

# Bale/Doneen Live Chat Session

July 29, 2011

4-5 pm PST

Bradley Bale, MD

# Intension of the live chats

- New data and slides
- Discuss “hot” topics
- Questions
- Case study
- Review upcoming meetings
- Open discussion for remaining

# New Data

- SEARCH
- Simvastatin restrictions
- When to dose BP meds?
- Genetics – MI vs CVA
- Optimism and stroke risk
- CIMT

# Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine

- Rory Collins and Jane Armitage  
on behalf of the SEARCH  
Collaborative Group

**University of Oxford, Nuffield Department of Clinical Medicine**  
11/92008 [www.ctsu.ox.ac.uk](http://www.ctsu.ox.ac.uk)

# SEARCH: 2 separate randomized treatment comparisons in 12,064 post-MI patients

- More versus less LDL-lowering comparison:
  - Simvastatin vs Simvastatin
  - 80 mg daily 20mg daily

Homocysteine-lowering comparison:

Folic acid 2mg plus vitamin B12 1mg daily vs Placebo tablets

Mean (SD) duration: 6.7 (1.5) years

# SEARCH: Eligibility criteria

- Previous myocardial infarction
- Men and women
- Aged 18 to 80 years
- Current use of, or clear indication for, statin
- No admission in previous 3 months for MI, unstable angina or coronary revascularisation (and none planned in next 3 months)

# AGE and SEX at baseline

Baseline feature	Number	Percentage
Age (years)		
<60	3765	31%
≥60 <70	4828	40%
≥70	3471	29%
Mean age 64 years (SD 9)		
Sex		
Male	10012	83%
Female	2052	17%

# SEARCH: Vascular outcome definitions

MAJOR CORONARY EVENTS = Non-fatal MI, coronary revascularisation or CHD death

STROKE = Any non-fatal or fatal stroke (including subarachnoid haemorrhage)

REVASCULARISATION = Coronary or non-coronary artery surgery or angioplasty (including amputation)

**MAJOR VASCULAR EVENTS = MCE**

**+ stroke**

**+ revascularisation**

**University of Oxford, Nuffield Department of Clinical Medicine**  
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# SEARCH: Baseline LIPID levels after 2 month pre-randomisation run-in on SIMVASTATIN 20mg daily

	Mean (SD) baseline mg/dl
Total cholesterol	163 (27)
Direct-LDL	97 (23)
HDL	39 (15)
Triglycerides*	168 (106)

\*Non-fasting

# Reduction in LDL CHOLESTEROL with allocation to 80mg versus 20 mg SIMVASTATIN daily

	<u>Reduction: 20mg – 80mg</u>	
	mg/dl	percent
Month 4	20	20%
Year 1	15	16%
Year 5	11	12%
<b>AVERAGE</b>	<b>14</b>	<b>14%</b>

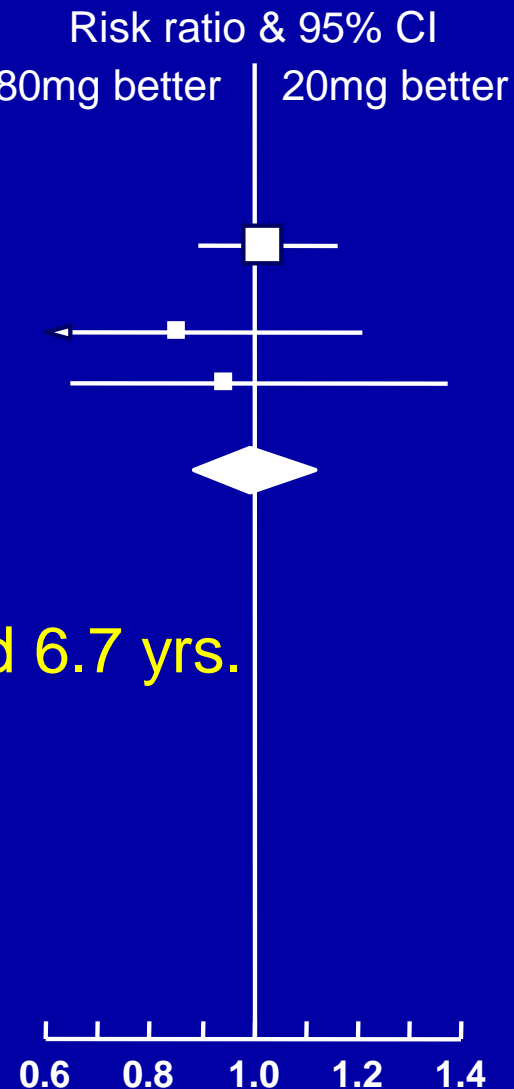
# SEARCH: Myopathy rates by SIMVASTATIN comparison

