [6]JAMA 1998;280:1930

Secondary Prevention

- 900 year old 'male' previous smoker with AMI and PCI 6 years ago while battling Vader
- Meds: Ramapril, metoprolol, atorvastatin, metformin and ASA.
- Asking if still needs to take.

ASA for Secondary CV prevention

- **1000** patients with CVD on ASA (compared to placebo) over 2-3 years will have:
  - 33 less CV events
  - 14 fewer deaths
  - 9 additional major bleeds

→5-6 fewer events or death / 1 major bleed

Am J Med 2008;121:43, BMJ 2002;324:71–86

Mrs. L.S.

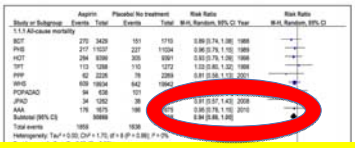
- 51 yo healthy mom comes to see you for a PHE. She starts with your medical student and states Dr. Oz said all > 50 years should take aspirin.
- No previous CVD, non-smoker, bp 130/78
  Lipids: HDL 1.2, LDL 3.4.
- Should she be taking ASA?

ASA Primary Prevention Guidelines

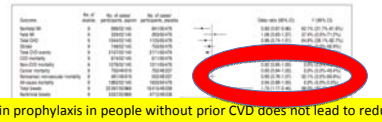
Guideline	ASA Recommended	Risk to which benefit > risk or special considerations
European 2012[1]	No	None
ACP 2012[2]	Yes	If > 50 years old (irrespective of risk)
CCVS 2011[3]	No	Consider for special circumstances (vascular risk high, bleed risk low)
TFP 2011[4]	No	Consider if 10 CVD year risk > 15%
USPSTF 2009[5]	Yes	Men 45-79 years if 10 year risk **CHD** > risk GI bleed[t] Women 55-79 years if 10 year risk **stroke** > risk GI Bleed[t]
BCMA 2008[6]	No	Consider if < 70 years AND 10-year CHD risk ≥ 20%.
ACP 2008[7]	Yes	10 year CVD risk > 10%

[1] European Heart J 2012;33:1635 [2]CHEST 2012; 141(2)(Suppl):e637S,
[3]Can J Cardio 2011; 27: S1–S59 [4]TFP # 31 2010, [5]Ann Intern Med. 2009;150:396,
[6]www.bcguidelines.ca, [7]CHEST 2008; 133:776S

2 Recent Systematic Reviews



"Aspirin reduced all-cause mortality"

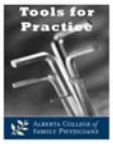


"Aspirin prophylaxis in people without prior CVD does not lead to reductions in cardiovascular death or cancer moratlity"

Am J Med 2011;124:621, Arch Intern Med 2012;172:209

Mike Kolber

August 9, 2010



ASA in Primary Prevention: Do the benefits outweigh risks?

Clinical Question: Are the benefits worth the risks of ASA in primary prevention (patients with no history of cardiovascular disease (CVD))?

Bottom-line: The majority of primary prevention patients will not benefit from daily ASA therapy. It is possible there is net benefit in higher-risk primary prevention patients. Although the best risk-level to initiate ASA is uncertain, it may be those with a 15% or more risk of CVD in 10 years.

Authors: G Michael Allan MD CCFP & Michael R. Kolber MD CCFP

Figure 2. Estimated MIs prevented and estimated harms of using aspirin for 10 years in a hypothetical cohort of 1000 men.

Variable	Estimated MIs Prevented (per 1000 Men), n		
	Age 45–59 Years	Age 60–69 Years	Age 70–79 Years
10-year CHD risk			
1%	3.2	3.2	3.2
2%	6.4	6.4	6.4
3%	9.6	9.6	9.6
4%	12.8	12.8	12.8
5%	16	16	16
6%	19.2	19.2	19.2
7%	22.4	22.4	22.4
8%	25.6	25.6	25.6
9%	28.8	28.8	28.8
10%	32	32	32
11%	35.2	35.2	35.2
12%	38.4	38.4	38.4
13%	41.6	41.6	41.6
14%	44.8	44.8	44.8
15%	48	48	48
16%	51.2	51.2	51.2
17%	54.4	54.4	54.4
18%	57.6	57.6	57.6
19%	60.8	60.8	60.8
20%	64	64	64
	Estimated Harms, n		
Type of event			
GI bleeding	8	24	36
Hemorrhagic stroke	1	1	1

Figure 4. Estimated number of strokes prevented and estimated harms of using aspirin for 10 years in a hypothetical cohort of 1000 women on the basis of age and 10-year stroke risk.

