25th ANNUAL DRUG THERAPY DECISION MAKING COURSE

April 11th and 12th, 2014
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
Steven Bellemare, Physician Risk Manager, CMPA, Ottawa, Ontario
Alan Cassels, Adj. Prof., Human and Social Development, University of Victoria, Victoria, BC.
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Asst. Prof., Family Medicine, University of Alberta
Victor Montori, Prof., Medicine, Mayo Clinic, Rochester, Minnesota

Local Faculty

Hannah Briemberg, Clin. Assoc. Prof., Medicine, Neurology, VGH & UBC
Martin Dawes, Prof. and Head, Dept. of Family Practice, UBC
Ken Gin, Clin. Prof., Medicine, Cardiology, UBC & VGH
Andrew Krahn, Prof. and Head, Div. of Cardiology, UBC
Peter Loewen, Assoc. Prof., Pharm. Sciences, UBC & VCHA
Val Montessori, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC

PHC – Providence Health Care
UBC – University of British Columbia
VCHA – Vancouver Coastal Health Authority
VGH – Vancouver General Hospital

25th Annual

DRUG THERAPY DECISION MAKING COURSE

Saturday, April 12, 2014

07:30 Registration (Muffins & Coffee)

Chairs - Bob Rangno and James McCormack

"HOOF HEARTED"

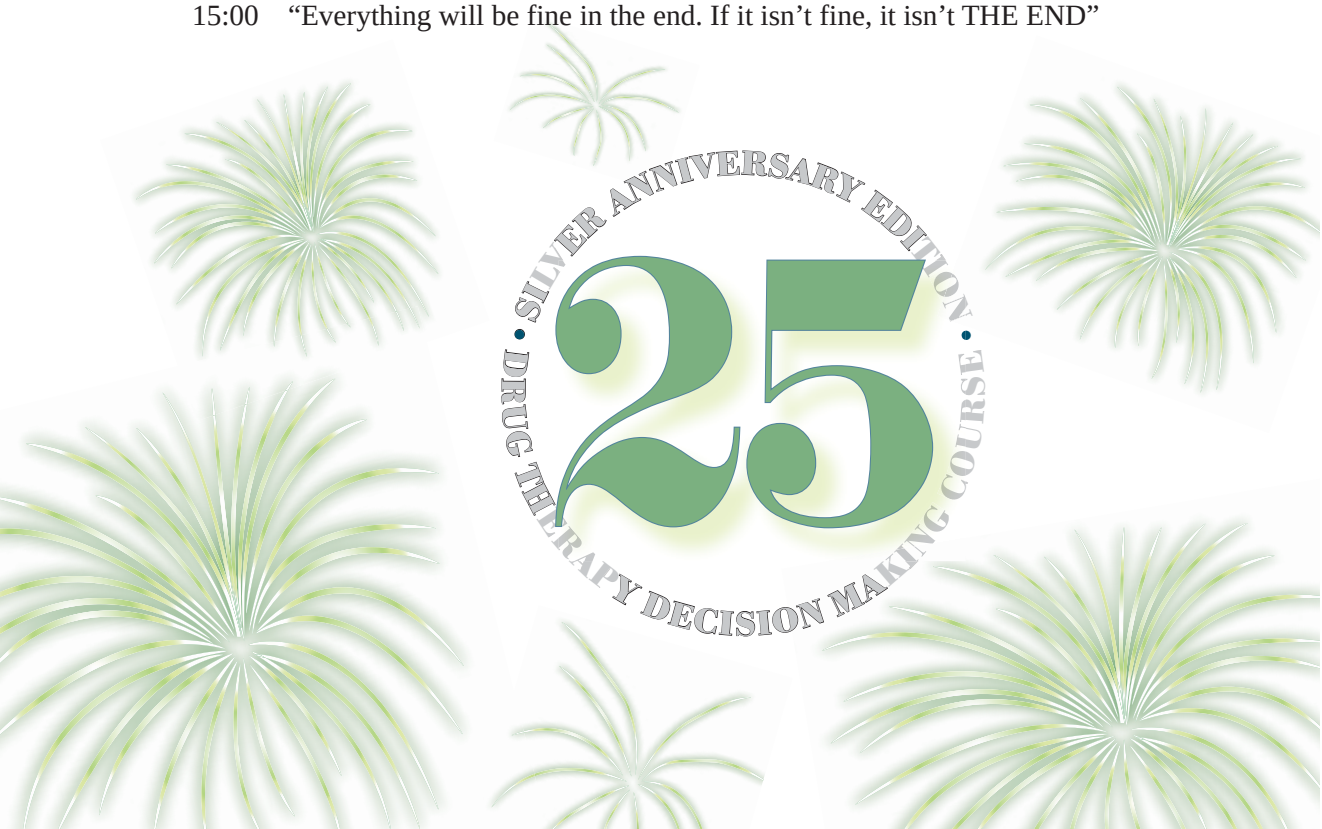
08:30	A Fib – how to control Silver's galloping heart – how to stop a fibrillating affair	Ken Gin
08:50	Warfarin versus NOAC – the shootout at the OK corral	Ken Gin
09:10	CVD risk reduction – the one with the most birthdays wins	James McCormack
09:30	Questions	
09:50	Refreshment Break	

"HOOF HEARTED #2"

10:10	Syncope – still falling for you after all these years	Andrew Krahn
10:30	Unmasking lone blood pressures	Martin Dawes
10:50	Questions	
11:10	Statin myalgias – when the pain in your muscles is worse than the pain in your heart	Hannah Briemberg
11:30	Questions	
11:50	Lunch	

"THE ENDING OVERTURE WILL TELL"

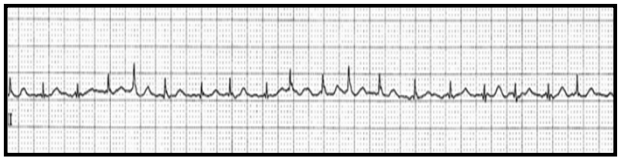
12:40	Sweet justice is what I seek – type 2 diabetes	Victor Montori
13:10	Media-um well done	Alan Cassels and James McCormack
13:40	Myth-busting – the silver anniversary game show edition	The Gang plus the Audience
15:00	"Everything will be fine in the end. If it isn't fine, it isn't THE END"	



Ken Gin

25th Annual
Drug Therapy Decision Making Course

Approach to Atrial Fibrillation



Ken Gin
April 12 2014

Disclosures

BI	**ACS Working Group/ Advisory Board**
Bayer	**Advisory board/PIONEER Study**
FOREST	**Advisory Board**
BMS	**Advisory Board**

Recommendations are Guidelines Based
No recommendations about specific NOAC

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

Objectives

- **To understand the clinical impact of atrial fibrillation on vascular events**
- **Review changes in atrial fibrillation management in 2012 and beyond:**
  - **Rate vs. Rhythm** Rate control preferred
  - **Antiarrhythmic therapy** Not effective 1/3 to ½ recur in 1 yr.
  - **AF ablation** High risk of recurrence over 5 yrs.
  - **Role of rate control** THR<100bpm
  - **New anticoagulation strategies** Less ASA/4 new agents
  - **Novel Devices** Phase 3/ promising initial results
  - **AF Clinics** Available

Case Mrs Anne Gina

Healthy 67 year old female Intermittent palpitations x 4 months
ECG demonstrates AF VR 130
BP 130/90. Overweight. BMI 35.
Otherwise normal

Assess risk of stroke
Assess bleeding risk
Assess best way to prevent stroke
Rate vs Rhythm
Routine investigations
Newer options

How Serious is AF?

Risk of stroke 1-20%/year

Average 5%/yr.

AF Is An Independent Risk Factor for Stroke

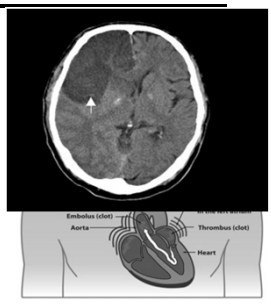
AF patients have a near 5-fold increased risk of stroke.

1 in every 6 strokes occurs in a patient with AF.

Stroke risk persists even in asymptomatic AF.

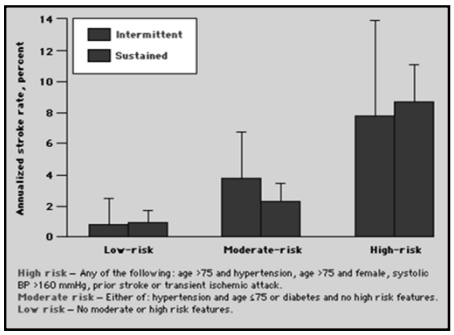
Ischemic stroke associated with AF is typically more severe than stroke due to other etiologies.

More death and disabilities



Ken Gin

Intermittent vs. Sustained AF



Recent studies Suggest 6 minutes of continuous AF increases risk of stroke by 2.5 fold

ASSERT Trial
NEJM Jan 12 2012

The $CHADS_2$ Index

Stroke Risk Score for Atrial Fibrillation

CHF(EF<40%)/Hypertension/Age>75/DM/Stroke

	Score (points)	Risk of Stroke (%/year)	
Approximate Risk threshold for Anticoagulation	0	1.9	ASA
	1	2.8	OAC > ASA
	2	4.0	OAC
	3	5.9	
	4	8.5	
	5	12.5	
	6	18.2	

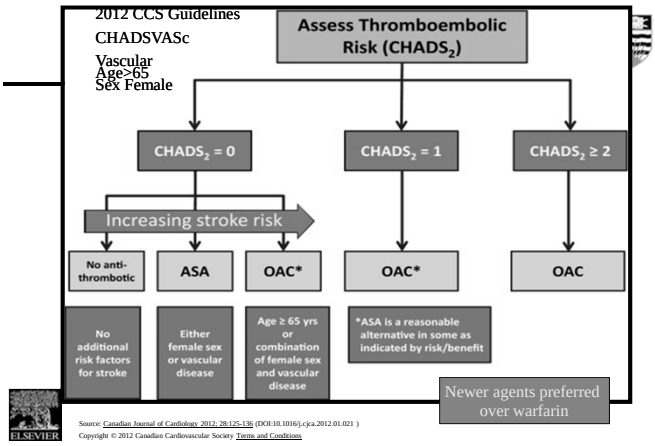
If CHADS 0 – 1, calculate CHADS 2

If CHADS2 = 0, Calculate CHADS-VASc score

CHADS2 = 0 Annual risk of stroke 1.9%

V = vascular disease(MI, Complex atheroma/PVD)
A = Age 65
S = Female sex

VASc score	Annual risk of stroke
0	0%/Yr.
1	1.3%/Yr.
2	2.2%/Yr.
3	3.2%/Yr.



HAS-BLED

Score of 3/9 = High Risk of bleed

Letter	Characteristic	
H	Hypertension>160mmHg	1
A	AbN renal (Cr>200) or liver Bili 2x / AST/alk phos. 3x or cirrhosis	1 or 2
S	Stroke	1
B	Bleeding Hx/anemia	1
L	Labile INR TTR<60%	1
E	Elderly> 65	1
D	Drugs (e.g. Antiplatelets/NSAIDS) or EToH>8 units/week	1 or 2

HAS-BLED score

Major bleed = requiring hospitalization/ Hb drop>20 / transfusion

Risk score	Bleeds/100 Pt. Yrs.
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5
6	-
7	-
8	-
9	-

Ken Gin

ASA Dose?

- 75 -100mg is as beneficial as 325 mg od with less bleeding
- ASA reduces stroke by 22%
  - -reduces non disabling stroke by 29%
  - -reduces disabling stroke by only 13%
- ASA less effective in pts >75 yrs

Meta-analysis anti-thrombotics for AF
Ann Int. Med 1999, 131:492-501

Real world study of AF

Thrombosis and Haemostasis 2011

CHADS2
CHADSVASc
HASBLED

132,372 Pts. Non-valvular AF
Denmark
1997-2008

Thromboembolism

VKA(28.3%)	ASA(18.9%)	No Rx(44.5%)	VKA/ASA(8.4%)
HR 1.0	1.81	1.86	1.14

Major bleeding

VKA(28.3%)	ASA(18.9%)	No Rx(44.5%)	VKA/ASA(8.4%)
HR 1.0	0.93	0.84	1.64

Largest real world cohort study of AF

Up to 12 year F/U

Randomized studies enrolled 10% of pts.

ASA is not beneficial for any pts. with AF

Risk of ASA induced bleeding only slightly lower than VKA

Combination VKA/ASA not more effective than VKA alone with 64% more bleeding

Presented ESC Aug 31/2010 Apixaban = FactorXa inhibitor

AVERROES

5600 pts. AF and 1 risk factor for CVA
Unsuitable for VKA therapy

Mean age 70
Mean CHADS 2.1

	Apixaban 5mg bid 2.5 mg bid in some	ASA 81-324 mg od (91% 162 mg od)	
CVA	1.7%/yr.	3.6%/yr.	RRR 0.48 p<0.001
Major bleed	1.4%/yr.	1.2%/yr.	RR 1.14 p=0.45
ICH	0.4%/yr.	0.3%/yr.	RR 1.09 p=0.83

NNT 53/yr. to prevent a stroke
NNH 500/yr. to cause major bleed (Hb drop by 20, 2 unit prbc, ICH, Fatal bleed)

AVERROES

Apixaban compared to ASA

NNT 53/yr. to prevent a stroke
NNH 500/yr. to cause major bleed (Hb drop by 20, 2 unit prbc, ICH, Fatal bleed)

1000 Pts. treated for one year prevents 18 strokes (mostly larger)/ 10 deaths and 31 CV hospitalizations

At a cost of 2 major bleeds (NS)

3.20 x 365 x 53 = $61,904
BURST Study 2010 $50,000 in first 6 months post stroke

How effective is ASA and Warfarin in reducing CVA?