	Simvastatin allocation (per 1000 person-years)	
Years of follow-up	80 mg (6031)	20 mg (6033)
0-1	25 (4.2)	1 (0.2)
2-7	28 (0.8)	2 (0.1)
Total	53	3

Myopathy: New, unexplained muscle pain or weakness  
plus CK > 10x ULN (7 vs 0 developed rhabdomyolysis)

# High Dose Statin No Better than Lower Dose in Stable CHD

Cause of death	Simvastatin allocation		Risk ratio & 95% CI	
	80mg (n=6031)	20mg (n=6033)	80mg better	20mg better
CHD	447 (7.4%)	438 (7.3%)	[Forest plot point estimate]	
Stroke	57 (0.9%)	67 (1.1%)	[Forest plot point estimate]	
Other vascular	53 (0.9%)	56 (0.9%)	[Forest plot point estimate]	
<b>All vascular</b>	<b>557 (9.2%)</b>	<b>561 (9.3%)</b>	[Forest plot diamond]	



12,064 stable post-MI patients; followed 6.7 yrs.  
83% male; 31% ≤60; 29% ≥70

SEARCH trial University of Oxford, Nuffield Department of Clinical Medicine

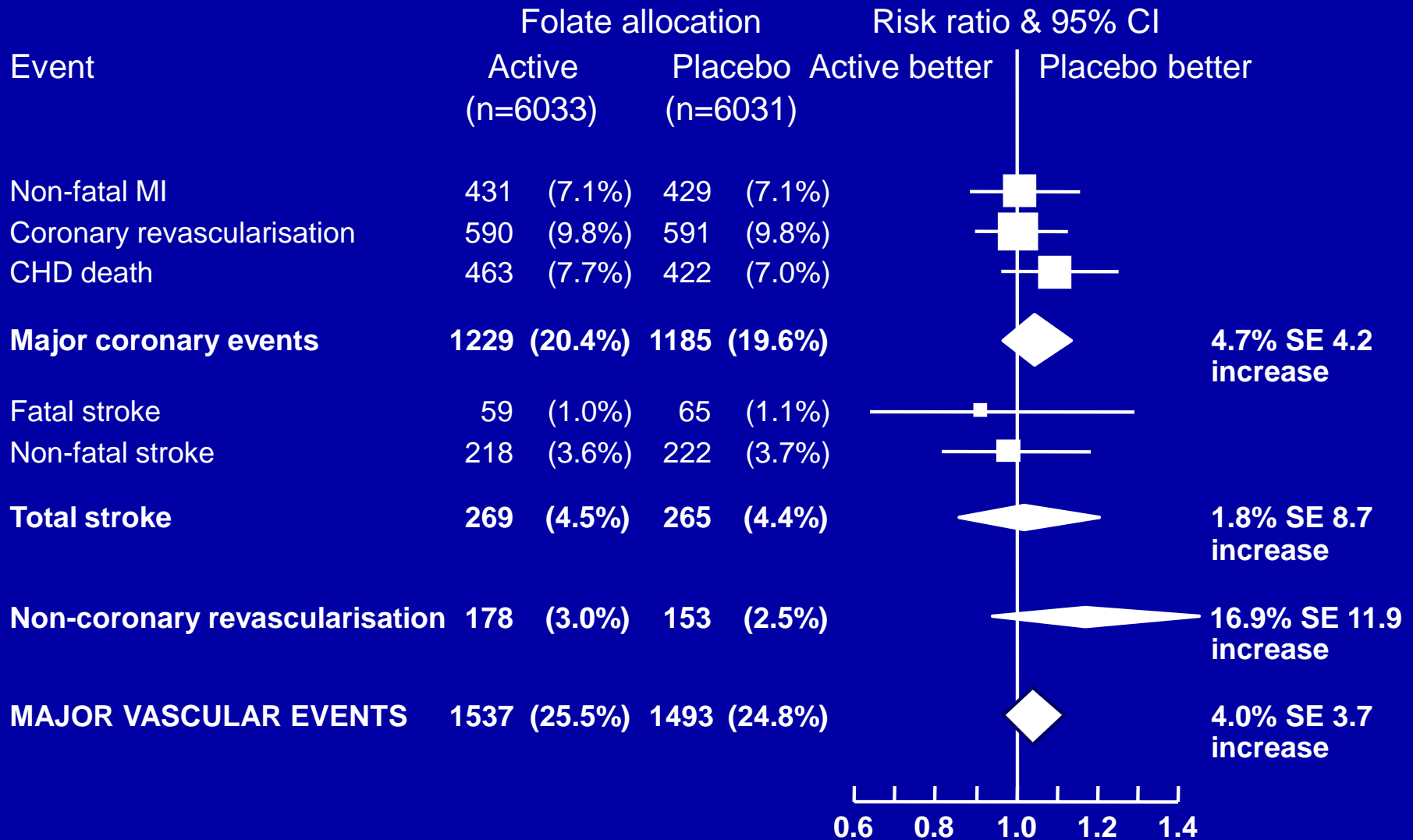
11/92008 www.ctsu.ox.ac.uk