Variable	Estimated Strokes Prevented (per 1000 Women), n		
	Age 55–59 Years	Age 60–69 Years	Age 70–79 Years
10-year stroke risk			
1%	1.7	1.7	1.7
2%	3.4	3.4	3.4
3%	5.1	5.1	5.1
4%	6.8	6.8	6.8
5%	8.5	8.5	8.5
6%	10.2	10.2	10.2
7%	11.9	11.9	11.9
8%	13.6	13.6	13.6
9%	15.3	15.3	15.3
10%	17	17	17
11%	18.7	18.7	18.7
12%	20.4	20.4	20.4
13%	22.1	22.1	22.1
14%	23.8	23.8	23.8
15%	25.5	25.5	25.5
16%	27.2	27.2	27.2
17%	28.9	28.9	28.9
18%	30.6	30.6	30.6
19%	32.3	32.3	32.3
20%	34	34	34
	Estimated Harm, n		
Type of event			
GI bleeding	4	12	18

USPSTF Ann Intern Med. 2009;150:405

Aspirin for primary prevention of coronary heart disease (Protocol)

Jackson PR, Aarabi M, Wallis JE

THE COCHRANE COLLABORATION®

Initial Primary Prevention studies

- Low risk patients = low event rates
  - (2% > 10% 5 year CHD risk)
- Benefits small: RRR >> ARR
- No difference in CV or all-cause mortality
- Issues: healthy health care profs, stopped early, non-blinded, run ins
- All showed ↑ bleeding

BMJ 1988; 296(30): 313, NEJM 1989; 321: 129, Lancet 1998; 351: 233
Lancet 1998; 351: 1755, Lancet 2001; 357: 89, NEJM 2005;352:1293

Primary Prevention- ASA in ♀

- **Study details:** Meta-analysis[1]
  - 3 RCT (51 K women)
  - Dose 100mg q2days – 100mg OD
  - 6.4 years f/u
- **Outcomes**:
  - No diff in mortality
  - Overall: risk balance benefits.

NNT (and NNH)

outcome	♀
CVD	333
Bleed	400
Specific outcomes	
stroke	500
MI	-

JAMA 2006;295:306-313.

Primary Prevention – ASA in ♂

- **Study details:** Meta-analysis[1]
  - 5 RCT (44 K men)
  - Dose 75mg – 500mg OD (most low)
  - Mean 6.4 years f/u
- **Outcomes**:
  - No diff in mortality
  - Stat sign ↑ hemorrhagic strokes
  - Overall: risk balance benefits.

NNT (and NNH)

outcome	♂
CVD	270
Bleed	303
Specific outcomes	
Stroke*	-
MI	125

JAMA 2006;295:306-313.

Mike Kolber

10,000 primary prevention patients Treated with ASA for 1 year:

- 6 ↓ CV events
- 3 ↑ extra-cranial bleeds
- 1 ↑intracerebral hemmorhage

→ **For every 1 ↓ CVE, 1 ↑ AE**

Lancet 2009; 373: *1849*

RRR Primary Prevention

Drug	Total CV Events	CHD	Stroke	All cause Mortality
Aspirin: women	12%	No diff	17%	6% (NSS)
Aspririn: men	14%	32%	No diff	7% (NSS)
BP Meds[3,5]	20-30%	16%	36%	11%
Statin[1,2]	30%	30%	19%	10-15%
Smoking cessation[4]				90% if < 40 yo 66% if < 54 yo

[1]BMJ 2009;338:b2376 [2]Cochrane Reviews 2013, CD004816
[3]BMJ 2009;338:b1665 [4]NEJM 2013;368:341
[5]Cochrane 2009, Issue 3. CD001841

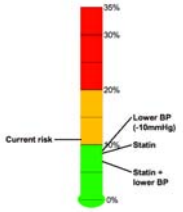
If wish to use ASA for 1' CV prevention "15% for 15%"

- RRR CV events 15%[1]
- Some patients will weigh CVD > bleeding
- Cost effectiveness 15-20%[2]
  - 10 year CVD risks
    - 5% x 0.15 RRR = 4.25%, ARD = 0.75%, NNT = 134
    - 15% x 0.15 RRR = 12.75%, ARD = 2% NNT = 50
    - 20% x 0.15 RRR = 17%, ARD = 3% NNT = 33

[1]Lancet 2009; 373: 1849, [2]Lancet 2009; 373:1821

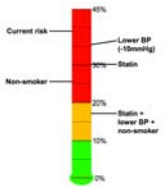
Mr. H.S.

- 53 yo male starship pilot, non-smoker, no CVD, lipids: HDL 1.2, TC 5.0, bp 128/78
- Should he be given ASA?
- 10 year risk = 9%



Mr. G. T.

- 62 yo male high stress job. No CVD but smokes 1 ppd. States if he quits his boss will kill him.
- His brother had a MI at 47 (same job)
- Bp 143/84, HDL 1.0, LDL 5.2.
- Should he consider ASA?



What about diabetics?

- Mr. J.H. 58 year old 'male' DM (dx 5 years ago), bp 142/86. Ex-smoker.
- Meds: atorvostatin, ramapril, metformin, viagra, flomax.
- Should he take ASA?