Primary ASA 22%	Primary Coumadin 68%
Secondary 30%	Secondary 80%

Average Dose = 4 mg

Ken Gin

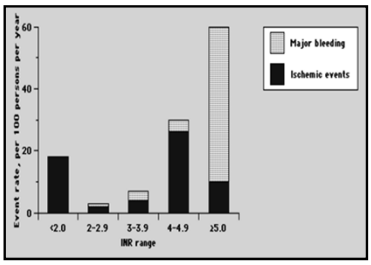
Warfarin in Special situations

Low Target INR

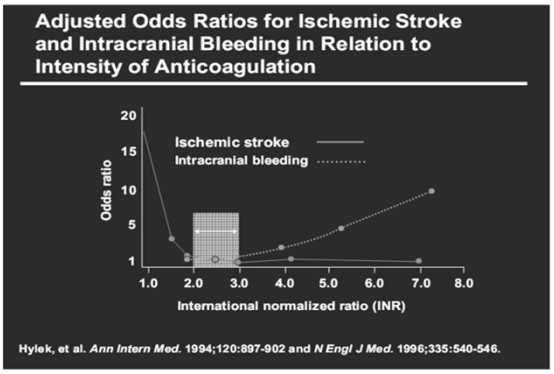
INR 1.5-2
CVA risk 2x INR 2-3

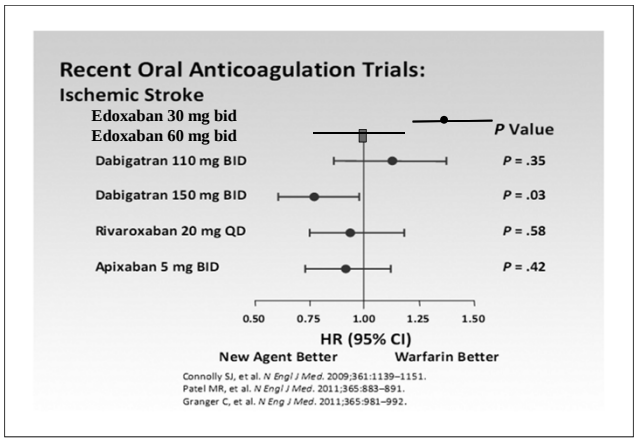
Labile INR

TTR usually 60-65%
If TTR< 60%, benefit of Coumadin reduced.
Bleeding increased

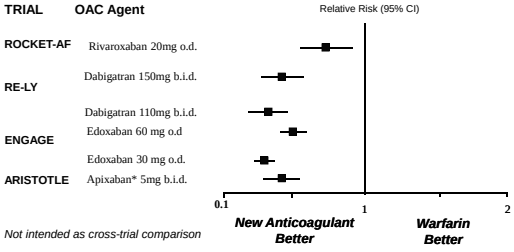


Warfarin reduces CVA by 62%





Novel Oral Anticoagulants vs. Warfarin† Intracranial hemorrhage

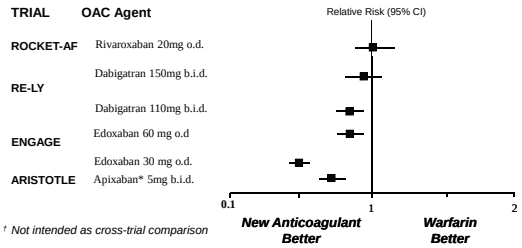


† Not intended as cross-trial comparison

Data obtained from intention-to-treat analysis

Connolly SJ, et al; for the RE-LY Steering Committee and Investigators. *N Engl J Med.* 2009;361:1139-51;
Connolly SJ, et al; for the RE-LY Investigators. *N Engl J Med.* 2011;363(19):1875-6. (updated);
Patel MR, et al; and the ROCKET AF Steering Committee for the ROCKET AF Investigators. *N Engl J Med.* 2011;365:883-91;
Granger CB, et al; for the ARISTOTLE Committees and Investigators. *N Engl J Med.* 2011; 365:981-92.
Giugliano RP, et al; for the ENGAGE AF-TIMI 48 Investigators. N Engl J Med. 2013. Nov 19

Novel Oral Anticoagulants vs. Warfarin† Major Bleeds



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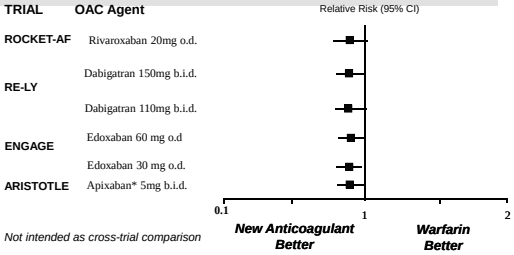
Novel Oral Anticoagulants vs Warfarin† All-cause mortality

The new OAC agents are consistently associated with a numerically lower risk for all-cause mortality compared to warfarin.†



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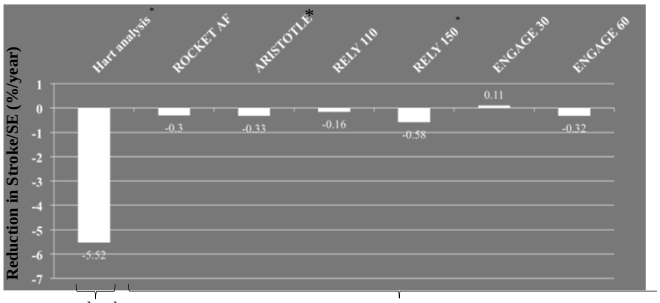
Ken Gin

Absolute Reduction in Stroke/SE†



Data obtained from intention-to-treat analysis

† Not intended as cross-trial comparison
* Statistically Significant

Xarelto® PM, 2013; Eliquis® PM, 2012; Pradaxa® PM, 2012; Hart 2007; Giugliano RP, et al; for the ENGAGE AF-TIMI 48 Investigators. N Engl J Med. 2013. Nov 19

NOAC Meta-analysis Lancet Dec 2013 Online

71,683 Pts. 4 agents
NOAC vs. Warfarin for AF

High Dose	NOAC	NNT
Stroke/SE	-19% p<0.0001	147
Major bleed	-15%	110
GI bleed	+25%p=0.04	185 NNH
Mortality	-10%	
Low Dose		
Stroke/SE	+3% NS	Same
Major bleed	-35%	??

Lack of Trust in "new product" by Pts. and Doctors
Number of Pts. in Randomized Trials

How many pts in Coumadin studies?
How many pts in new OAC studies?

Warfarin vs. Placebo	**2,900 Pts**
ASA vs. Placebo	**3,990 Pts**
Warfarin vs. ASA	**3,647 Pts**
Apixiban vs. ASA	**5,500 Pts**
New OAC vs. Warfarin	**72,000 Pts**

Warfarin is still a good drug

No benefit of NOAC if TTR >74%

Strong benefit if TTR<55%

KR study of INRs from life lab TTR in Vancouver 55%

Special populations

Non Valvular AF(Cannot use in mitral stenosis)
ACS/stenting Guidelines recommend warfarin
Renal failure
GFR<30 Use Warfarin
If on dialysis, No treatment?

If using warfarin or NOAC in stable CAD, ASA is not required.

Dabigitran for Cardioversion

Circulation Jan 3/2011

Retrospective substudy of RELY
18,113 Pts with AF
1983 cardioversions 86% DC/ 14% Drug
TEE encouraged

	Dabigitran 110 bid	Dabigitran 150bid	Coumadin	
TEE	**25.5%**	**24.1%**	**13.3%**	
Thrombus	**1.8%**	**1.2%**	**1.1%**	
Rx >3 weeks	**76.4%**	**79.2%**	**85.5%**	**Sig.**
CVA/SE 30 days	**0.8%**	**0.3%**	**0.6%**	
Major bleed	**1.7%***	**0.6%**	**0.6%**	**p=0.06**

Largest cardioversion study to date
Dabigitran is a reasonable alternative to coumadin for CV
Properly powered study 15-30,000 cardioversions

Ken Gin

Lack of Monitoring

PTT /TT can be used to assess presence of Dabigitran
PT can be used to assess presence of Riva/Apixiban
These do not correlate well with activity

Specific marker for Dabigitran available soon (Hemoclot)
Assays for others in development

How can levels be measured?

Test		Dabigatran	Rivaroxaban	Apixaban
Specific Assay*	Drug specific	Hemoclot	Anti-Xa	Anti-Xa
Non-specific assays	aPTT	↑↑↑	↑	↑
	PT	↑	↑↑	↑
	TT	↑↑↑↑	No effect	No effect

*Mass spectrometry can be used to measure drug levels

Concerns about bleeding

Approx. 10% of pts./yr. will require interruption of OAC

This should be a strength-shorter period of interruption, less need for bridging

Challenge: More education required about management, too many players

Lack of reversal agent

Specific reversal agent for warfarin takes time

How serious is the lack of a reversal agent?

Dabigitran and Peri-procedural bleeding

Pacemaker
Dental
Colonoscopy
Joint replacement
Others

RELY
4591 Pts. requiring surgery
Major surgery > 1 hour

Circulation 2012

Dabigitran stopped 49 hours pre-op. Bridging used in 16%
Coumadin stopped 114 hours pre-op. Bridging used in 29%
Major bleed=20 pt. drop in Hb or 2 unit prbc or severe organ bleed

	Dabi 110	Dabi 150	Coumadin	
Elective	3.8%	5.1%	4.6%	NS
Urgent <24h	17.8%	17.7%	21.6%	NS

No difference in bleeding rates of Dabigitran vs. Coumadin In elective or urgent surgery

Cost Effectiveness of Dabigitran for prevention of CVA/SE in AF

Thrombosis and Haemostasis March 22/2011

Markov model based on RELY
Mean age 69 yrs./ Mean CHADS score 2.1
65% Men
Canadian costs
(CVA/ SE/ Hemorrhage/ Functional disability)

Dabigitran
150mg bid <80 yrs.
110mg bid >80 yrs.

365 x 3.20/day
= $1168/Yr.

Warfarin
Trial like
TTR 64.4%

365 x 0.06= 22/yr.
Monitoring 524/yr.
Total = $546/yr.

Real world
Warfarin/ASA/
No treatment

Ken Gin

Lifetime events per 100 Pt. yrs. F/U

	Dabigitran	Warfarin	Real world	p
ICH	0.49	1.13	1.05	Sig
Ischemic CVA	4.40	4.66	5.16	Sig

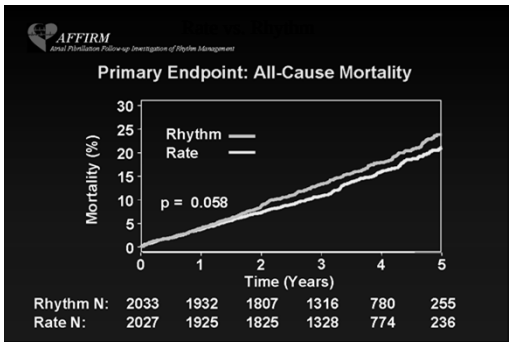
ICER Dabigitran vs. Warfarin $10,440/QALY
ICER Dabigitran vs. Real world $3962/QALY

Dabigitran is a highly cost effective alternative to current care for the prevention of CVA and SE among Canadian AF pts.

Level of evidence: Moderate

Overview of Talk

Calculation of risk of stroke CHADSVASc
Calculation of risk of bleeding HASBLED
Effectiveness of ASA -22%
Effectiveness of OACs -68%
Warfarin vs. NOACS NOACs preferred
Safety of the NOACS Lower CVA. Bleeding, Mortality
Cost effectiveness of NOACS Cost effective
What if Pt. cannot tolerate OAC? LAA occlusion

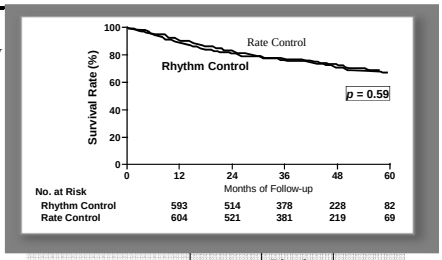


Higher rate of torsades de pointes VT and bradycardia / cardiac arrest / hospitalizations/ increased cost in the rhythm control arm
Trend to higher CVA and Death rates

AF- CHF trial*: no difference in rate of death from CV causes, but higher hospitalization rates with rhythm control

Kaplan Meier estimates of annual rate of death from CV causes

***82% of patients on amiodarone in the rhythm control group**



		Rhythm	
Any hospitalization	**39%**	**46%**	**0.001**
Hospitalization for AF	**9%**	**14%**	**0.001**

Patients requiring hospitalization at 1 year

Roy D, *et al. N Engl J Med. 2008*;358:2667-77.