# Reduction in HOMOCYSTEINE with allocation to FOLATE/B12 versus placebo

Mean (SD) baseline: 13.5 (5)  $\mu\text{mol/l}$

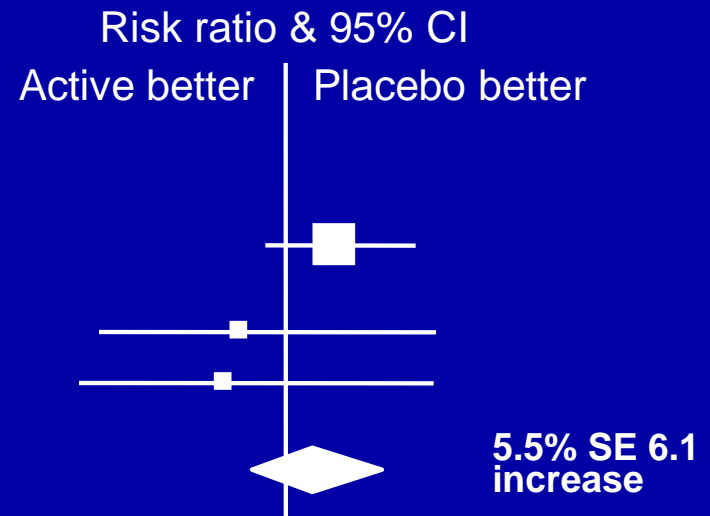
	Reduction	
	$\mu\text{mol/l}$	percent
Month 4	4.2	31%
Year 1	4.0	30%
Year 5	3.7	27%
<b>AVERAGE</b>	<b>3.8</b>	<b>28%</b>

# FOLATE/B12 on MAJOR VASCULAR EVENTS



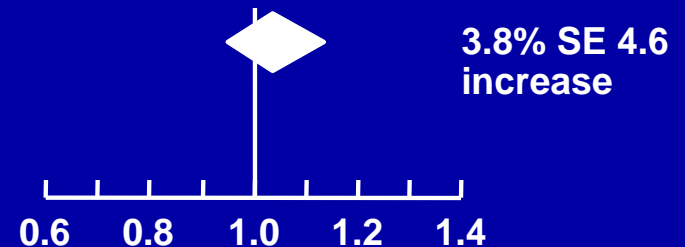
# Lowering Homocysteine does not reduce Mortality

Cause of death	Folate allocation			
	Active (n=6033)		Placebo (n=6031)	
CHD	463	(7.7%)	422	(7.0%)
Stroke	59	(1.0%)	65	(1.1%)
Other vascular	51	(0.8%)	58	(1.0%)
<b>All vascular</b>	<b>573</b>	<b>(9.5%)</b>	<b>545</b>	<b>(9.0%)</b>



12,000 stable post MI pts.; followed 6.7 yrs.  
 Homocysteine lowered average 28%;  
 30% baseline levels  $\geq 14$

All causes	983	(16.3%)	950	(15.8%)
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SEARCH trial University of Oxford, Nuffield Department of Clinical Medicine

11/92008 [www.ctsu.ox.ac.uk](http://www.ctsu.ox.ac.uk)