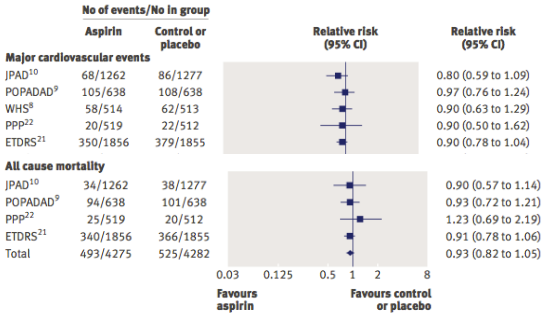
Mike Kolber

DM and ASA

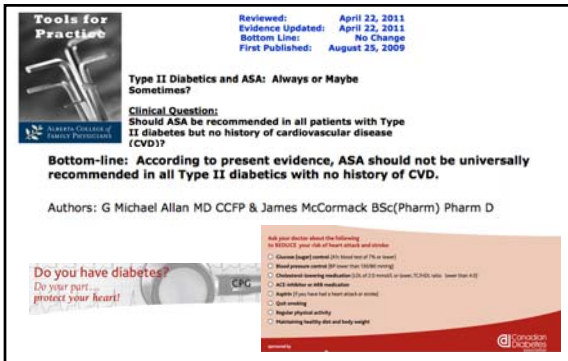
- PPP subgroup[1]: 1031 Italian DM ≥ 50 ASA or placebo
  - Stopped @3.7 yrs: MI ↓ in overall ASA group
  - Diabetics benefit < non-DM
    - **No diff: CV death, stroke or MI** (RR = 0.90: 0.50, 1.62)
    - NSS ↑ CV deaths
- POPADAD[2]: 1276 Scottish DM ≥ 40 yo with asymp. PVD, ASA or placebo, FU 6.7 yrs.
  - **no diff in CV events or death**
- JPAD[3]: 2500 Japan DM, RCT ASA vs placebo, FU 4.3 yrs
  - **No diff in CV events, all cause mortality**
  - > 65 yo: 2.9% ARD (NNT = 35)

[1]Diabetes Care 2003; 26: 3264, [2]BMJ 2008; 337a: 1840
[3]JAMA. 2008;300(18):2134 BMJ 2009;339:b4531 (SR)

ASA, 1'prevention and DM
Meta-analysis: 6 studies, 10,000 DMs



BMJ 2009;339:b4531

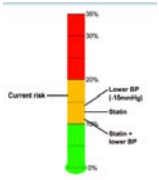


ADA Circulation 2010: "aspirin is reasonable in diabetics if the 10 year CVD risk is ≥ 10% who are not at increased risk of GI bleeding (previous bleed or on NSAIDs or warfarin. Assess risk and treat other risk factors"

Circulation 2010, 121:2694

Case #4 : Hypertension

- 66 yo quiet male always travelling. Bp 145/95, not keen on exercise or bp meds, but asks about ASA to prevent heart disease. Non diabetic, HDL 1.2, LDL 4.4



Hypertension and ASA

- HOT trial: ↑ Bleeds (0.7%) > ↓ MI (0.5%)
- NNH (154) > NNT (200) over 5 years
- No diff all cause or CV mortality
- "Antiplatelet therapy with ASA for 1' prevention in patients with elevated BP provides a benefit, (reduction in MI) which is negated by a harm of similar magnitude, increase in major hemorrhage".

Cochrane Reviews 2011, CD003186, *Lancet 1998; 351: 1755-62*

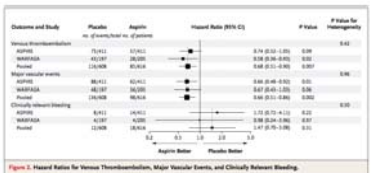
Mrs. Hatta Clot

- 44 year old with unprovoked DVT after a long space ship ride
- Treated for 6 months with warfarin
- You remember reading something about using ASA for preventing VTE recurrence
- Should she be offered ASA?

Mike Kolber

ASA post VTE

- 1200 unprovoked VTE, post warfarin 6-12/12 → RCT to ASA vs placebo, FU 2-3 years
- Recurrent VTE:
  - placebo 19.1%, ASA 13.8%, ARD = 5.3%, NNT = 19
- Similar rates of AEs, ↑ bleeding (NSS)



NEJM 2012;366:1959, NEJM 2012;367:1979

ASA and Colorectal Cancer

- Prevention:
  - USPSTF not recommended[1]
  - 2010[2]: CRC mortality ↓: NNT = 148 x 20 years for 1 CRC death
  - 10,000 patients given ASA for 20 years[3]:
    - 70 ↓ CRC deaths
    - 900 ↑ GI bleeds
    - 100-240 ↑ major GI bleeds (admit, transfuse or die)
- CRC treatment: ASA may ↓ mortality[4,5]
  - ARD = 5%, NNT = 20 x 5 years
  - Greater if cancer expresses certain mutations[6]

[1]USPSTF Ann Int Med 2007;146:361 [2]Lancet 2010: 376: 1741 [3]TFP # 47, 2011
[4]JAMA 2009; 302(6): 649 [5]British J of Cancer 2012; 106: 1564 [6]NEJM 2012;367:1596

ASA and All cancers

- Meta-analysis of 1' and 2' CV prevention trials
- Cancer mortality: 2.4% (ASA) vs 3.0% (no ASA)[1]
  - ARR = 0.6% NNT = 167 over 4-8 years to prevent 1 cancer death
  - Benefit only after 5 years of treatment
  - Absolute numbers: 327 vs. 347 (or 335 vs 351)
    - ↓ **15-20** / 25,000 patients
    - Better for GI cancers
- Re-look (included shorter RCTs)[2]: similar #s, no diff all-cause mortality
- Limitations: multiple comparisons, adjusting numbers (favors ASA) clinical significance

Interpretation Alongside the previously reported reduction by aspirin of the long-term risk of cancer death, the short-term reductions in cancer incidence and mortality and the decrease in risk of major extracranial bleeds with extended use, and their low case-fatality, add to the case for daily aspirin in prevention of cancer.

