

Comparative Efficacy of Strategies for Risk Screening and Prevention for Cardiovascular Disease

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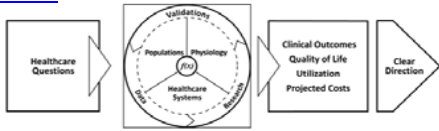
Introduction

- In over 50% of patients the initial presentation of coronary disease consists of a major event
- HMG Co-A Reductase Inhibitors (statins) and aspirin (ASA) have been shown to be of value in the primary or secondary prevention of CAD events.
- A number of screening strategies have been developed to identify patients at high risk for events who might benefit from prophylactic therapy.
- However, it is unknown which of these screening strategies is superior or how they would compare to universal administration of statins and ASA to the population at a given age.

Objective

Use a well validated large-scale computer simulation model to compare the clinical and cost effectiveness of several screening strategies to universal treatment and to no treatment at all.

The Archimedes Model



- The Archimedes Model is a clinically detailed simulation of human physiology, disease progression and healthcare delivery.
- The core of the model is a set of algebraic and differential equations representing the physiological pathways pertinent to diseases and their complications.
- Use of a single model enables Archimedes to address co-morbidities, multiple organ syndromes, drugs with multiple effects, and combinations of treatments.
- The use of differential equations preserves the continuous nature of biological variables and time, as well as the interactions between them.
- Diseases and outcomes are defined in terms of underlying variables, enabling diseases to occur and progress in the same continuous fashion as reality. Interventions to both prevent and manage diseases are modeled at the level of the underlying biology.
- The model accuracy has been validated against over 50 major clinical trials, including several statin trials relevant to this study such as HPS, 4S, IDEAL, and TNT.

Simulation Structure

- Multi-arm trial**, comparing current standard of care with leading candidates representing alternate approaches.
- Trial arms are:
- Standard care via ATP-III guidelines
 - Unconditional treatment: aspirin + statin for all
 - Imaging modalities via SHAPE proposal (2 variations)
 - Using coronary artery calcium score (CACS)
 - Using carotid intima-media thickness (CIMT)
 - Also compare to "do nothing" arm, where aspirin + statin not prescribed
- Population**
- Approx 50,000-person sample
 - Representative cross-section of US primary-prevention population, aged 40-75
 - Simulated individuals derived from people in NHANES, 1999-2004, to capture correct correlations & distributions of risk factors, histories
- Duration**
- Track for 35 years – until youngest members turn 75 – reporting results annually

Arms of the Trial

Standard Care

- Cholesterol management as specified in NCEP's ATP-III guidelines
 - Low risk: 0-1 risk factor LDL target: 160 mg/dl
 - Moderate risk: 2+ risk factors LDL target: 130 mg/dl
 - High risk: established CHD or equiv LDL target: 100 mg/dl
 - Very high risk: establ CHD + add'l risk LDL target: 70 mg/dl

- Management of hypertension, diabetes, etc. consistent with JNC-7, ADA guidelines, etc.
- Regular screening and care visits

Unconditional Treatment Arm

- All subjects receive statin therapy (simva 20mg) and low-dose aspirin (81mg)
- No screening process to initiate treatment; no titration of treatment for primary prevention
- Following CHD (or equivalent) events, change to "standard care" for secondary prevention
- No explicit modeling of side effects nor discontinuation of treatment
- Side effects of treatment were captured indirectly through their influence on long-term adherence

SHAPE Arms

- Replace risk assessment of "standard care" with stratification based on imaging modalities
 - Using coronary artery calcium score (CACS)
 - Using carotid intima media thickness (CIMT)
- Follow the SHAPE proposal for LDL targets and screening
 - SHAPE Task Force [Am J Cardiol 2006; 98S: 2H-15H]
- One exception: treatment begins at age 40 for all (for comparability across arms)
- Switch to unconditional treatment at age 75

Additional Features of the Simulation

Outcomes

- Primary health outcome: composite of MI, stroke, and CV death
- Benefit, via quality-adjusted life-years (QALYs)
- Cost-effectiveness, via $\Delta cost / \Delta QALY$

[Costs and QALYs discounted 3% per year]

Intervention Details

- Statin usage
 - Titration of dosage to reach LDL goal [except "unconditional" where simva 20 for all]
- Aspirin usage
 - Subjects begin taking low-dose aspirin when they reach the "intermediate" risk level [except in "unconditional"]
- Adherence rate: assumed 50%; can be varied

Costs

General healthcare costs computed based on Medicare 2006 reimbursements, plus these simulation-specific ones:

Visit	Cost	Intervention	Annual Cost
special screening visit	\$53.24	aspirin (81 mg)	\$18.80
LDL management visit	\$53.24	simva (5 mg)	\$174.29
		simva (10 mg)	\$202.65
		simva (20 mg)	\$283.79
		simva (40 mg)	\$295.94
		simva (80 mg)	\$344.63
		atorva (80 mg)	\$1,350.32
Procedure			
ABI	\$0.00		
CACS	\$132.77		
CIMT	\$38.55		

A note on CAD Equivalents

- For all arms except SHAPE: angina or MI, coronary revascularization, history of ischemic stroke or Diabetes
- For SHAPE: include PAD (ABI < 0.9); do not include diabetes
- Advance to secondary-care protocol after any cardiovascular event

Results: Clinical Effectiveness and Cost Effectiveness

	DO NOTHING	STANDARD CARE	SHAPE (CIMT)	SHAPE (CACS)	UNCOND'L
35-yr probability of first hard CVD event	35% *	28.8% *	28.6% *	28.4% * †	27.4% * †
total cost	\$49,479	\$49,505	\$50,022	\$50,238	\$49,343
total QALYs	16.62	16.95	16.95	16.97	17.02
$\Delta cost / \Delta QALY$ vs DO NOTHING	---	\$80	\$1,649	\$2,206	cost saving
$\Delta cost / \Delta QALY$ vs STANDARD CARE		Reduces QALYs	---	no benefit	cost saving

Costs and QALYs per initial person in the population. Figures based on a primary-prevention population, age 40-75, followed 35 yrs. Adherence rates of 50% for all four screening and prevention scenarios. * P < 0.0001 vs DO NOTHING; † P < 0.0001 vs STANDARD CARE; ‡ P = 0.06 vs STANDARD CARE

Limitations

- The model does not include any adverse effects that drug therapy may produce. Adverse events are acknowledged only through their possible effect in reducing patient compliance to medication, but not in terms of explicit modeling of health outcome complications.
- This is a simulation. It is a valuable exploratory tool, but is no replacement for an actual RCT, the cost and sample size of which would likely be prohibitive.
- The superiority of universal treatment and all strategies is directly related to the degree of adherence.
- The modeling of "standard care" used (including care for BP and glucose control) may be better than actual standard care.

Conclusions

- The Archimedes Model provides a powerful tool for simulation and exploration of alternative treatment scenarios
- Screening with standard care (ATP-III), CACS and CIMT as per SHAPE, and Unconditional treatment strategies all reduce hard CV events at low cost/QALY compared to doing nothing
- Unconditional treatment with statin and ASA is cost saving and is the only strategy that is significantly superior to ATP-III

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Results: Sample profiles of effect of screening protocols on biomarkers and health outcomes