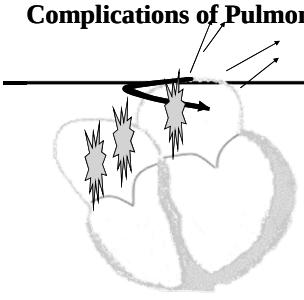
Effectiveness of Anti-arrhythmics

If 2 episodes of AF
Recurrence rate at one year

75% **50%** **35%** **20%**

Placebo **Standard** **Amiodarone** **Ablation**
Sotalol/Propafenone
? Dronedarone

Complications of Pulmonary Vein ablation



Death 1:1000
Tamponade 1%
Pulm. vein stenosis 1-2%
Stroke 1%

Success rate 60-80%
40% recurrence at 6 yrs
Improved QOL

Recurrence of AF is a surrogate Mortality/ CVA/ Costs/ Complications

HRS/EHRA/ECAS Expert Consensus Statement for Ablation Europace 1012 14(528-606)

Ken Gin

Outcome Studies of AF Ablation

- No Outcome RCT completed
- CABANA trial funded by NIH
  - Mortality trial in paroxysmal/persistent AF
  - One risk factor
- CABANA pilot presented at ACC 2010
  - Superior one year efficacy with ablation
  - No deaths
- New Canadian Study

Clinical Trials Update
JACC 2010
Eur. J Heart Failure
June 2010;12:623-29

If CHADS=2,
OAC

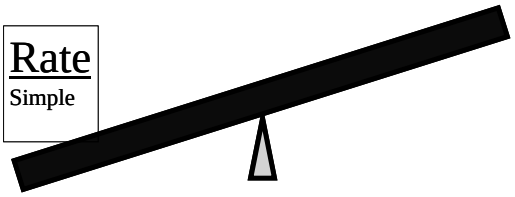
Conclusions

- AF patients are at increased risk of vascular events and death
- Rate control and Rhythm control are both reasonable options
  - Symptoms need to guide therapy
- Antiarrhythmic agents have not be been shown to reduce cardiovascular events
- Ablation therapy is promising but has been adopted without carefully done large trials
  - Outcome trials are just being started and will be challenging to adequately complete

Rate vs Rhythm

Rhythm
Complex
Pro-arrhythmia
Expensive $5,000/pt.
No proof of reduction in CVA

Rate
Simple



RACE II

Lenient vs. Strict
Rate Control in AF

NEJM March 21/2010

614 Pts.
<80 yrs.
Permanent AF
Mean HR>80 bpm
OAC

Lenient
Rest HR<110

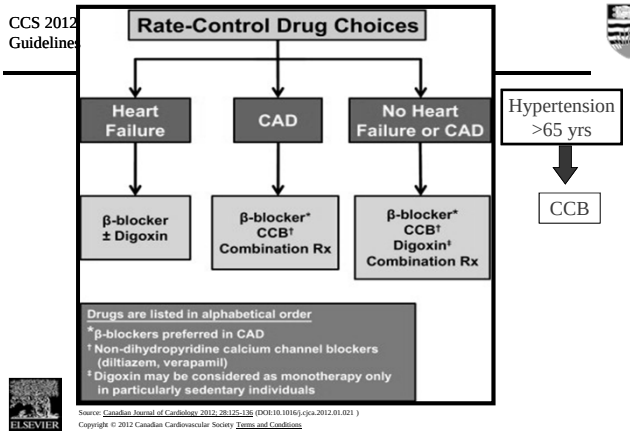
Strict
Rest HR<80
Exercise HR<110

	Lenient Rest HR<110	Strict Rest HR<80 Exercise HR<110	
Mean F/U 2.5 yrs.			
Mean HR	**93 bpm**	**76 bpm**	**p<0.001**
Goal HR achieved	**97.7%**	**67%**	**p<0.001**
Provider visits	**75**	**684**	**p<0.001**

	Lenient Rest HR<110	Strict Rest HR<80 Exercise HR<110	
Primary endpoint CV Death/ CHF admission/ CVA/ SE/ bleeding/ Syncope/ sustained VT/ Cardiac arrest/ life threatening effects of drugs/ pacemaker/ AICD	**12.9%**	**14.9%**	**p<0.001**
Symptoms Palpitations/dyspnea/ fatigue	**45%**	**46%**	**NS**

CCS Recommendations
THR<100 bpm

CCS 2012
Guidelines



What tests should be ordered?

- **TSH 2-5% of AF pts.**
- **Hb/Cr/Platelets Baseline**
- **Echo Class 1 recommendation**
- **ETT only when CAD suspected or rhythm control**
- **Holter – selected cases**

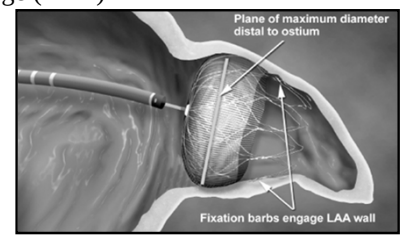
Ken Gin

Device Therapy

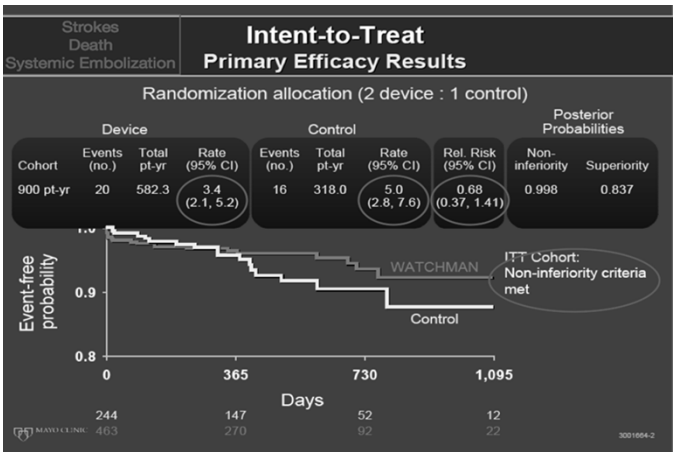
>90% of thrombus accumulation originates in the LA appendage (LAA)

Fabric covered
Nitinol Device with sharp
Fixation barbs

Occludes LAA



Stollberger C et al. Am Heart J 2006, 151:e101-9.



AF Clinics

NP led clinics
Reduce wait list
Improved pt satisfaction
Pts. are contacted within 2 weeks
Reduction in hospitalization

SPH Victoria VGH RCH

Prevention is the Key

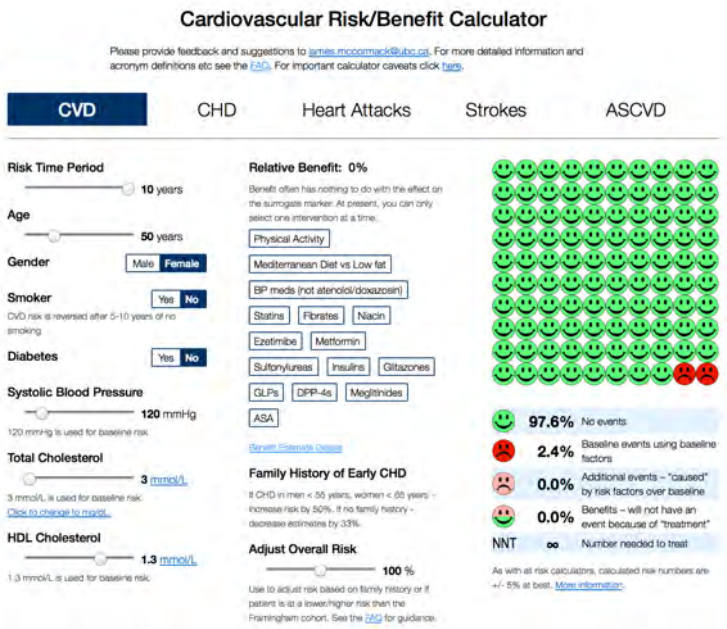
CCC 2012 AF Guidelines

James McCormack

Faculty/Presenter Disclosure

- **Faculty:** James McCormack
- **Relationships with commercial interests:**
  NONE

Objective - to be able to use the Cardiovascular Risk/ Benefit Calculator to estimate CVD risk and the benefit and harm associated with treatments



James McCormack

Intervention	Relative Benefits			Evidence
	CVD	CHD/MI	Strokes	
Activity	**~25%**	**~25%**	**~25%**	Eur J Cardiovasc Prev Rehabil 2008;15:239-46, Int J Environ Res Public Health 2012;9:391-407
Mediterranean Diet vs Low Fat	**~30%**	**~20%**	**~40%**	N Engl J Med 2013 DOI:10.1056/NEJMoa1200303
Blood pressure (only if SBP 140 or higher)	**~30% (~50% if diabetic)**	**~20%**	**~40%**	J Htn 1993;11(suppl4):S61-73, Cochrane, Lancet 2004;364:1684–9, Ann Intern Med 2003;138:587-92, CD004349
Statins	**~25%**	**~30%**	**~20%**	Lancet 2008;371:117-25; Women-J Am Coll Cardiol 2012;59:572–82; Over age 65-J Am Coll Cardiol 2013 Aug 14 pii:S0735-1097(13)03880-1
Fibrates	**~0%**	**~20% only non-fatal MIs**	**~0%**	NEJM 2010;362:1563-74, Amer J Med 2009;122:962.e1-962.e8, Int J Cardiol 2009 doi:10.1016/j.ijcard.2008.11.211
Niacin	**No studies**	**No studies**	**No studies**	
Ezetimibe	**~0%**	**~0%**	**~0%**	NEJM 2008;358:1431-43
Sulfonylureas	**~0%**	**~0%**	**~0%**	Diabet Med 2013;30:1160–71
Insulin	**~0%**	**~0%**	**~0%**	N Engl J Med 2012; 367:319-328
Metformin	**~35%**	**~35%**	**~35%**	UKPDS 34
Glitazones	**~0%**	**?**	**?**	CD006063,CD006060
Dipeptidyl peptidase-4 inhibitors (DPP-4)	**~0%**	**~0%**	**~0%**	SAVOR-TIMI 53, EXAMINE
Glucagon-like peptide (GLP) agonists	**No studies**	**No studies**	**No studies**	
ASA	**~15%M ~10%F**	**~30%M ~0%F**	**~0%M ~15%F**	Arch Intern Med 2012;172:209-16
Combinations of the above interventions	Nobody really knows but hopefully there is some sort of additive benefit. If you have data on this or a way this can be shown or calculated please let me know.			

Andrew Krahn

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BCIAP

Syncope: The Challenge of Diagnosis and the Conundrum of Therapy

Andrew Krahn MD FHRS
Sauder Family and Heart and Stroke Foundation Chair in Cardiology
Paul Brunes Chair in Heart Rhythm Disorders
University of British Columbia Vancouver Canada

CIHR IRSC

Institute for HEART•LUNG Health
Strong beats. Clear breaths. Full lives.

HEART AND STROKE FOUNDATION

Faculty/Presenter Disclosure

- **Faculty:** Andrew Krahn
- **Relationships with commercial interests:** none

Learning Objectives

- To discuss the diagnostic evaluation focusing on history taking in patients with syncope.
- To understand the role of lifestyle changes in prevention of syncope.
- To review non-pharmacological, pharmacological and pacing indications in the management of vasovagal syncope.