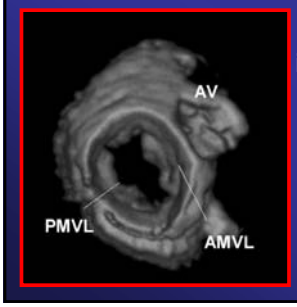
[1]Lancet 2011; 377: 31, [2]Lancet 2012; 379: 1602

Aspirin in Primary Care Summary

Primary CV Prevention	No: benefit ⍰ potential harm Treat other risk factors first Consider if 10 year CVD risk > 15%
Primary: Diabetics	Not always, treat other risk factors first Consider if 10 year CVD risk > 15% or > 65 yo
Primary: Hypertension	No, benefit ⍰ potential harm Treat other risk factors first Consider if 10 year CVD risk > 15%
Secondary CV Prevention	Yes, NNT 30 in 3 years (CVE), 71 (mortality)
VTE post warfarin therapy	Offer NNT 19 over 2-3 years (recurrent VTE)
CRC prevention	No, potential benefit < potential harms
CRC treatment	Consider (not RCT): NNT 25 over 5 years (mortality)
All cancer prevention	No, potential benefit ⍰< potential harms

Ken Gin

24th Annual Drug Therapy Course



The Top Trials in Cardiology 2012/13

Ken Gin
April 13/2013

Disclosures

Research with Astra Zeneca

Advisory Board ACS Working Group BI

"If the lights stay on for more than 4 hours, call the Erectrician"

- Use of Digoxin in AF
- Duration of B blocker in stable CAD
- Is chelation effective?
- Is low Na diet useful in CHF?
- Does Omega 3 prevent CV events?
- Do multivitamins reduce CV events?
- Is PCI or CABG better in diabetics? Non diabetics?
- Target BP in DM?

Digoxin in AF

AFFIRM
4060 Pts. with AF
High risk of stroke

Rate | Mean F/U 3.5 yrs | Rhythm

Rate control as good as rhythm control and much simpler.

Rate control strategy now preferred in most pts.

Rate control in AF

B Blockers | Ca Blockers | Digoxin

Surveys:Digoxin used in 35-70% of pts. with AF
Narrow therapeutic index
Increased levels assoc. with increased mortality

European Heart J
Sept 27/2012

AFFIRM
4060 Pts.

69.4% Digoxin | 666 Deaths | 30.6% No Digoxin

All cause mortality HR 1.41(1.19-1.67) p<0.001
CV Mortality HR 1.35(1.06-1.71) p=0.016
Arrhythmic mortality HR 1.61(1.12-2.30) p=0.009

All cause mortality CHF HR 1.37(1.05-1.79) p=0.19
All cause mortality No CHF HR 1.41(1.09-1.84) p=0.01

No interaction with gender

Digoxin use associated with increased mortality in AF
No information on drug levels/renal function
New guidelines suggest THR <100 rather than 80bpm

B-blockers in Stable CAD

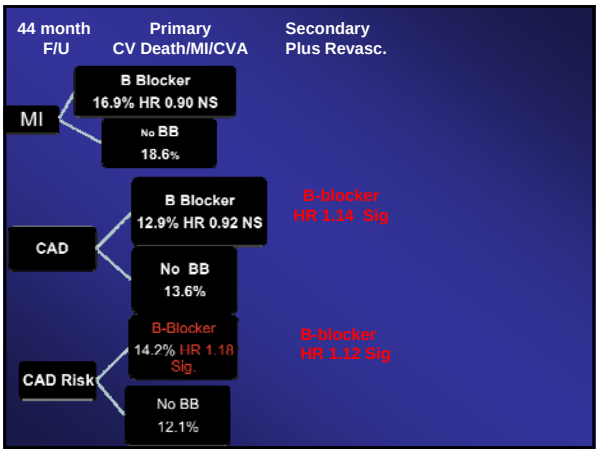
JAMA Oct 2/ 2012

- Data showing benefit of B Blockers based on old studies
- B Blocker beneficial in acute MI
- Duration of B blocker use unknown

- Analysis of REduction in Atherothrombosis for Continued Health registry
  - 44,708 pts
  - 14,043 prior MI(31%)
  - 12,012 CAD, no MI(27%)
  - 18,653 CAD risk factors(42%)

Mean F/U 44 months

Ken Gin



Other recommendations

- AHA Class I. Post MI x 3 yrs. / CHF EF<40%
- AHA Class IIb. Chronic therapy for all other pts.
- ESC recommend long term use only if poor LV function
- CHEP BB not first line for hypertension >60yrs
- No modern randomized studies of BB in modern era of modern medical and reperfusion therapy.