# Simvastatin Restrictions

- 80mg dose not recommended
- Based on data from SEARCH  
7 yr trial 20mg vs 80mg in post MI pts  
myopathy with CK >10X normal  
3 out of 6,033 pts in the 20-mg group  
53 out of 6,031 pts in the 80-mg group

FDA Safety Announcement 6/8/2011



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Myopathy: New, unexplained muscle pain or weakness  
plus CK > 10x ULN (7 vs 0 developed rhabdomyolysis)

# Simvastatin Restrictions

- Patients currently taking 80-mg should:
  - 1) Not stop taking unless told to by their healthcare professional.
  - 2) Review their medical history and their other current medications
  - 3) Know meds never to be taken with simvastatin
  - 4) Immediately contact healthcare professional, if they experience muscle pain, tenderness or weakness, dark or red colored urine, or unexplained tiredness.

FDA Safety Announcement 6/8/2011

# Simvastatin Restrictions

- Contraindicated with simvastatin:
  - Itraconazole
  - Ketoconazole
  - Posaconazole (New)
  - Erythromycin
  - Clarithromycin
  - Telithromycin
  - HIV protease inhibitors
  - Nefazodone
  - Gemfibrozil
  - Cyclosporine
  - Danazol

FDA Safety Announcement 6/8/2011

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# Simvastatin Restrictions

- Do not exceed 10 mg simvastatin daily with:
  - Amiodarone
  - Verapamil
  - Diltiazem
- Therefore, the above are contraindicated with Simcor

FDA Safety Announcement 6/8/2011

# Simvastatin Restrictions

- Do not exceed 20 mg simvastatin daily with:
  - Amlodipine
  - Ranolazine

FDA Safety Announcement 6/8/2011

# Relative LDL-lowering Efficacy of Statin and Statin-based Therapies

Atorva	Fluva	Pitava	Lova	Prava	Rosuv	Vytor	Simva	%↓ LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----		-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----		-----	-----	20 mg	10/40 mg	-----	55%
	-----		-----	-----	40 mg	10/80 mg	-----	63%