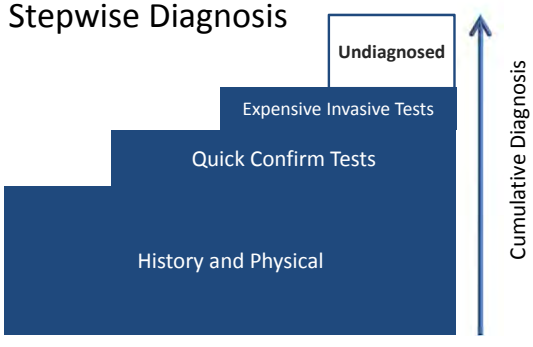
Conflict of Interest: No Disclosures

Case Presentation

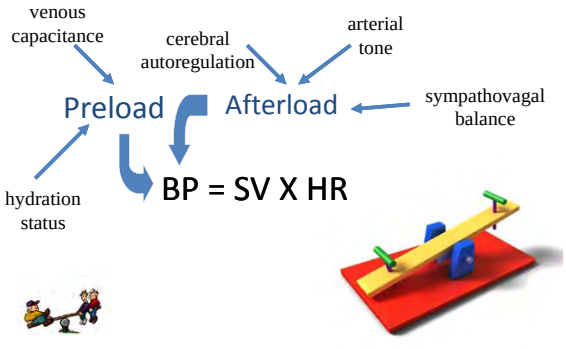
27 year old athlete

- Syncope while jogging, 5 mile run in the park
- Felt "off", stopped running, then fainted
- Woke up uninjured and walked back to the car, drove home
- Saw her family Doctor 2 days later, who called to refer her urgently

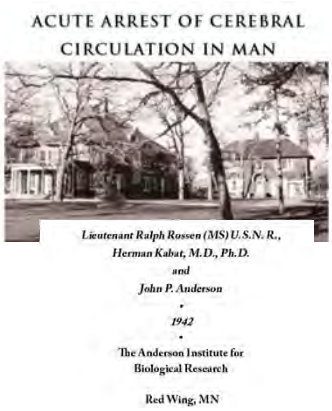
Stepwise Diagnosis



Transient Loss of Consciousness (TLOC)



Andrew Krahn

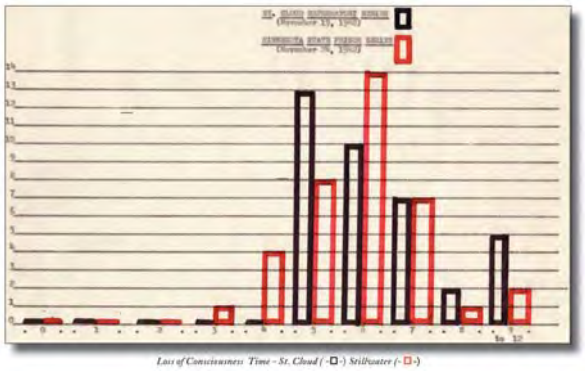

ACUTE ARREST OF CEREBRAL CIRCULATION IN MAN

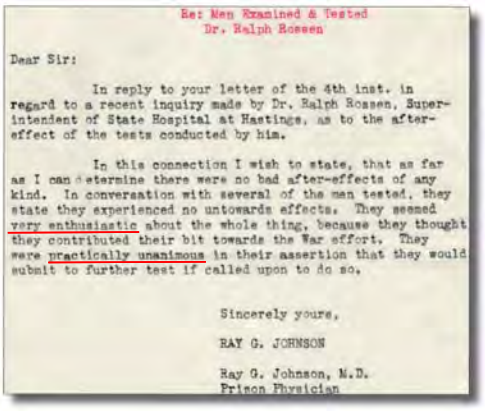
Lieutenant Ralph Rossen (MS) U.S.N.R.,
Herman Kabat, M.D., Ph.D.
and
John P. Anderson
•
1942
•
The Anderson Institute for Biological Research

Red Wing, MN


The first version of the cuff with the cutoff valve

The revised cuff with straps added


Loss of Consciousness Time - St. Cloud (-□-) Stillwater (-□-)


Re: Men Examined & Tested
Dr. Ralph Rossen

Dear Sir:

In reply to your letter of the 4th inst. in regard to a recent inquiry made by Dr. Ralph Rossen, Superintendent of State Hospital at Hastings, as to the after-effect of the tests conducted by him.

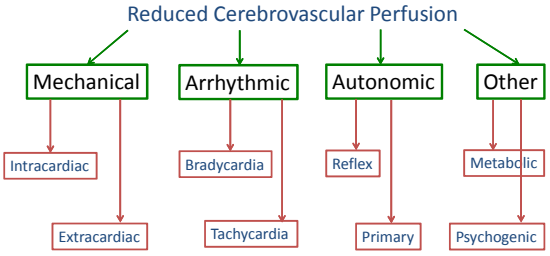
In this connection I wish to state, that as far as I can determine there were no bad after-effects of any kind. In conversation with several of the men tested, they state they experienced no untowards effects. They seemed very enthusiastic about the whole thing, because they thought they contributed their bit towards the War effort. They were practically unanimous in their assertion that they would submit to further test if called upon to do so.

Sincerely yours,

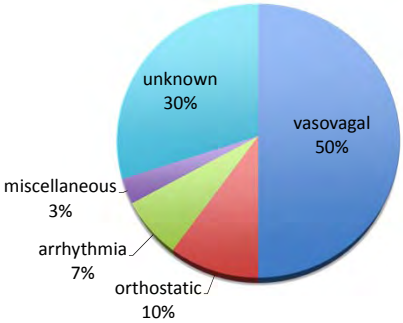
RAY G. JOHNSON

Ray G. Johnson, M.D.
Prison Physician

What is Going On in TLOC?



Causes of Syncope



Andrew Krahn

"Dr House – what test should I order?"

1. Transrectal MRI of the reticular activation center
2. Carotid Doppler
3. History
4. ECG
5. ILR
6. Echocardiogram
7. Exercise treadmill
8. Coronary angiogram

Take a History

- Is this life threatening?
- Talk to the bystander
- History drives testing
- You don't solve them all

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Syncope

Historical Criteria That Distinguish Syncope From Seizures

Robert Sheldon, MD, PHD,* Sarah Rose, PHD,* Debbie Ritchie, MN,* Stuart J. Connolly, MD,† Mary-Lou Koshman, RN,* Mary Anne Lee, MD,‡ Michael Frenneaux, MD,§ Michael Fisher, BSc,* William Murphy, MD‡
Calgary, Alberta; Hamilton, Ontario; and Cardiff, Wales

Table 3. Point Scores for the Diagnosis of Seizures With Knowledge of the Numbers of Spells and the Length of the History of Losses of Consciousness and Lightheaded Spells

Criteria	Regression Coefficient (SE)	p Value	Points
Loss of consciousness with stress	4.73 (1.43)	0.001	2
Head turning to one side during loss of consciousness	4.56 (1.84)	0.013	2
Number of spells >30	3.60 (1.02)	< 0.001	1
Unresponsiveness during loss of consciousness	3.89 (1.09)	< 0.001	1
Diaphoresis before loss of consciousness	−2.72 (1.25)	0.029	−1
Any presyncope	−4.90 (1.30)	< 0.001	−2
Loss of consciousness with prolonged standing or sitting	−7.36 (2.11)	< 0.001	−3

Classify as seizure for point scores ≥0. The reported p value is for the Wald statistic. SE = standard error.

Evidence based checklist medicine

Sheldon et al JACC 2002;40(1):142

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Loss of consciousness with prolonged standing or sitting	−7.36 (2.11)	< 0.001	−3

Negative for syncope; positive for seizure

Sheldon et al JACC 2002;40(1):142

Back to our Case - Worried?

- Exercise induced:
  - Arrhythmia (tachy, brady)
  - Obstruction
  - Anaphylaxis
- Historical details CRUCIAL
  - URTI, felt very congested
  - Running and started coughing, stopped to catch her breath, felt lightheaded and passed out
  - Fainted in church age 14, hates needles

Treatment

Which Of The Following Have Been Proven to Reduce The Risk Of Recurrent Vasovagal Syncope?

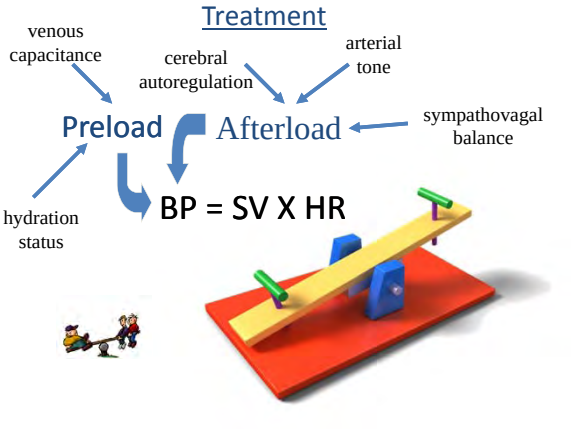
1. Salt and water lifestyle recommendations
2. Counter pressure maneuvers
3. Beta blockers
4. Fludrocortisone
5. Dual chamber pacemakers

Andrew Krahn

"Doctors pour drugs of which they know little, into patients about whom they know less, for diseases of which they know nothing."

-Voltaire

1760 C.E.



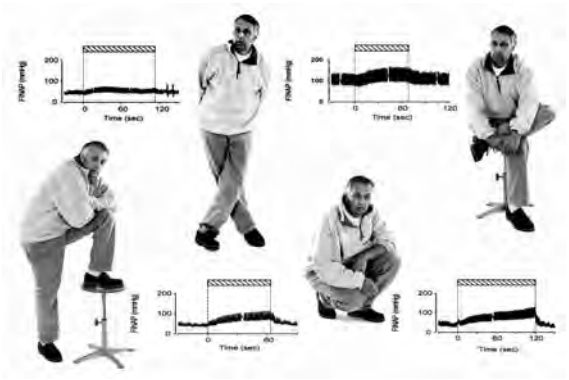
"The treatment of vasovagal syncope is salt and water"

+

Lifestyle Measures

Lifestyle Measures

- Water intake and doping
- Increase salt intake
- Tilt training
- Trigger aversion
- Counterpressure maneuvers



STOP

Drug Therapy

the hypotensives

- Paroxetine
  - ✓Single randomized trial
- Fluorinef
  - ✓Anecdotal conflicting evidence
- Beta blockers – negative overall effect but may benefit age > 42
- Midodrine:
  - ✓Decreases syncope and presyncope
  - ✓88 patients with syncope & positive tilt test
  - ✓Randomized studies; open and blinded

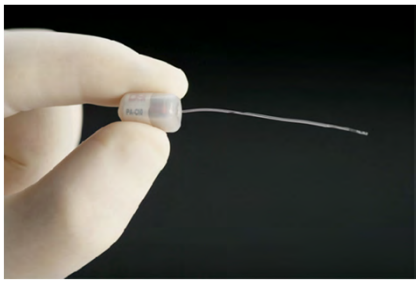
Ward et al Heart 1998; 116; 79: 45
Sra et al JCE 1997; 82: 42
Perez-Lugones et al JCE 2001;12: 935

Andrew Krahn

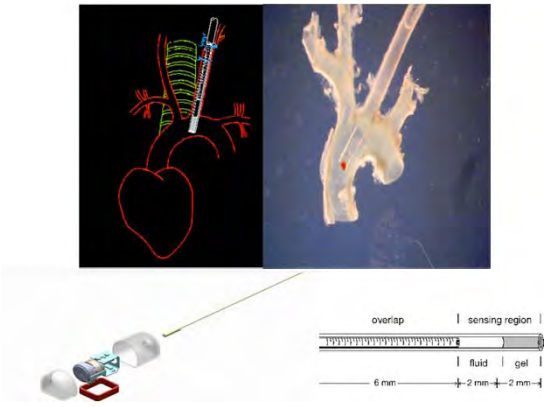
What's New in Diagnostics?

New Injectable Loop Recorder

Chronic BP Monitoring - Is it Possible?



DSI PA C10



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American Heart Association®
Learn and Live

Conclusions

- Syncope is almost always cardiovascular (predominantly orthostatic)
- The history establishes your hypothesis and working diagnosis
- Testing often confirms the diagnosis unless provocation or extended monitoring is required
- Raise the blood pressure with lifestyle measures
- Drugs and devices are a last resort

Questions

akrahn@mail.ubc.ca

Martin Dawes

Unmasking lone blood pressures

Martin Dawes
UBC

Disclosures

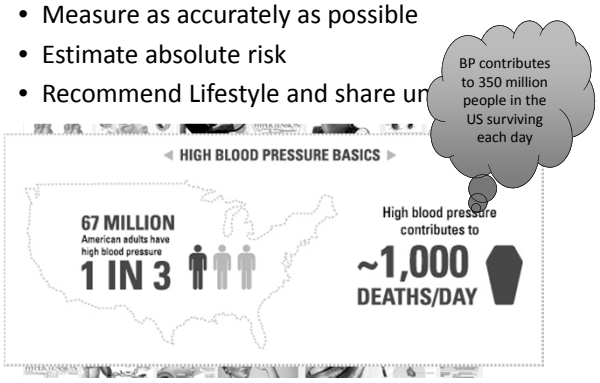
- **Faculty:** Dr. Martin Dawes
- **Relationships with commercial interests:**
  - 700k in Pharma (Rx&D) funding for a genetics project as a partner in a 2.1 m$ Genome Canada funded grant
  - Expert 24 company to help with risk prediction algorithms for Norwich Union and others every year

Learning Objectives

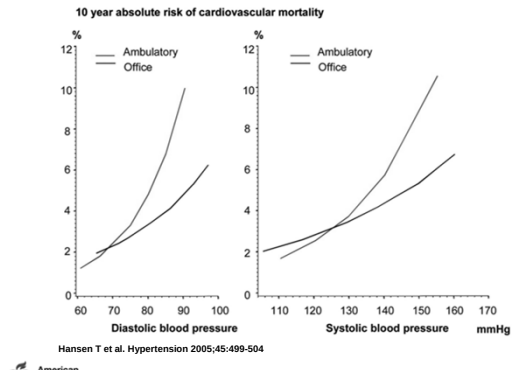
1. Increase knowledge of BP measuring issues
2. Come away with a plan to reassess your clinic's BP measurement process
3. Have more knowledge of the limitations of pharmacotherapy in low to moderate risk
4. Look at a way of providing lifestyle advice in your clinic
5. Knowledge of individual variation in response to therapy

What to remember

- Measure as accurately as possible
- Estimate absolute risk
- Recommend Lifestyle and share un



. The 10-year absolute risk of cardiovascular mortality for a 60-year-old person based on ambulatory blood pressure and office blood pressure.