This study supports less use of B blockers.
Level of evidence: Moderate.
No proof of mortality benefit in stable CAD.
Post MI continue B-blocker if poor LV function.

Trial to Assess Chelation Therapy

NIH sponsored
Presented AHA Nov 2012

Planned 2372 pts Post AMI
F/U 1 yr

40 x 3 hour infusion
EDTA/ascorbic acid/MgCl/
B vitamins/procainamide/
heparin

Placebo
Saline
+
glucose

Slow recruitment
Trial stopped and restarted/change in endpoints
1708 pts extended F/U 4 yrs

65% completed 40 infusions
17% dropout

1º endpoint
All cause mortality
MI/CVA/
Coronary revasc.
Hospital. for angina

26.5% 30%

Overall HR 0.82 CI 0.69-0.99 p=0.035(Pre-specified Sig p<0.036)
Main effect= decreased revasc.
31% Diabetics HR0.61 CI 0.45-0.83 p=0.02
69% Non Diabetics HR 0.96 (CI 0.77-1.20 p=0.725
No effect on QOL

AHA Position

"As intriguing as the results are, they're unexpected, and should not be interpreted to adopt chelation therapy into clinical practice.

Much more information is needed about which elements of the complex infusion mixture might provide benefit: the marked discordance between the observed treatment effect in diabetics vs. non diabetics needs to be understood…

TACT raises more questions that must be answered before we are ready to act…"

Low Sodium diet in CHF

Heart Aug 21/2012

- Guidelines suggest low Na diet to reduce CHF admissions
- Possible adverse neurohormonal activation

Meta-analysis of randomized trials
of restricted vs control diet
2747 pts. with systolic CHF

	Low Na diet 1.8 grams	Normal Na diet 2.8 grams/day
All cause mortality	RR 1.95 (1.66-2.29)	
Sudden death	RR 1.72 (1.21-2.44)	
CHF Death	RR 2.23 (1.77-2.81)	
CHF readmissions	RR 2.10 (1.67-2.64)	

Conclusion: Compared to a normal Na diet, a low Na diet increases CV morbidity and mortality
Level of evidence:Moderate

Meta-analysis
Omega-3 and CV Events

JAMA Sept 12/2012

Omega 3 1.51 g/day
EPA 0.77 g/day
DHA 0.06 g/day

Randomized clinical trials of Omega 3 > 1Yr
20 studies (13 secondary)
68,680 pts
Two trials dietary counseling
Seventeen trials supplements
Mean duration 2 years (longest 6.2 yrs)

	No. events	RR	p
Deaths	7044	0.96	NS
CV Death	3993	0.91	NS
Sudden death	1150	0.87	NS
MI	1837	0.89	NS
Stroke	1490	1.05	NS

Ken Gin

- Initial studies(1989) demonstrate benefit of omega 3 in reducing CV events
- Later studies show diminishing benefit and non-significance
- Current analysis shows no benefit of omega 3 in reducing mortality/CV mortality/MI/stroke
- Studies consistent over past 5 yrs.

Do Vitamins reduce CVD?

24 billion $ in heath supplement sales in 2008
1/3 of US pop'n takes daily multivitamin

JAMA 2012

Physicians Health Study
Launched 1997
14,641 male physicians>50 yrs
5% had Hx of MI/CVA

Median F/U 11.2 yrs: 1732 CV events

	Multivitamin	Placebo	
Major CV events	11/1000 Pt-yrs	10.8/1000 Pt-yrs	NS

Long term treatment with multivitamins did not reduce MI/ CVA/ CHF/Angina/ Coronary revasc. / CV mortality/ All cause mortality

Multivitamins and cancer

Physicians Health Study
Launched 1997
14,641 male physicians>50 yrs
1312 had Hx of cancer

Median F/U 11.2 yrs: 1732 CV events

	Multivitamin	Placebo		
Cancer	17.0/1000 Pt-yrs	18.3/1000 Pt-yrs	HR0.92	p=0.04

Multivitamins modestly decreased cancers, but not prostate or colorectal. No difference in cancer related mortality.

CABG vs. Stenting in Multi-Vessel disease

- Previous studies short term F/U 1-2 years
- No difference in hard outcomes
- 2 Recent studies of modern stenting vs. modern CABG

SYNTAX 5 yr results

1800 pts. complex CAD
Europe/US

1095 Pts. 3 VD

549 pts.
CABG
IMA grafts

546 pts.
DES 1st Taxus

MAACE	24.2%	37.5%	p<0.001
Mortality	9.2%	14.6%	p=0.006
CV Death	4.0%	9.2%	p<0.001
MI	3.3%	10.6%	p<0.001
CVA	3.4%	3.0%	p 0.66
Revasc.	12.6%	25.4%	p<0.001

In pts with 3 VD, CABG superior to stenting with 35% reduction in death, 66% reduction in MI, and 50% reduction in need for repeat revasularization

DES=CABG in lowest 20% of SYNTAX scores.