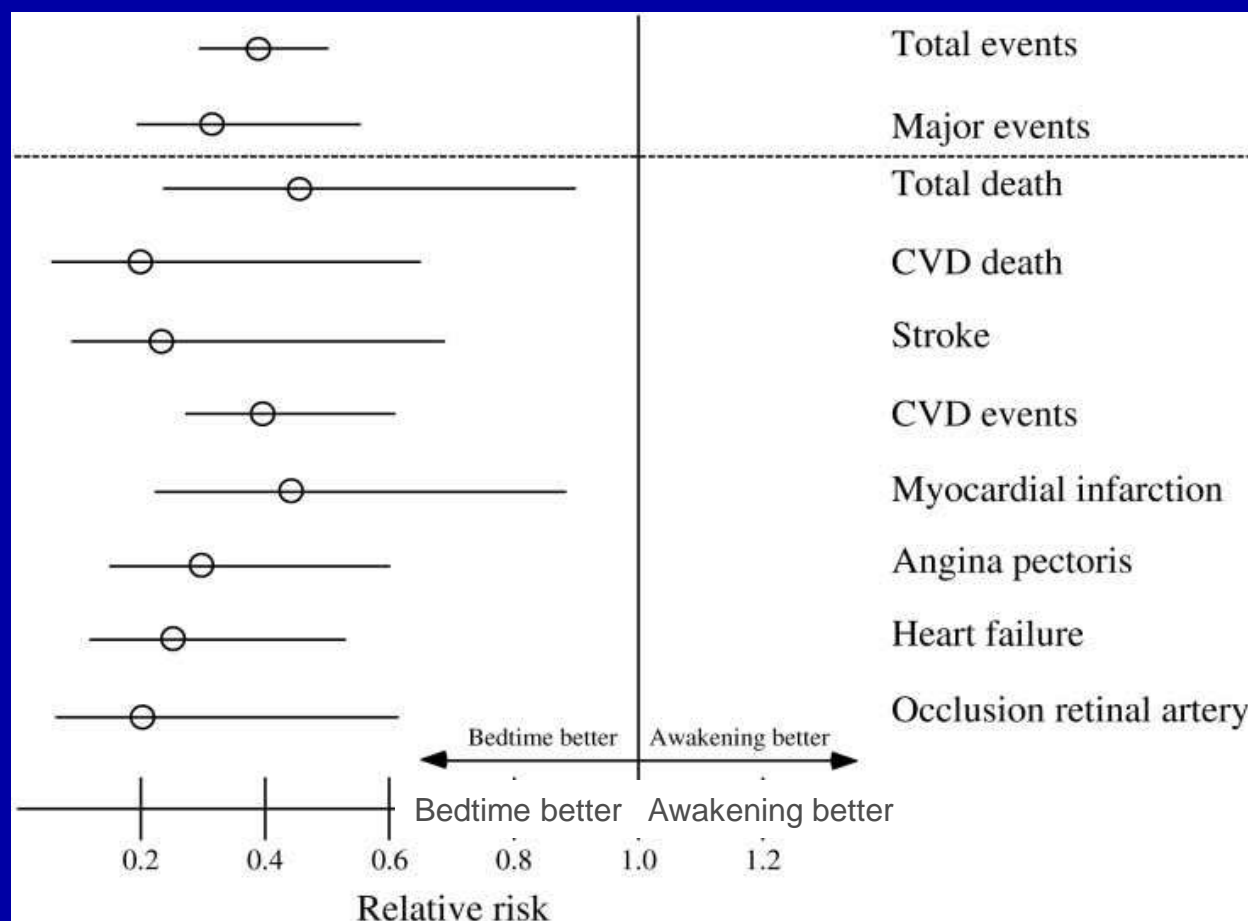
FDA Safety Communication 6/8/2011

# Bedtime Dosing of BP Meds More Effective

- 2156 hypertensive subjects, 1044 men/1112 women,  $55.6 \pm 13.6$  (mean  $\pm$  SD) yrs of age
- About 43% on monorx; 15% dual; 41% triple; about 60% on an ARB and 20% on ACEI (ramipril or spirapril) ; 40% CCB; 40% BB; 50% diuretic
- Diastolic about 1.5 points lower and systolic about 3 mm less in nighttime dosing

Hermida, R. C., et. al. *Chronobiology International* 2010, 27(8): 1629–1651

# Relative risks of CVD Events as a Function of Time-of-Day of Hypertension Treatment



95% confidence intervals ; adjusted by age, sex, and DM  
 Number of events 187 versus 68;  $p < .001$

Hermida, R. C., et. al. *Chronobiology International* 2010, 27(8): 1629–1651



# Heart Attack Under More Genetic Influence than Stroke

- Data from the prospective OXVASC
- Compared about 1,000 pts with ACS vs about 1,000 pts with TIA/Stroke. Pts had an average of three siblings.

Famhx same event	TIA/Stroke	ACS
% one parent	21.3	30.6
% two parents	2.1	5.2
% one sibling	8.1	21.1
% two siblings	1.4	7.1

Banerjee A, et. al. *Circ Cardiovasc Genet* 7/26/2011;  
DOI:10.1161/CIRCGENETICS.110.959114.

# Heart Attack Under More Genetic Influence than Stroke

- One parent with MI: 1.48-X likelihood of having a sibling with MI (95% CI 1.04-2.10)  $p=0.03$
- Two parents with MI: 5.97-X likelihood of having a sibling with MI (95% CI 3.23-11.03)  $p<0.0001$
- Parental stroke was not associated with sibling stroke
- Stroke is a very complex phenotype and has more diverse etiologies

Banerjee A, et. al. *Circ Cardiovasc Genet* 7/26/2011;  
DOI:10.1161/CIRCGENETICS.110.959114.

# Optimism Reduces Stroke Risk

- Prospective 2 yr. observation of 6,044 adults  $\geq 50$  yo; 88 strokes
- Utilized an optimism measure ranging from 3 to 18
- Each unit increase in optimism associated with an OR of 0.90 for stroke (95% CI, 0.84 to 0.97)  $p=0.01$
- Significant post fully adjusting for: age, behavioral, biological, and psychological stroke risk factors

Kim ES, et. al. *Stroke* 7/21/2011; DOI:10.1161/?STROKEAHA.111.613448.

# CIMT Predicted Presence of Diabetes

- 355 pts >40yo ;  $\geq 1$  CV risk factors; 75% had abnormal CIMT (AbnICUS): >75th percentile or plaque.
- AbnICUS presence independently predicted diabetes mellitus ( $\beta = 3.81$ ; 95% CI, 1.53–6.08;  $P = .001$ ).