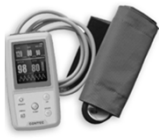


Hansen T et al. Hypertension 2005;45:499-504

American Heart Association.

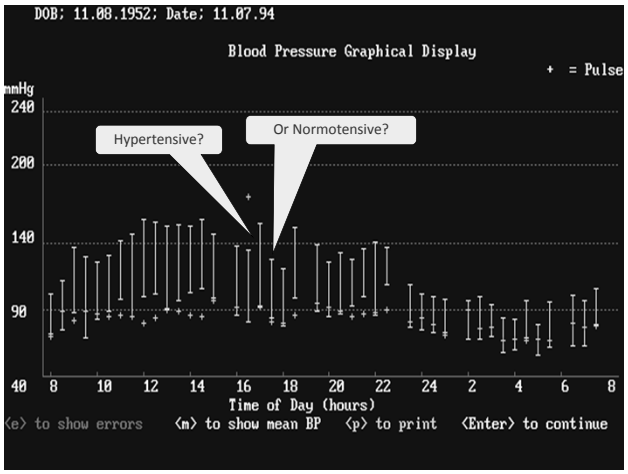
Ambulatory BP

- Gold Standard (unless intra arterial considered)
- $599 to $1700
- Use one used in trials
- FDA approved with a BHS AAMI algorithm –
- connects to a computer
- Don't use without a computer
- Use just the averages



Martin Dawes

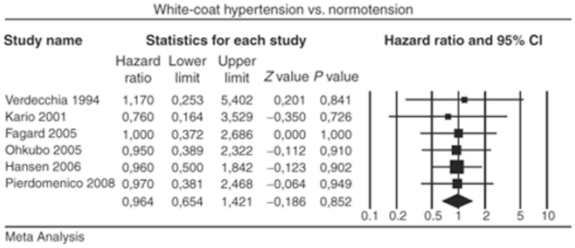
- A baseline blood pressure (BP) should be established in all adults and reassessed periodically, commensurate with age and the presence of other risk factors.1
- Have known or newly detected elevated BP
- Have cardiovascular target organ damage *
- Have other risk factors
- Are receiving antihypertensive therapy



What is WCH?

- White coat hypertension is defined when a patient has a persistently elevated clinic BP and a normal home or ambulatory BP day time average i.e. <135/85mmHg.
- Hypertension (WCH) 15% to 30% of the population
- It is more common in pregnancy and with increasing age.

White Coat Hypertension is Safe



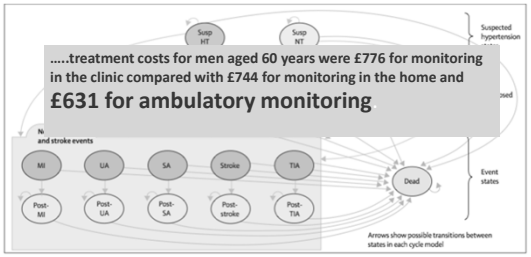
Prognostic Value of White-Coat and Masked Hypertension Diagnosed by Ambulatory Monitoring in Initially Untreated Subjects: An Updated Meta Analysis
Sante D. Pierdomenico and Franco Cuccurullo

National Institute of Clinical Excellence 2011

- If the first and second blood pressure measurements taken during a consultation are both higher than 140/90 mmHg,
- offer 24-hour ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension.

Why?: Cost effectiveness

- Lovibond, K., Jowett, S., Barton, P., Caulfield, M., Heneghan, C., Hobbs, F. R., Hodgkinson, J., et al. (2011). Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *The Lancet. doi:10.1016/S0140-6736(11)61184*



Martin Dawes

Office Cannot detect WCH

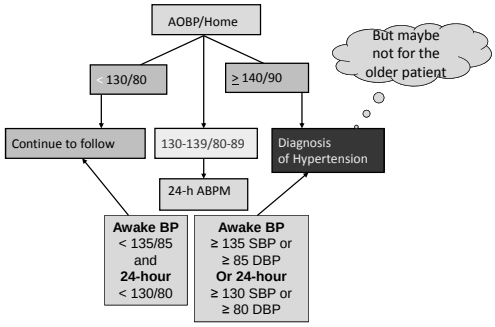
- But ABPM is expensive
- The equipment
- Needs computer analysis
- Two appointments

- Plan B Automated Office BP

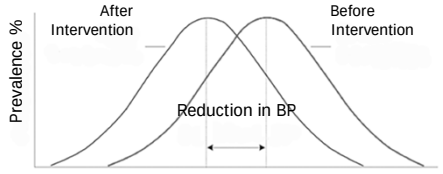
Automated Office

- Measures BP alone
- Does it 6 times BPTru
- Does it three times with Intellisense
- Takes averages

My Own **Proposed Algorithm for AOBP/Home BP in Clinical Practice in non diabetic or renal patients (not validated and not policy)**



Epidemiologic impact on mortality of blood pressure reduction in the population



Reduction in SBP (mmHg)	% Reduction in Mortality		
	Stroke	CHD	Total
2	-6	-4	-3
3	-8	-5	-4
5	-14	-9	-7

Adapted from Whelton, P. K. et al. JAMA 2002;288:1882-1888

Impact of Lifestyle Therapies on Blood Pressure in Hypertensive Adults

But what about hard outcomes

Intervention	Amount	
Reduce foods with added sodium	1.8g or 78 mmol/d	-5.1 / -2.7
Weight loss	per kg lost	-1.1 / -0.9
Alcohol intake	- 3.6 drinks/day	-3.9 / -2.4
Aerobic exercise	120-150 min/week	-4.9 / -3.7
Dietary patterns DASH diet	Hypertensive Normotensive	-11.4 / -5.5 -3.6 / -1.8

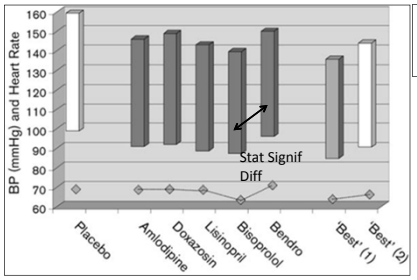
Applying the 2005 Canadian Hypertension Education Program recommendations: 3. Lifestyle modifications to prevent and treat hypertension
Padwal R. et al. CMAJ SEPT. 27, 2005; 173 (7) 749-751

Where were CCB?

- 1980's - Great drug
- 1990's – "*Causes death*" (Nifedipine scare)
  - Subsequent guidelines produced without CCB
- ASCOT – Great drug
  - (*better than atenolol or diuretic*)
- **BOTTOM LINE**
- **Epidemiology is not patient care**

Martin Dawes

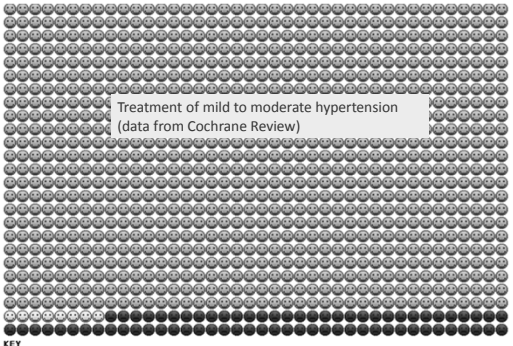
Which Drug First?



Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs.
Deary, Alison; Schumann, Anne; Murfet, Helen; Haydock, Stephen; Foo, Roger; Brown, Morris

Journal of Hypertension. 20(4):771-777, April 2002.

Fig. 1 (n=34) Comparison of blood pressures and heart rate on five different drugs. The columns represent mean values for systolic and diastolic blood pressure after 6 weeks on each double-blind treatment during rotation. The diamonds represent mean heart rate. The order of drugs was randomized, except for the 'best' drug repeated at the end of rotation (right-hand column). The left-hand (closed) column labelled 'Best' represents the mean of all patients' best blood pressure during rotation. On repeated measures analysis of variance the only differences between active drugs significant at P < 0.01 were for both systolic and diastolic blood pressure between bisoprolol and bendrofluazide.



In the control group 80 people out of 1000 had Mortality over 5 years, compared to 72 (95% CI 67 to 77) out of 1000 for the active treatment group.

…in light of the findings of this Cochrane review, it would be reasonable to emphasize pharmacotherapy in patients with stage 2 hypertension and to emphasize lifestyle changes in patients with mild hypertension and no cardiovascular disease. Larger double-blinded RCTs in this population of patients with stage 1 hypertension are needed to clarify the potential long-term benefits of pharmacologic therapy.

Pharmacotherapy for mild hypertension (Review)

Diao D, Wright JM, Cundiff DK, Gueyffier F

Antihypertensive drug therapy vs placebo in patients with mild hypertension*

Outcomes†	Number of trials (*n*)	Weighted event rates	RRR (95% CI)	NNT
Mortality	4 (8912)	1.7% vs 2.0%	15% (–15 to 37)	Not significant
Stroke	3 (7080)	0.29% vs 0.56%	49% (–8 to 76)	Not significant
Total CV events	3 (7080)	2.3% vs 2.4%	3% (–32 to 28)	Not significant
			RRI (CI)	NNH
CHD	3 (7080)	2.0% vs 1.8%	12% (–20 to 57)	Not significant

CHD = coronary heart disease; CV = cardiovascular; other abbreviations defined in Glossary. Weighted event rates, RRR, RRI, and CI calculated from risk ratios and control event rates in article using a fixed-effect model.

†Quality of evidence was very low (mortality and total CV events) or not reported (stroke and CHD) based on Grading of Recommendations Assessment, Development, and Evaluation criteria (4 grades: very low, low, moderate, and high quality).

Costs

- The estimated wholesale drug acquisition cost to prevent one major event (MI or stroke or death)
- ranged from $4730 to $346,236 among middle-aged patients,
- and from $1595 to $116,754 in the elderly;
- generic diuretic or β-blocker therapy was more economical than treatment with an ACEI, α-blocker, or CCB.
- The associated 5-year NNT was 86 for middle-aged patients and 29 for elderly patients.
- Diuretic therapy remained more cost-effective even under the unlikely assumption that the newer drugs were 50% more effective than diuretics at preventing these major events.
- Pearce 1998

Means nothing if people don't take them

Persistence was highest in users of ARBs 62.0%,
lower in users of ACE-inhibitors, 59.7%
Beta blockers (35.0%),
calcium channel blockers (34.7%),
and diuretics (33.0%)
The persistence of AHT use in women was substantially lower (40.1% vs. 50.2%, OR 0.7 [95%CI: 0.6–0.8]) and differences between drug classes were larger than in men.

Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study†

Joëlle A. Erkens PhD[1]*, Martien M. J. Panneman MSc[1], Olaf H. Klungel PhD[2], Guido van den Boom PhD[3], Margaret F. Prescott PhD[3] and Rem M. C. Herings PhD[1,2]

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[4]Novartis Pharma, Cardiovascular Clinical Development, East Hanover, NJ, USA

SUMMARY

Objective The objective of the study is to investigate factors related to treatment persistence among users of antihypertensive (AHT) drugs in daily practice.

Methods The study cohort was obtained from the PHARMO database including pharmacy records and hospitalizations in the Netherlands (n = 950 000). Patients who newly received AHT therapy (n = 17 115) between 1997 and 2001 were selected. Of these patients, random samples of 500 patients per drug class were drawn. One-year persistence was defined as (1) the percentage of patients using AHTs at least 270 days and receiving AHT in 3 months after the 1-year follow-up period, and (2) Cramér method (Kaplan–Meier curves). Gender-specific persistence rates per drug class were adjusted for significant factors including age, use of antidiabetics and lipid lowering drugs, and prior cardiovascular hospitalizations (OR and 95%CI).

Results Persistence was highest in users of angiotensin II receptor blockers (ARBs) (62.0%), progressively lower in users of angiotensin converting enzyme inhibitors (ACE-inhibitors, 59.7%), beta-blockers (35.0%), calcium channel blockers (34.7%), and diuretics (33.0%), resulting in the highest OR of 3.6 (95%CI: 2.8–4.5) for ARBs compared to diuretics. The persistence of AHT use in women was substantially lower (40.1% vs. 50.2%, OR 0.7 [95%CI: 0.6–0.8]) and differences between drug classes were larger than in men. Multivariate differences in persistence between AHT classes, with the highest persistence for ARBs and lowest for diuretics. Women were less persistent with their AHT compared to men. This low persistence leads to suboptimal treatment with a potential for substantial clinical consequences. Especially in women, more attention paid to AHT persistence patients could improve their cardiovascular outcome. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — hypertension; persistence; switching; antihypertensive drugs

INTRODUCTION

Hypertension is a major risk factor for vascular disease[1] and effective blood pressure treatment has been shown to reduce both cardiovascular and cerebrovascular events.[2] Despite the availability of effective treatment, hypertension persists in a substantial proportion of the population due to a combination of under-diagnosis and undertreatment leading to poor blood pressure control.[3,4] The percentage of patients in whom blood pressure control is achieved varies by country. For example, the US National Health and Nutrition Examination Survey (NHANES III) documented a control rate of 27%,[5] while the Canada heart health survey found that only about 13% of Canadians with hypertension were adequately

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†Conflict of interest was not declared.
Contract grant sponsor: Novartis Pharma B.V., The Netherlands.