Future Revasc. Eval. Diabetics Optimal Management

NEJM Dec 20/2012

32,966 screened

3309 eligible

1900 enrolled

1900 DM
>70% in 2 or more major coronary A.
LMCA excluded
Mean Age 63.1 Yrs (83% 3VD)

Intense Medical Rx

	DES DAPT>12 months	CABG 94.4% IMA graft	Mean F/U 3.8 Yrs
5 Yr. Outcomes			
1⁰ Death/MI/CVA	26.6%	18.7%(RRR 30%)	p=0.005
Death	16.3%	10.9%	p=0.049
MI	13.9%	6.0%	p<0.001
Stroke	2.4%	5.2%	p=0.03

Ken Gin

- In diabetics with multi-vessel disease, CABG vs PCI is associated with a 30% decrease in death/MI/CVA.
- Absolute reduction 7.9%

Based on new evidence, most pts with multi-vessel disease should be treated with CABG rather than PCI

Level of evidence:Strong

ACCORD BP

NEJM March 14/2010

10,251 Type II DM <80 yrs.
>40 and CVD or >55 and 2 risk factors

4733 Cr<132 (1.49) / 24 hr. protein<1.0 gram
SBP 130-180 mmHg
3 or less BP medications

62.2 yrs.
47.7% women
33.7% CVD
139.2/76.0

	Intensive <120mmHg	Standard <140mmHg	
SBP	119.7/64.4	133.5/70.2	-14.2/6.1
# Meds	3.4	2.1	
K+/Cr/ Syncope	3.3%	1.1%	p<0.001

Mean F/U 4.7 Yrs.

	Intensive <120mmHg	Standard <140mmHg	
1^{0}MI/CVA/ CV Death	1.87%/Yr.	2.09%/Yr.	-12% p=0.20
Death	1.28%/Yr.	1.19%/Yr.	+ 7% p=0.55
CVA	0.32%/Yr.	0.53%/Yr.	-41% p=0.01

Lowering SBP< 140mmHg did not reduce CV Death or MI.
There was a decrease in CVA.
NNT 89 x 5 yrs to prevent one CVA
Intensive BP lowering required more medication and caused more side effects

ACCORD EYE

SBP 137mmHg

NEJM July 13/2010

	SBP Target <120mmHg SBP 117 mmHg	SBP Target<140mmHg SBP 133 mmHg	
Progression	10.4%	8.8%	HR 1.23 p=0.29
Mod. visual loss	19.4%	15.8%	HR 1.27 p=0.06

UKPDS SBP <150mmHg <180mmHg F/U 7.5 yrs.
Progression 34% 51.3% p=0.004
Mod visual loss 10.2% 19.4% p=0.004

ADVANCE No benefit SBP difference 5.6mmHg

No benefit of aggressive BP control on retinopathy

Duration of study too short? Study underpowered?

No benefit of very low BP?

2013 ADA Guidelines

Diabetes Care Jan 2013

- Most diabetics should be targeted to BP of 140/80mmHg
- Lower target 130/80mmHg may be appropriate for younger pts. if achievable without undue burden
- CHEP 2012 guidelines target 130/80mmHg

Digoxin in AF
Less use

Duration of B blocker in stable CAD
3 yrs post MI if no ischemia/CHF/EF>40%

Is chelation effective?
Inconclusive but possible

Is low Na diet useful in CHF?
Not proven

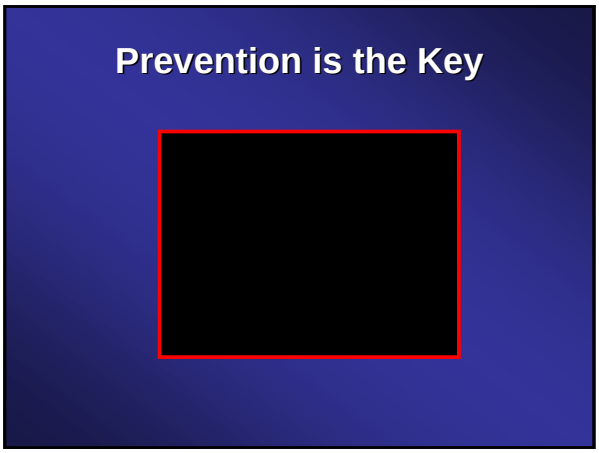
Does Omega 3 prevent CV events?
No

Does multivitamin reduce CV Events?
No, but slight reduction in new cancers

Is PCI or CABG better in diabetics? Non-diabetics?
CABG

Target BP in DM?
140/80mmHg in most pts.