Johnson HM, et al. *J Am Soc Echocardiogr* 7/2011; 24:738-747

# CIMT Results Effects Therapeutic Goals

- 355 pts >40yo ;  $\geq 1$  CV risk factors; 75% had abnormal CIMT: >75th percentile or plaque.
- CIMT findings altered LDL goals in 50% -  $p < 0.001$
- CIMT resulted in initiating aspirin rx in 26% -  $p < 0.001$

Johnson HM, et al. *J Am Soc Echocardiogr* 7/2011; 24:738-747

# CIMT Results Effects Patient Behaviors

- Immediate effect - abn report increased:
  - 1) CVD risk perception (OR, 4.14; P < .001)
  - 2) intentions to exercise (OR, 2.28; P = .008)
  - 3) intentions for dietary changes (OR, 2.95; P < .001)
  - 4) intentions to quit smoking (OR, 4.98; P = .022)
- 30 days later – abn report resulted in:
  - 1) reduced dietary sodium (OR, 1.45; P = .002)
  - 2) increased fiber (OR, 1.55; P = .022)
  - 3) 11.1% of the 45 smokers reported cessation - ?S
  - 4) 34% increased exercise frequency – NS
  - 5) 37% reported weight loss - NS

Johnson HM, et al. *J Am Soc Echocardiogr* 7/2011; 24:738-747

# Sodium/potassium Ratio Important

- Data from NHANES III; prospective; 12,267 US adults; mean follow-up 14.8 years; 825 CV deaths and 443 CAD deaths
- After multivariable adjustment, sodium-potassium ratio, comparing the highest quartile with the lowest quartile were HR - 1.46 for CVD mortality, and 2.15 for CAD mortality.
- Sodium/potassium ratio of  $<1$  is protective
- Simple solution is to replace regular snacks with fruit: doughnut contains 210 mg of Na and 120 mg K ; orange 1.6 mg of Na and 150 mg K

Yang Q, et. al. *Arch Intern Med* 7/11/2011; 171:1183-1191.





# CardioHealth<sup>®</sup> Station



## What is the CardioHealth® Station?

The CardioHealth® Station is a multi-modality platform that encompasses the following:

- **Non-Invasive, High-Resolution Ultrasound Imaging (IMT/Plaque)**
- **Electrocardiogram \***
- **Point of Care Blood Testing: includes Genetic, Lipid, & Proteomic Testing \***
- **Blood Pressure & Ankle Brachial Index (ABI)\***
- **Body Measurements: includes Height, Weight, & Body Mass Index (BMI)\***
- **Risk Factor Profile and Cardiovascular Risk Calculator**



# “This is Not Your Father’s Oldsmobile!”



## Standard Carotid Scan – “Old Way”

- Complex Setup. Too many buttons & knobs.
- Advance Training Required.
- Heavily Dependent on Operator.
- Complex Report, explanation required.
- Longer patient wait time.
- Offline software required for IMT measurement.
- No Medical Bluetooth available for standard ultrasound.
- Unavailable on Standard Imaging Equipment.
- EKG Needed for Standard Carotid Scan.



## CardioHealth® Station

- Easy to use. Interactive Touch Screen.
- Minimal Operator Training Required.
- Operator Independent.
- Easy to Read Report, Color Graphics,
- Patient wait time – approximately five minutes.
- Fully Automated. Real Time IMT measurement.
- Seamless connectivity through Continua® - (Medical Bluetooth Technology).
- Will include EKG, Blood Pressure, Ankle-Brachial Index, Lipid Testing and Body Measurement Applications.\****

*\* FDA approval pending*



**NO EKG NEEDED**  
with CardioHealth® Station

## CardioHealth<sup>®</sup> Station

In order to provide a consistent and repeatable Carotid Scan measurement, several carotid ultrasound features have been automated:

- 1) Auto-ROI : Automated Region Of Interest gate for vertical direction.
- 2) Auto-Trigger : Automated cardiac cycle trigger. Eliminates the need for external ECG.
- 3) Auto-IMT : Automated IMT measurement. No need for offline storage and/or additional interpretation software.
- 4) Auto-Freeze : Automated freeze. Scanning image is frozen automatically once quality index reaches predefined threshold.
- 5) Auto-Angle : Automated angle measurement. The angle of the ultrasound probe is measured in real time.
- 6) Auto-Report : Automated report. When the measurement ends, the report has been automatically completed.