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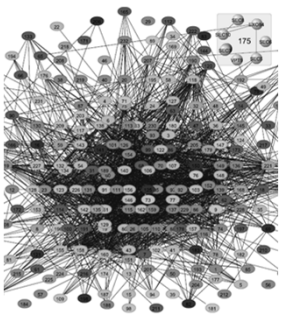
It's Complex –



- Measure as accurately as possible
- Estimate absolute risk
- USE LIFESTYLE
- Share uncertainty

Hannah Briemberg

Statin Myalgias:
when the pain in your muscles is worse than the pain in your heart

Hannah Briemberg MD, FRCPC
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Faculty/Presenter Disclosure

- **Faculty:** Hannah Briemberg
- **Relationships with commercial interests:**
  - **Grants/Research Support**: past research support from Biogen/IDEC, Teva Pharmaceuticals
  - **Speakers Bureau/Honoraria:** ALS Society of British Columbia (honoraria)
  - **Consulting Fees:** None
- **I have no conflicts to report related to this talk**

Learning Objectives

- To better understand the incidence, clinical characteristics and morbidity of statin myopathy
- To be able to incorporate the relevant evidence into shared, informed decision making around "co-management" of statin-related muscle symptoms and hyperlipidemia

Statin myopathy: what is it?

1. Statin related myalgia: muscle pain without rise in CPK
2. Statin related "myositis": muscle symptoms (pain and/or weakness) with elevation in CPK < 10,000
3. Rhabdomyolysis: muscle symptoms (pain and/or weakness) with rise in CPK > 10,000 (+/- increased creatinine)

Incidence

- Prospective trials suggest:
  - Myalgias 10-15%
  - Myositis: 5-11 per 100,000 patient years
  - Rhabdomyolysis: 0.7-3.4 per 100,000 patient years or 0.01% (mortality 0.3 per 100,000 patient years or 1 in 15 million prescriptions)
- Median time to onset 1 month (range 1 week to 12 months)

UK statin myopathy study
1056 patients attending a lipid clinic

- 10% patients developed statin myopathy
  - 55% normal CPK
  - 39% CPK $\leq$ 5x upper limit of normal
  - 3.7% CPK between 5 and 10x upper limit of normal
  - 2% CPK > 10x upper limit of normal
  - None developed rhabdomyolysis

Hannah Briemberg

Statin myopathy: symptoms

- PRIMO (2006) observational study: 7924 patients; 832 muscle symptoms:
  - Generalized muscle pain, primarily affecting thighs and/or calves
  - Muscle "heaviness", stiffness or cramps
  - Exertional weaknesss
  - Tendonitis-associated pain was reported by almost a quarter of patients; affected multiple tendons in more than half of cases.
  - More than 80% of patients had not experienced similar symptoms before beginning statin treatment.

Impact of muscle symptoms

- 25% continuous muscle pain
- 46% exertional muscle pain
- 39% required analgesics for pain relief
- 38% avoided even moderate exertion during everyday activities
- 4% suffered "major disruption" to their everyday life (being confined to bed or unable to work) due to muscle pain

Is there a difference between statins?

Rate of occurrence of muscular symptoms with individual statins in the PRIMO study

Statin	#	% myopathy	p-value
• Pravastatin	1901	10.9%	
• Atorvastatin	1844	14.9%	0.035
• Simvastatin	1027	18.2%	0.0001
• FluvastatinXL	3121	5.1%	0.0001

Statin myopathy: risk factors

- Data concerning risk for statin myopathy comes from studies on rhabdomyolysis and severe myositis NOT from minor symptoms such as myalgia and myositis with CPK elevations less than 10x ULN
- Current strategies are based on the extrapolation that the same risk factors contribute to both major and minor myopathic adverse effects

Statin myopathy: risk factors

- Based on data from risk for severe myositis/rhabdo:
  - Higher dose
  - Older age
  - Female > male
  - Family history
  - Frailty/low BMI
  - Concommitant renal/hepatic disease
  - Multiple medications (concommitant **nitrates, fibrates**, cytochrome P-450 metabolized medications)

Statin myopathy: Risk factors identified in PRIMO

- PERSONAL HISTORY of myalgias, cramping or statin myopathy
- History of ELEVATED CPK
- FAMILY HISTORY of statin myopathy
- INCREASED PHYSICAL ACTIVITY
- 30% identified starting a NEW MEDICATION as the trigger

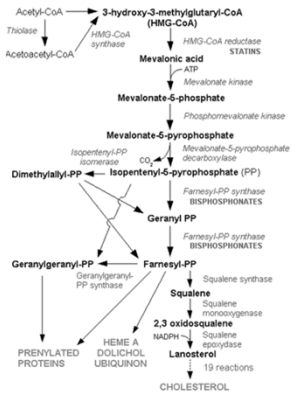
Hannah Briemberg

Fibrate-statin combinations

- Increased risk of rhado compared with either statin or fibrate monotherapy
- 0.44 hospitalizations per 10,000 person-years with statin monotherapy
- 5.98 per 10,000 patient-years when fibrates were added to the regimen
- 0.58 per million prescriptions for the fenofibrate/statin combination
- 8.6 per million prescriptions for **gemfibrozil**/statin combination

Competitive inhibition of HMG-CoA reductase by statins → decreased cholesterol production by liver → increased hepatic LDL receptor activity → decreased blood LDL levels

First results: 1 week
Maximal effect: 4-6 weeks



Statin myopathy--mechanism

- Unknown
- Correlates with decrease in mevalonic acid NOT decrease in lipid levels
- Proposed mechanisms:
  - Genetic polymorphisms (SLCO1B1 gene)
  - Mitochondrial dysfunction
  - Myocyte apoptosis

? relationship to Coenzyme Q10

- Mevalonic acid is a precursor to CoQ10
- CoQ10 plays key role in mitochondrial function
- Protects against oxidative stress
- Statins may decrease serum CoQ10 levels
- **However**, myocyte CoQ10 levels do necessarily decrease with statins
- RCT's to date have been equivocal
- Thus, NLA does not recommend treatment

Management recommendations
(NLA muscle expert panel)

- **routine** check of CPK pre or post treatment not cost-effective
- Muscle symptoms→ check CPK
- Tolerable myalgias:
  - CPK < 5x normal → continue statin (? Decrease dose)
  - CPK > 5x normal → discontinue statin
- Intolerable myalgia → discontinue statin
- Consider other causes of high CK and/or myalgias
  - Hypothyroidism, polymyalgia rheumatica

What to do next?

- If muscle symptoms resolve and CPK less than 2500 when symptomatic, options are:

(a) Rechallenge with same statin at prior dose
(b) Rechallenge with same statin at reduced dose (+/- ezetimibe or bile acid sequestrant)
(c) Rechallenge with different statin

Hannah Briemberg

Which statin to choose?

- Trial comparing fluvastatin XL 80 mg qd alone with ezetimibe 10mg qd alone with combination fluvastatin/ezetimibe in patients with prior statin myopathy:
  - Showed target reductions in LDL with fluvastatin XL and with combination treatment
  - Incidence of recurrent statin myopathy was low (≈14-24%)

Simvastatin-induced myopathy study

Medication	# tried	# myopathy
• Rosuvastatin	21 (20.6%)	17/21 (81.0%)
• Atorvastatin	32 (31.4%)	22/32 (68.8%)
• Pravastatin	20 (19.6%)	16/20 (80.0%)
• Fluvastatin	21 (20.6%)	13/21 (61.9%)
• Fibrates	12 (11.8%)	2/12 (16.7%)
• Colestyramine	14 (13.7%)	3/14 (21.4%)
• Colesevelam	4 (3.9%)	3/4 (75.0%)
• Ezetimibe	38 (37.3%)	12/38 (31.6%)

Fung EC, Crook MA. Cardiovascular Therapeutics 30 (2012) e212–e218

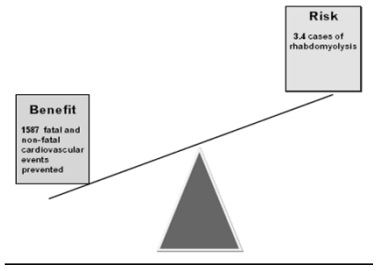
Statin-induced **autoimmune** myositis

- Case reports/case series suggest increase risk of immune-mediated myositis with statin use
- linked to antibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (upregulated in regenerating muscle fibres)
- Clinically, looks like polymyositis

Clues to differentiate from statin myopathy

- Increased CPK the rule
- Weakness may or may not start while on statin but **will** continue to progress after statin d/c'd
- CK continues to rise off statin
- Onset of symptoms after > 12 months on same statin at same dose
  - Mean duration of treatment prior to onset was 3 years (2 months- 10 years)

Risk-benefit analysis treating 100,000 patients with a statin for one year



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Victor Montori

Sweet Justice Is What I Seek

A 14-year journey into diabetes territory

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CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty: VICTOR MONTORI**
- **Relationships with commercial interests:**
  - **Grants/Research Support:** NONE
  - **Speakers Bureau/Honoraria:** NONE
  - **Consulting Fees:** NONE
  - **Other:** NONE

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has not received financial or in-kind support from any organization.**
- **Potential for conflict(s) of interest:**
  - None

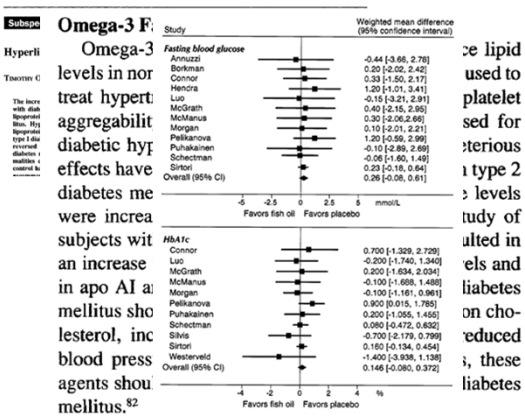
CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- NONE

Learning objectives

- To enumerate at least three challenges to diabetes care derived from:
  - The interpretation of trials
  - The individualization of therapy based on preferences
  - The contextualization of therapy based on capacity



Montori VM et al. Diabetes Care. 2000 (9):1407-15.

Victor Montori

199 diabetes trials in top journals (2003)
Allocation concealment: 11%
Blinding: 6-50%
Loss to follow-up: 71%

Highest reported* methodological quality
For-profit patient-oriented parallel trials

Montori VM et al, Diabetes Care 2006; 29: 1833-8
* Devereaux PJ et al. J Clin Epidemiol 2004; 57: 1232-6

SPIN

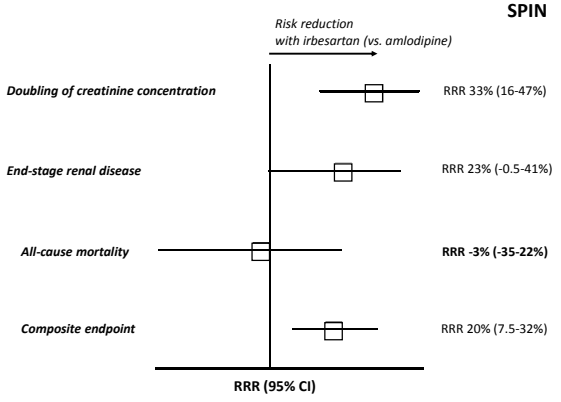
High quality RCT
1715 HTN DM2 nephropathy
Amlodipine vs. ARB
2.6 years of follow-up

"Treatment with irbesartan was associated with a risk of the primary composite end point* that was 23 percent lower than that in the amlodipine group (P=0.006)"

*Doubling of creatinine, onset of end-stage renal disease, or death from any cause

Lewis EJ et al N Engl J Med 2001; 345: 851-60

SPIN



SPIN

UKPDS: 3867 DM2 x 10y

Diabetes-related endpoints

Sudden death
Death from hypoglycemia
Death from hyperglycemia
Fatal MI
Nonfatal MI
Angina
Heart failure
Stroke
Renal failure
Amputation
Vitreous hemorrhage
Retinal photocoagulation
Blindness in one eye
Cataract extraction

Intensive therapy: 35.3%
Conservative therapy: 38.5%
Difference: 3.2% (*P*=0.029)

2.7%

SPIN

De-spinning composite endpoints

Gradient of patient importance?
Gradient of treatment effects?
Gradient of events?

112 of 242 Cardiology RCTs used CEP
86% fail first 2 criteria

BMJ 2007; 334:786

This large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially **reduces the risk of diabetes or death** by 60% in individuals at high risk for diabetes.

Rosiglitazone vs placebo to reduce death or diabetes at median 3 years†

Outcomes	Rosiglitazone	Placebo	RRR (95% CI)	NNT (CI)
Composite outcome‡	11.6%	26%	56% (50 to 62)	7 (7 to 8)
			RRI (CI)	NNH (CI)
Heart failure	0.5%	0.1%	601% (60 to 2944)	167 (34 (1668)

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from hazard ratios in article.

‡Death from any cause (1.1% vs 1.3%) or diabetes (10.6% vs 25%).