Ken Gin



Andrew Merkur

Keeping an eye out on diabetic retinopathy

James McCormack

Why regularly repeating BMD, LDL, and SBP is BAD medicine

James McCormack
B.Sc. (Pharm), Pharm.D.
Professor
University of British Columbia
Vancouver
BC, Canada

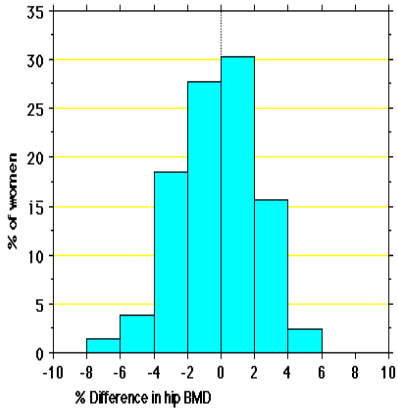
CMAJ REVIEW

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"

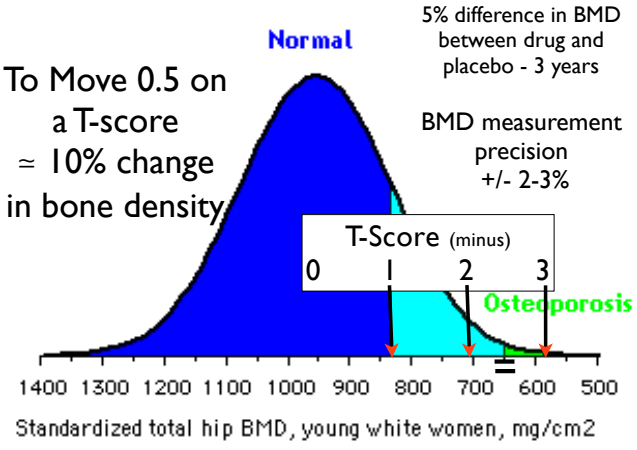
"For individuals with low risk of fracture and without additional risk factors for rapid loss of bone mineral density, a testing interval of 5–10 years may be sufficient"

BONE DENSITY
There are NO studies that have looked at getting patients to different BMDs and seeing if that makes a clinically important difference



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

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



5% difference in BMD between drug and placebo - 3 years

BMD measurement precision +/- 2-3%

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"

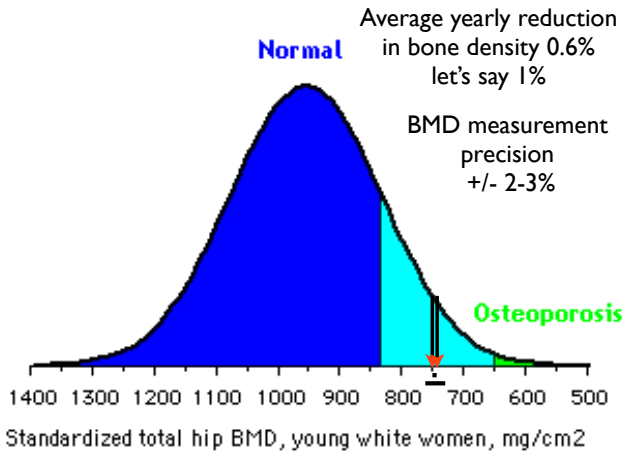
BMJ 2009;338;b2266

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

James McCormack



Other Smarter People

Evaluating the Value of Repeat Bone Mineral Density Measurement and Prediction of Fractures in Older Women

The Study of Osteoporotic Fractures

Teresa A. Hillier, MD, MS; Katie L. Stone, PhD; Doug C. Bauer, MD; Joanne H. Rizzo, MS; Kathryn L. Pedula, MS; Jane A. Cauley, DrPH; Kristine E. Ensrud, MD, MPH; Marc C. Hochberg, MD; Steve R. Cummings, MD

Arch Intern Med. 2007;167(2):155-160.

"repeat BMD [8 years] measurement provides little additional benefit as a screening tool"

Average bone loss/year 0.6%

Arch Intern Med 2007;167:155-6

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

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

+/- 2.0%

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

+/- 2.0% to 4%

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

+/- > 4%

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

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

2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

"The frequency of follow-up measurements is debated but should probably be performed semiannually, or with any changes in lipid-lowering therapy"

CHOLESTEROL

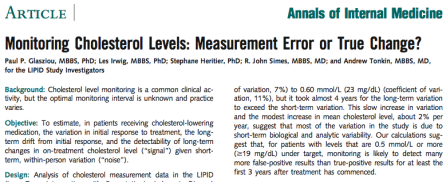
There are NO large studies that have looked at getting patients to different cholesterol levels

Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes
The SANDS Randomized Trial

3 years - 499 American Indian men and women aged 40 years or older with type 2 diabetes and no prior CVD events
Results - surrogates improved - no change in clinical outcomes

JAMA 2008;299:1678-89

James McCormack



ARTICLE | Annals of Internal Medicine

Monitoring Cholesterol Levels: Measurement Error or True Change?

Paul P. Glasziou, MBBS, PhD; Les Irwig, MBBS, PhD; Stephane Heritier, PhD; R. John Simes, MBBS, MD; and Andrew Tonkin, MBBS, MD, for the LIPID Study Investigators

Background: Cholesterol level monitoring is a common clinical activity, but the optimal monitoring interval is unknown and practice varies.