## CardioHealth® Station

The CardioHealth Station *improves workflow.*

### Current Method

1. The patient lies on the bed.
2. The EKG leads are placed.
3. The angle measuring instrument tool is set up.
4. The ultrasound scan is begun.
5. The carotid artery is found.
6. The region of interest (ROI) is selected by hand.
7. The quality of the measurement is judged.
8. The image of the ventricular end-diastolic is selected.
9. The IMT boundary is traced.
10. The angle of the probe is recorded.
11. The report is made.



### CardioHealth Station

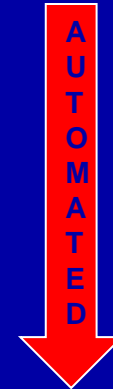
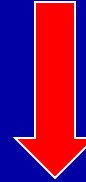
1. The patient lies on the bed.

(Steps eliminated)

2. The ultrasound scan is started.
3. The carotid artery is found.

(Steps eliminated)

4. The report is made.





## Interpreting the CardioHealth® Report

### Traditional Risk Factors

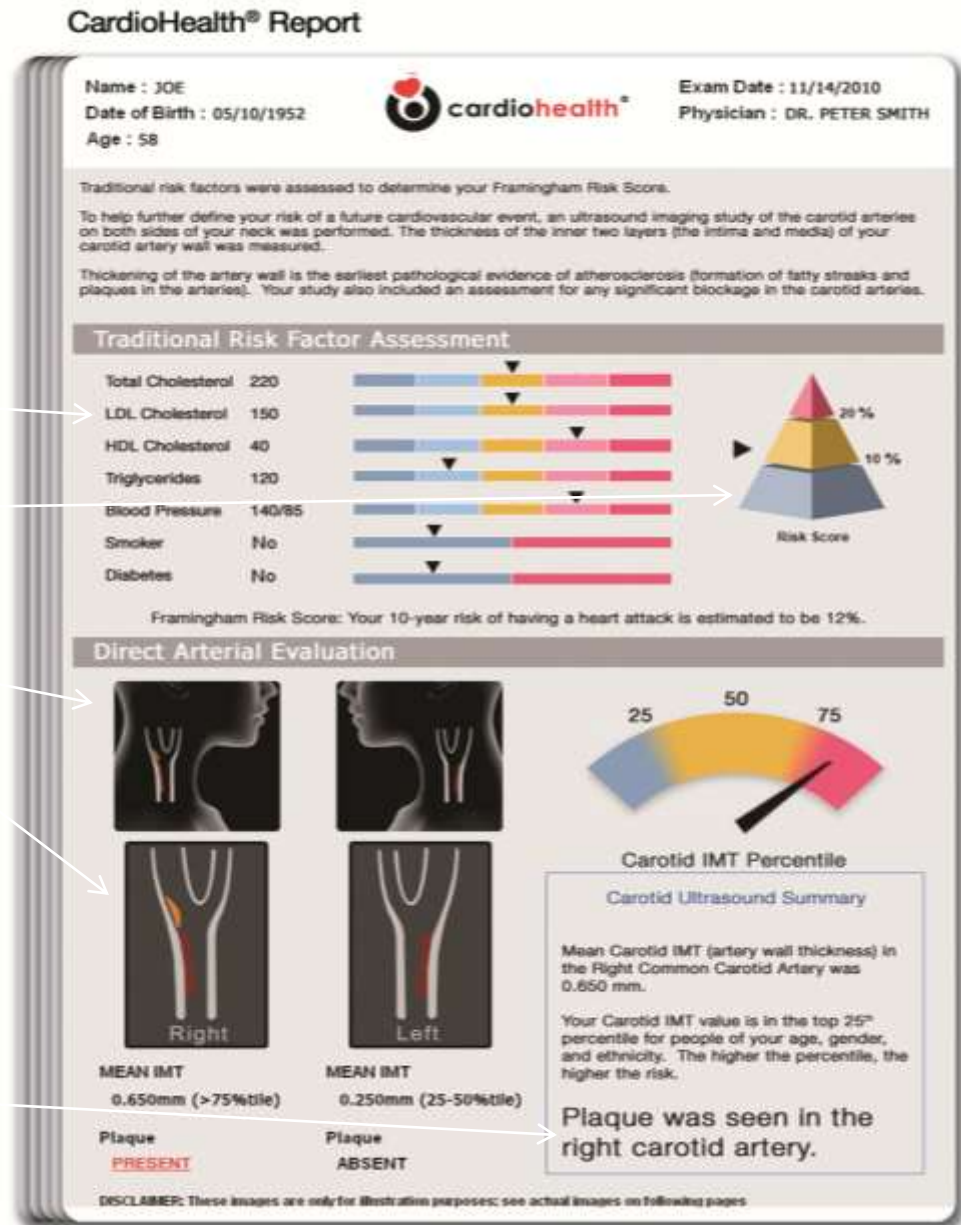
Such as Total Cholesterol, LDL, HDL and Blood Pressure.