Lancet 2006; 368: 1096-1105

Victor Montori

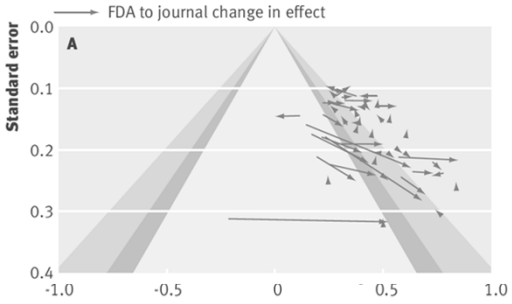
“Controversies”

FACTS: Rosiglitazone and pioglitazone increase risk of heart failure, but rosi increases the risk of MI by 40%.

92 opinion articles (2007-2009)
“Rosi is safe” “Use Rosi”
90% had $ relation, 13% did not
RR 6.2 (95% 2.7-14)

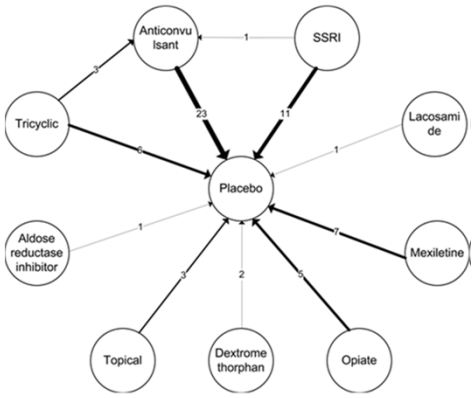
Wang et al. BMJ 2010;340:c1344

Reporting bias - antidepressants
FDA vs. peer-reviewed journals

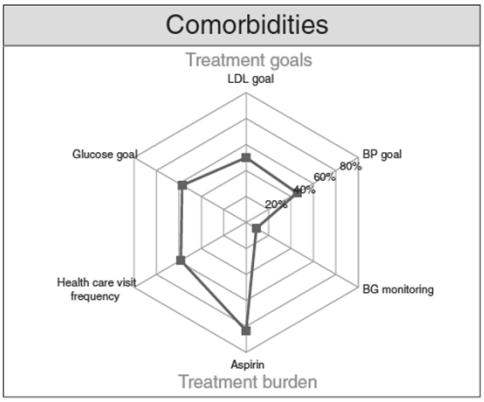


Moreno et al. BMJ 2009

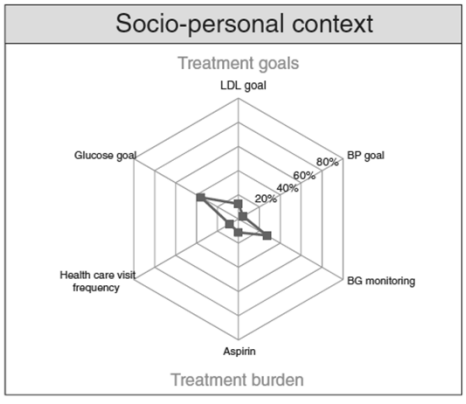
The shape of the evidence base



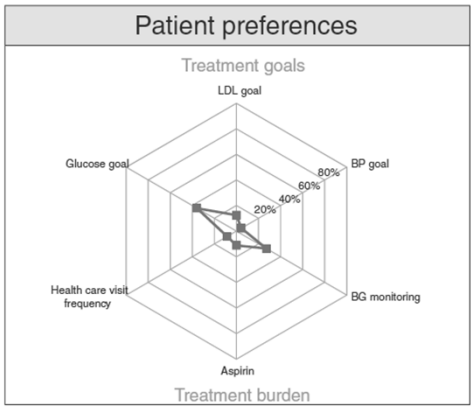
Griebeler et al. In submission



Wyatt KD et al. Med Care. 2014;52 Suppl 3:S92-S100.



Wyatt KD et al. Med Care. 2014;52 Suppl 3:S92-S100.



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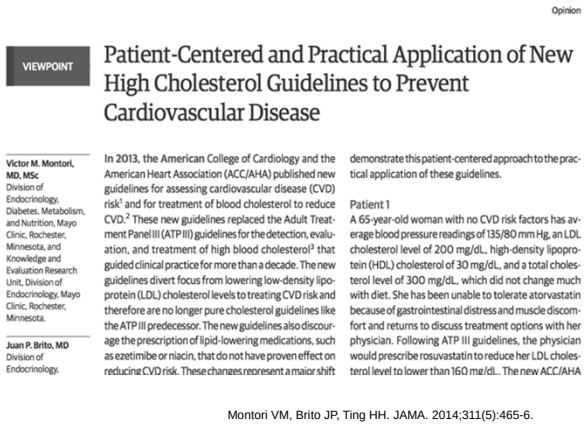


Opinion

VIEWPOINT

Patient-Centered and Practical Application of New High Cholesterol Guidelines to Prevent Cardiovascular Disease

Victor M. Montori, MD, MSc
Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota, and Knowledge and Evaluation Research Unit, Division of Endocrinology, Mayo Clinic, Rochester, Minnesota.

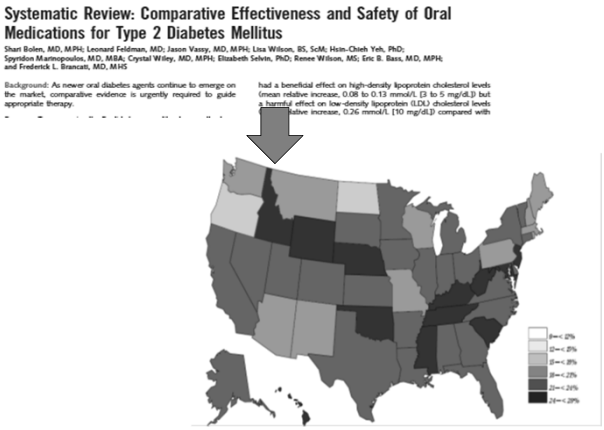
Juan P. Brito, MD
Division of Endocrinology.

In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) published new guidelines for assessing cardiovascular disease (CVD) risk[1] and for treatment of blood cholesterol to reduce CVD.[2] These new guidelines replaced the Adult Treatment Panel III (ATP III) guidelines for the detection, evaluation, and treatment of high blood cholesterol[3] that guided clinical practice for more than a decade. The new guidelines divert focus from lowering low-density lipoprotein (LDL) cholesterol levels to treating CVD risk and therefore are no longer pure cholesterol guidelines like the ATP III predecessor. The new guidelines also discourage the prescription of lipid-lowering medications, such as ezetimibe or niacin, that do not have proven effect on reducing CVD risk. These changes represent a major shift demonstrate this patient-centered approach to the practical application of these guidelines.

Patient 1

A 65-year-old woman with no CVD risk factors has average blood pressure readings of 135/80 mm Hg, an LDL cholesterol level of 200 mg/dL, high-density lipoprotein (HDL) cholesterol of 30 mg/dL, and a total cholesterol level of 300 mg/dL, which did not change much with diet. She has been unable to tolerate atorvastatin because of gastrointestinal distress and muscle discomfort and returns to discuss treatment options with her physician. Following ATP III guidelines, the physician would prescribe rosuvastatin to reduce her LDL cholesterol level to lower than 160 mg/dL. The new ACC/AHA

Montori VM, Brito JP, Ting HH. JAMA. 2014;311(5):465-6.



Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus

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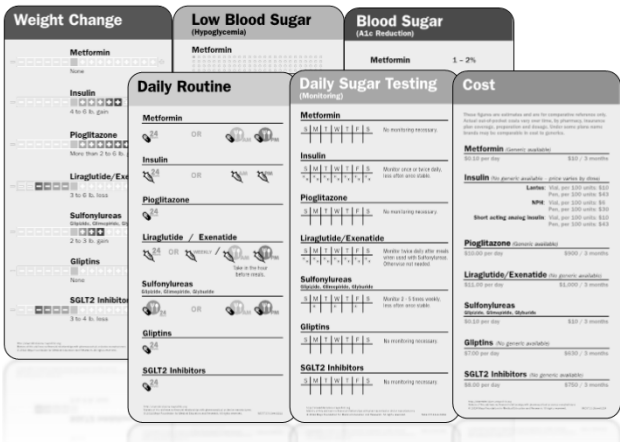
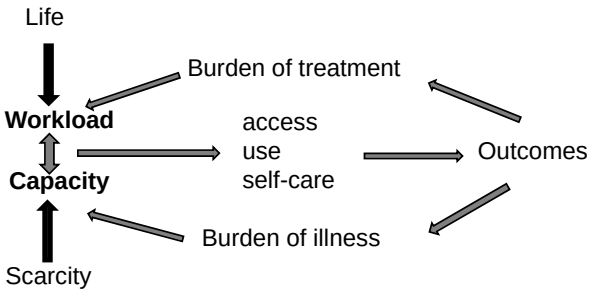
Background: As newer oral diabetes agents continue to emerge on the market, comparative evidence is urgently required to guide appropriate therapy.

had a beneficial effect on high-density lipoprotein cholesterol levels (mean relative increase, 0.08 to 0.13 mmol/L [3 to 5 mg/dL]) but a harmful effect on low-density lipoprotein (LDL) cholesterol levels (mean relative increase, 0.26 mmol/L [10 mg/dL]) compared with

Shah ND et al N Engl J Med. 2010 363:2081-4.





Shippee N et al JCE 2012

Encounter Research

More about shared decision making:
http://shareddecisions.mayoclinic.org

More about MDM:
http://minimallydisruptivemedicine.org

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Alan Cassels and James McCormack

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** James McCormack, Alan Cassels
- **Relationships with commercial interests:**
  NONE

Media-um, Well done….

Alan Cassels, School of Health Misinformation Science, University of Victoria

James McCormack, Faculty of Farmaceutical Sciencey stuff, UBC

Cover issue, Drugs in The News, CMAJ • April 29, 2003; 168 (9)

Objectives

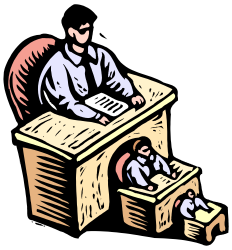
- to know what to do when journalists call
- list the 10 key components of a balanced news story about health
- list 5 reasonably good health or drug reporting sites

Outline

- Who are Alan Cassels and James McCormack?
- How does a newsroom actually work?
- How to judge a 'drug' story: Media Doctor and Drugs in the News
- Success Stories—Examples of good reporting.
- Failure Stories—Examples of spectacular reporting
- What to do when journalists call.
- Good sources of quality media related to health

How does a newsroom work? Newsroom Hierarchy

- Managing editor
  - City editor
    - Assignment editor
      - Beat Reporter
      - General Reporter



<u>Scorecards we've developed to evaluate medical media.</u>
<u>Does the story…</u>

- Adequately discuss costs?
- Quantify potential benefits?
- Quantify potential harms?
- Evaluate quality of the evidence?
- Avoid disease-mongering?
- Establish true novelty of the idea?
- Establish true availability of the idea?
- Use independent sources & identify COI?
- Compare the new idea with existing options?
- Appear to rely on a news release?

media doctor canada

Alan Cassels and James McCormack

What to do when journalists call?

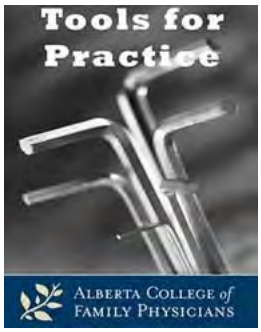
- Answer the phone.
- Find out their deadline.
- Find out what the story is about.
- If you can't talk to them refer them to someone competent.
- If you like the piece that is published let them know
- Bottom line: Don't curse the media, become the media.

Where to go for reasonably good health or drug reporting?

- Evidence Network
- Cochrane Collaboration
- Consumer Reports on Health
- US Public Citizen: Best Pills Worst Pills
- Very popular podcasts produced by McCormack and Allan.

The Gang plus The Audience

Medical Myths: Forgotten & Forgettable Interventions



Faculty/Presenter Disclosure

- **Faculty:** G Michael Allan, Michael R Kolber, Christina Korownyk, and James McCormack
- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

Objectives Myth-Busting

- Increase understanding of the benefits of vitamins/ supplements like anti-oxidants, multivitamins, oral (vs IM) B12, calcium and omega-3
- Increase understanding of care of the elderly including cholinesterase inhibitors, dosing iron, repeat BMD, stopping bisphosphonates, bell's palsy.
- Increase understanding of the benefits/harms of diet, activity, coffee, BMI and alternative meds for smoking cessation
- Increase understanding of treatments of renal stones, gout, MSK pain, sterile repair of lacerations, and anti-histamines for the cold.

Jeopardy

SUPPLEMENTS	ELDERLY	LIFESTYLE	URGENT CARE
Omega-3: Igloo Fix	The Bell Tolls	Coffee: Nice Vice	He who is __ pass the first stone
Need a Little, Take a Lot	BMD Tests: The More the Merrier	Diet vs Health	Don't get Sterile for me!
Need a Little, Take a Multi-Lot	Old Iron Doses	Weight of Evidence	Talking about pain topic (al)
Calcium: Good, Bad, or Don't Ask	Memory Aid	Exercise 2 4-letter words	Cold on Antihistamines
It's like a B12 shot	Bisphosphonates To infinite &,...	TCA 4 Smoking	Gout & Gut cramp

Do antiviral medications provide any benefit to patients with Bell's Palsy?