Objective: To estimate, in patients receiving cholesterol-lowering medication, the variation in initial response to treatment, the long-term drift from initial response, and the detectability of long-term changes in on-treatment cholesterol level ("signal") given short-term, within-person variation ("noise").

Design: Analysis of cholesterol measurement data in the LIPID

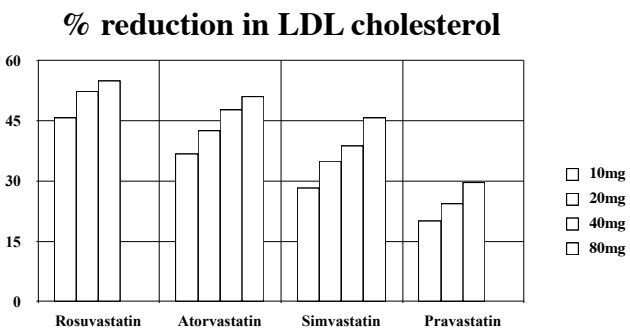
of variation, 7%) to 0.60 mmol/L (23 mg/dL) (coefficient of variation, 11%), but it took almost 4 years for the long-term variation to exceed the short-term variation. This slow increase in variation and the modest increase in mean cholesterol level, about 2% per year, suggest that most of the variation in the study is due to short-term biological and analytic variability. Our calculations suggest that, for patients with levels that are 0.5 mmol/L or more (≥19 mg/dL) under target, monitoring is likely to detect many more false-positive results than true-positive results for at least the first 3 years after treatment has commenced.

"After initial change only measure every 3-5 years"

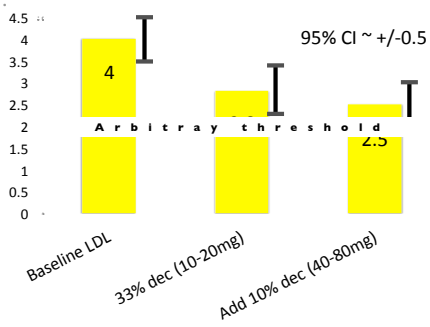
Average increase in chol is 0.5-1%/year

Within-person coefficient of variation is ~7%
Single measurement - 95% CI
Total chol ~ - 0.80 to 0.80 mmol/L
LDL chol ~ - 0.5 to 0.5 mmol/L

Ann Intern Med 2008;148:656-61



LDL cholesterol mmol/L



Statins in secondary prevention

10-20 mg - 5-6% ARR in MIs and strokes

Inc. dose 4-8X you get an additional 1-2% ARR

short-term variability - a combination of analytic variability and week-to-week biological fluctuation around a stable average

BLOOD PRESSURE
Less than 135/85 "Despite a -4/-3 mmHg greater achieved reduction in systolic/diastolic BP, attempting to achieve "lower targets" instead of "standard targets" did not change total mortality, MI, stroke, CHF, major CV events or ESRD"

Cochrane Review 2009;Issue 3:CD004349

AJH American Journal of Hypertension

Editorial

American Journal of Hypertension (2008) 21 3–4; doi:10.1038/ajh.2007.20

Blood Pressure Variability: The Challenge of Variation

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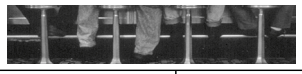
Need changes of at least 10/5 mmHg before you can say there has been a change

Am J Hyper 2008;21:3–4

"clinicians cannot identify individuals who have good or poor responses to drugs. A sample size calculation reveals that some 40 office blood pressure measurements are required both before and after prescription to be reasonably confident of detecting a true reduction of 5 mmHg"

Br J Gen Pract 2010; 60: 675–80

The Bottom Line



	Bone density	Cholesterol
Before treatment	If pt would consider treatment one time measurement translate T-score into 10-year fracture risk	If pt would consider treatment one time measurement translate cholesterol into 10-year CVD risk
After treatment	Don't bother as the test just isn't precise enough	Don't bother because all you can do is raise the statin dose - that decision should be based on magnitude of CVD reduction not cholesterol

The New Therapeutics: Ten Commandments

Thou shalt treat according to level of risk rather than level of risk factor.

Thou shalt exercise caution when adding drugs to existing polypharmacy.

Thou shalt consider benefits of drugs as proven only by hard endpoint studies.

Thou shalt not bow down to surrogate endpoints, for these are but graven images.

Thou shalt not worship Treatment Targets, for these are but the creations of Committees.

Thou shalt apply a pinch of salt to Relative Risk Reductions, regardless of P values, for the population of their provenance may bear little relationship to thy daily clientele.

Thou shalt honour the Numbers Needed to Treat, for therein rest the clues to patient-relevant information and to treatment costs.

Thou shalt not see detailmen, nor covet an Educational Symposium in a luxury setting.

Thou shalt share decisions on treatment options with the patient in the light of estimates of the individual's likely risks and benefits.

Honour the elderly patient, for although this is where the greatest levels of risk reside, so do the greatest hazards of many treatments.

Thanks for your questions and discussion.

Thanks for completing your course evaluations.

HAVE A SAFE TRIP HOME

We hope to see you next year!