### Risk Score Pyramid

This derives from the Framingham Risk Score.

**Direct Arterial Evaluation** Schematic images of both right and left carotid artery. Color-coded symbols depict CIMT level and presence or absence of plaque.

**Carotid Ultrasound Summary** This section displays the higher mean CIMT value (left versus right) and where this CIMT value falls in relation to that of others of the same age, gender, and ethnicity. It also shows if plaque was detected during the exam. In this case, plaque was seen in the right carotid.



# The Graphic User Interface

The colorful, touch screen, graphic user interface was designed to simplify and automate the entire risk assessment study, including the carotid ultrasound scan.



# “Hot” Topics

- Chantix
- Actos and Bladder Cancer
- Prevention

# Varenicline Increases CV Risk

- Meta-analysis; 14 trials; 8,216 pts without CAD; 7 to 52 wks

Outcome	Varenicline (n=4908), n (%)	Placebo (n=3308), n (%)	Odds ratio (95% CI)
Serious CV events	52 (1.06)	27 (0.82)	1.72 (1.09-2.71)

1 in 10 on Chantix quit smoking; the NNT to cause 1 CV event is 28

FDA warning: varenicline may increase CV event risk in patients with CVD; based on study of 700 pts. with known CAD

Singh S, et. al. *CMAJ* 7/2011. Available at: <http://www.cmaj.ca>



# European Medicines Agency Statement on Varenicline

- EMA believes the benefit/risk balance for varenicline "remains positive"
- Number of limitations in the meta-analysis, the most striking of which was the low number of overall events.
- Asked Pfizer to submit additional information on CV events

European Medicines Agency. European Medicines Agency confirms positive risk-benefit balance for Chantix. July 21, 2011.

# Pioglitazone and Bladder Cancer Risk

- FDA AERS 1/04-12/09: 31 cases of bladder cancer in pio pts out of 37,841 AERs for pio
- Only 4 cases in pts on pio >24 mos.
- 24 cases involved multiple drug use
- Reporting odds ratio (ROR) is calculated by case/noncase methodology ('noncases' were all the AERs reported for pio - not bladder CA)
- ROR was only significant in older pts and in the yrs. '04, '06, '07, '08 – 4, 9, 5, 6 cases respectively
- Takeda is doing 10 yr. observational study

Piccinni, C., PhD, et. al. *Diabetes Care* 6/2011 Vol. 34: 1369-1371

# European Medicines Agency Pioglitazone Statement

- Pioglitazone should not be considered in those with current or past history of bladder cancer or those with uninvestigated macroscopic hematuria
- Risk factors for bladder cancer should be "investigated," particularly in elderly patients, prior to therapy

European Medicines Agency. European Medicines Agency recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer. July 21, 2011.

# AHA Preaches Prevention

- Review conducted by the AHA Advocacy Coordinating Committee
- "True healthcare reform will be realized only when we focus attention on disease prevention and not disease management," AHA president - **Dr Gordon F Tomaselli**
- Every \$1 spent in wellness programs would save \$3.27 in medical costs and \$2.73 in absenteeism costs.
- "What we spend on cardiovascular disease is not sustainable. But we can afford to prevent it," - **Dr William S Weintraub**

Weintraub WS, et. al. *Circulation* 7/2011. DOI: 10.1161/CIR.0b013e3182285a81

# Bale/Doneen: Upcoming meetings

- BHL 5 hr Saturday Program
  - Aug 20: Charleston, SC
- Bale/Doneen CME Preceptorship Program
  - August 26-27: Chicago, IL
- BHL 5 hr Saturday Program
  - Sept 10: Houston, TX
- Cleveland HeartLab & Bale/Doneen Reunion
  - September 15-17: Cleveland, OH
- CHL dinner lecture
  - Sept 22: New Orleans, LA