- Evidence: Meta-analysis, 2 high-quality RCTs
  - Unsatisfactory recovery at ≥4 months: corticosteroid 16% vs Placebo 26% (NNT 10)
  - Antivirals, with or without steroid, no additional benefit
- **Bottom-line:** The best evidence indicates that corticosteroids (in doses of prednisolone 25 mg BID or 60 mg x5 days then tapered by 10 mg/day) improve the odds of complete recovery from Bell's Palsy. Antivirals (used either alone or in addition to prednisolone) seem to offer no advantage (although research continues in severe Bell's Palsy).

What weight (BMI) has the lowest risk of mortality?

- Multiple cohort studies, compared to BMI 20-25
  - BMI 25- <30: HR 0.95 (0.91-0.99)
  - BMI ≥35: HR 1.35 (1.22-1.50)
  - If age ≥65: BMI 25-30 was HR 0.90, BMI ≥35 HR 1.28
- **Bottom-line:** The best available evidence suggests that being overweight (BMI 25.1-29.9) does not increase mortality (and may slighlty reduce mortality). The evidence is strongest for patients over 65.

The Gang plus The Audience

Does daily supplementation with antioxidant vitamins (A, E and C) decrease mortality in the general population?

- Evidence: Meta-analysis with 296,707 patients
  - Beta-carotene (pro-vitamin A): RR 1.05 (1.01-1.09)
  - Vitamin E (RR 1.03, 1.00-1.05)
  - Vitamin A all doses (RR 1.07, 0.97-1.18)
    - High dose vitamin A (? ≥5000IU) does increase mortality (p=0.002)
  - NNH likely 200-250 over 3.5 years or so.
- **Bottom-line:** The current evidence does not support the use of antioxidant supplementation, and patients should be dissuaded from using beta-carotene, vitamin E and perhaps high dose vitamin A, as they appear to increase mortality.

#10 September 22, 2009 Updated June 28, 2013

In elderly adults with iron deficiency anemia, what is the appropriate dose of iron?

- **Evidence:** 15 vs 150mg elemental iron = Hgb (14)
  - Drop-out NNH 5, Abdo cramps or N/V=2, constipation=5
  - Ferrous Sulfate 300mg = elemental iron
- **Bottom-line:** In elderly patients with iron deficiency anemia, low doses of iron raise hemoglobin similar to higher doses with considerably less adverse events in most patients. Options for dosing include ½ of a 300mg ferrous gluconate per day or 2.5ml of Fer-In-Sol syrup a day. Clinicians should work-up the cause of anemia as appropriate.

#30 July 6, 2010

In patients ready for smoking cessation, how effective are first-line medications and what are the potential concerns?

- Evidence: Assuming 10% placebo cessation rates:
  - NTT: Varenicline 8, nortriptyline 10, bupropion 10, NRT 16
  - Buproprion 150mg ≈300mg; Varenicline: 0.5mg ≈1mg BID
  - Nortriptyline: 25mg qhs, ↑ 25 mg q3-4d, 75-100 mg max
- **Bottom-line:** In addition to nicotine replacement, buproprion, nortriptyline (off-label) and varenicline are all effective in smoking cessation, perhaps the latter more so. Adverse events vary and may in part relate to quitting smoking, but are important and require monitoring.

#27 May 26, 2010

How do I motivate my patients to participate in regular physical activity?

- Evidence: 2 Sys Rev + RCTs: +2000 steps/day.
  - Also reduce BP, Weight, glucose at $30/pedometer.
- **Bottom-line:** Pedometers, used with specific exercise goals, provide an inexpensive, tangible measure of a patient's physical activity, and have been demonstrated to increase physical activity levels - at least in the short term.

#5 July 14, 2009

How do I motivate my patients to participate in regular physical activity?

1. Wear your pedometer every day for 1 week.
2. Calculate your daily steps.
3. Add 500 steps per day to your daily average. Walk that each day for the next week.
4. Repeat step 3, adding 500 steps to last week's daily goal, and walk that each day for the next week.
5. Continue until you reach 10 000 steps per day.

#5 July 14, 2009

Does calcium (Ca+) supplementation contribute to increased risk of MI and other CVD?

- Evidence: Sys Rev 15 RCT
  - Calcium increased MI risk: RR 1.27 (1.01 - 1.59)
  - NNT 135 to 211 x4 years.
  - Others find no effect or NNT 240 (x5yr)
- **Bottom-line:** The present evidence suggests that calcium supplementation, particularly ≥1000mg/day, may lead to an increase risk of MI. This evidence is poor and the risk, if present, is likely <1%.

#41 February 7, 2011

The Gang plus The Audience

Does medical expulsion therapy (MET) improve passage of renal stones and other clinically relevant outcomes?

- Evidence: Meta-analysis of 33 Trials (3105 patients)
  - Stone Expulsion is statistically significantly better with MET vs Placebo (80% vs 54%) by 28 days NNT 4.
  - Small stones less benefit (because they pass anyway)
- **Bottom-line:** The current evidence indicates that patients with renal stones <10mm, who are eligible for observation, can be offered alpha-blockers or nifedipine to increase the chance of stone expulsion, decrease pain and decrease the time to stone expulsion.

#18. January 18, 2010. Updated April 22, 2011

Does drinking coffee impact mortality or other health outcomes in the general population?

- Evidence: 400,000 (US) x 14 yrs (+ other cohorts)
  - Increased mortality with coffee (but lots of confounders)
  - Men: About 10% relative reduction for ≥2 cups/day
  - Women: About 15% relative reduction for ≥2 cups/day
- **Bottom-line:** Coffee consumption is associated with no change or a small reduction in mortality in cohort studies. While the evidence is not strong enough to recommend non-drinkers to start consuming coffee, coffee drinkers can be reassured that it does not appear to result in excess harm (except in pregnancy).

#74 October 1, 2012

Do antihistamines (alone or combo) improve cold Sx?

- Evidence: 3 Systematic rev (mostly moderate-poor RCTs)
  - Antihistamine alone: no meaningful effect.
  - Antihistamine with decongestants and/or decongestants improved global symptoms NNT 4-7.
    - Limited evidence of benefit in peds
  - Antihistamines and "cold and cough preparations" are 2nd and 6th most common substances involved in (age ≤5 years) pediatric deaths.
- **Bottom-line:** Antihistamines alone have no meaningful impact on the common cold. Although evidence is at moderate to high risk of bias, antihistamines combined with decongestants and/or analgesia may have a small impact on improving symptoms for one in 4-7 patients but should not be used in children under 6.

#80 January 7, 2013

Is oral Vitamin B12 as effective as intramuscular (IM) Vitamin B12?

- Evidence: 2 RCTs and lots of cohort data
  - Oral and IM = Equal outcomes
  - 5-20% elderly B12 Def
  - In people with confirmed disease (like IBD), unclear
  - Up to 10% may have B12 drop on oral, so check level
- **Bottom-line**: Oral Vitamin B12 is as effective as IM in most B12 deficient patients. A dose of 1000mcg (1mg) orally a day appears to be adequate and most commonly recommended.

#19 Feb 02, 2010

For patients with acute gout, is colchicine an effective treatment and when would its use be indicated?

- Evidence: Low dose (1.2 + 0.6 at 1 hr) vs Placebo,
  - 50% reduction in pain 38% vs 16% (NNT 5)
  - High dose no better but more side effects
  - Diarrhea: High dose NNH 2; Nausea NNH 8
- **Bottom-line:** Colchicine is a reasonable option for the treatment of acute gout, especially in patients in whom NSAIDs are contraindicated. Optimal dosing which balances treatment benefit with potential adverse events still remains to be determined, but low dose is recommended.

#57 November 29, 2011

Once we have initiated bisphosphonate therapy, how frequently should we check bone mineral density (BMD)?

- Evidence: Too much variance for frequent testing
  - Over 2 weeks, BMD variance = 2.4-5%
  - Over 3 yrs BMD improves on Tx by 1-6%.
- **Bottom-line: "**Repeating BMD in the first three years after starting treatment with a bisphosphonate is unnecessary and potentially confusing." The vast majority of patients taking a bisphosphonate will get an adequate increase in BMD after three years and have a reduced fracture risk regardless of BMD changes.

#32 September 8, 2010

The Gang plus The Audience

Can osteoporosis patients on bisphosphonates for 5 yrs d/c meds without increasing future fracture risk?

- Evidence: FLEX RCT, bisphosphonate x 5 yrs, off 5 yrs
  - No difference in fractures
  - HORIZON-Pivotal Fracture Trial (PFT) Extension: Zoledronic
  - Also, no effect on preventing fractures.
- **Bottom-line**: Available evidence suggests that after 5 years of treatment, discontinuation of bisphosphonates carries little to no increased future fracture risk. Choosing appropriate patients to continue therapy beyond 5 years and determining when or if to reinitiate therapy in those discontinued, remains uncertain.

#33 September 20, 2010. J Bone Miner Res. 2012;27:243-54

Are topical NSAIDs effective in reducing pain in acute & chronic (including OA) musculoskeletal pain?

- Evidence: Acute MSK pain (Sys rev 47 RCTs)
  - 6-8 days NNT=4 and 9-14 days NNT=9.5
  - 3 Sys Rev: NNT 4.6 short term.
  - Long-term (=12 weeks) effects: present but less
- **Bottom-line:** In acute and chronic (like osteoarthritis) musculoskeletal pain, topical NSAIDs are superior to placebo and equivalent to oral NSAIDs. Topical NSAIDs adverse event rates are not statistically greater than placebo.

#40 January 24, 2011

Do omega-3 fatty acid supplements reduce the risk of recurrent CVD in patients with existing CVD?

- Evidence: Evidence: 3 RCTs (2500-5000): No effect
  - Meta-analysis (20,000): No effect
  - RCT 12,000 diabetics (60% with CVD): no effect
  - RCT 12,000 past non-MI CVD or high risk: no effect[2]
- **Bottom-line:** Although guidelines recommend increased dietary omega-3 consumption, evidence does not support using omega-3 fatty acid supplements to prevent recurrent CVD events in patients with cardiovascular disease.

CFP. 2012;58:1225. NEJM. 2013;368(19):1800-8.

Is any diet better for weight loss or preventing -ve health outcomes like heart disease or mortality?

- Evidence: No difference in low vs high carb,
  - No evid: DASH, very low cal (≤ 800 cal), & cohort wgt loss
  - Med diet: CVD NNT 12-14, mortality NNT 25 x2-3 yrs
    - NNT for CVD in primary prevention over 5 yrs = 77.
- **Bottom-line:** Weight loss for all diets is best at 6 months, regain is common, and by two years there is no consistent difference between diets. Only the Mediterranean diet has demonstrated positive results in hard outcomes like mortality, despite not having differences in weight or surrogate markers like lipid profiles.

#46 April 18, 2011. N Engl J Med 2013;368:1279-90.

Daily multivitamins reduce mortality ?

- Evidence: Meta-analysis of 21 RCTs (91,074 patients) x3.5 years. Most are primary prevention studies from Europe or North America.
  - No effect on overall mortality: RR 0.98 (0.94-1.02)
  - No effect on cancer mortality: RR 0.96 (0.88-1.04)
  - No effect on CVD mortality: RR 1.01 (0.93-1.09)
- **Bottom-line:** Present evidence does not support the routine use of multivitamins to reduce mortality, cardiovascular disease or cancer for people in developed countries.

#87 April 15, 2013

When repairing lacerations, do sterile gloves or sterile water make a difference?

- Evidence: 1 RCT & 1 meta-analysis, infection rates
  - sterile gloves 6% vs non-sterile 4.3% (no diff)
  - Sterile saline 6.7% vs tap water 4.4.% (no diff-pooled)
  - Sterile saline vs tap water - no diff in best study
- **Bottom-line**: The present evidence indicates that simple lacerations can be cleaned with tap water and repaired with clean non-sterile gloves without an increased risk of infection.

#2 June 1, 2009

The Gang plus The Audience

What are the benefits and harms of cholinesterase inhibitors (ChEI) for Alzheimer's dementia?

- Evidence: Over 20 meta-analyses, focus on Cochrane review of 13 trials (7,298 patients) and 4 other Sys reviews
  - ChEI vs. placebo, no clinically meaningful mean change in cognition:
    - MMSE: overall 1.37, vary from -0.04 to 1.37 depending on study
  - Number who had clinically meaningful improvement:
    - ADAS-Cog > 4 (out of 70): NNT = 6-18
  - Drop-out due to adverse events: NNH = 10 overall
- **Bottom-line:** Evidence for ChEI in Alzheimer's dementia is limited by small differences and high drop-out rates. Approximately 1 in 10 patients show meaningful improvement when treated for six months and 1 in 10 patients stop using the drug due to adverse events.

Thanks for your questions and discussion.

Thanks for completing your course evaluations.

HAVE A SAFE TRIP HOME

We hope to see you next year!