"Managing Carotid Artery Disease Through the Looking Glass of Comparative Effectiveness Research: Lessons and Future Prospects"

Internal Medicine Grand Rounds

May 28, 2010

Ethan Halm, M.D.

Ethan Halm, M.D., M.P.H.
Professor and Walter Family Chair in Internal Medicine

Dr. Halm is a Professor in Internal Medicine and Clinical Sciences. He is Chief of the William and Gay Solomon Division of the Division the General Internal Medicine at UT Southwestern. He is also the Chief of a Division of Outcomes and Health Services Research in the Department of Clinical Sciences. Dr. Halm's research interests are:

- Understanding the patient, provider, and system factors that influence the quality and outcomes of care
- Improving chronic disease management
- Assessing the impact of patient health beliefs on medication adherence and self-management
- Changing physician, patient, and organizational behavior
- Developing evidence-based approaches to the management of common conditions

This is to acknowledge that Dr. Halm has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Halm will not be discussing off-label uses in his presentation.

Managing Carotid Artery Disease Through the Looking Glass of Comparative Effectiveness Research: Lessons and Future Prospects

Ethan A. Halm, MD, MPH
Departments of Internal Medicine and Clinical Sciences
UT Southwestern Medical Center

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Talk Outline

- Intro to Comparative Effectiveness Research
- Carotid disease and its management
  - Review of the evidence base and controversies
  - Practical clinical info
- Parable of progression of CER studies
- Lessons and future prospects

Comparative Effectiveness Research: Rationale

- Evidence base in health care is suboptimal
- Much not rigorously evaluated
- Little info about pros/cons of competing drugs, devices, procedures, devices
- Little info about head to head treatment or effectiveness in real world practice & patients

Andy Grove: CEO on CER

"When I was doing semiconductor device research, it was expected that I would compare my results with other people's previously published results and that I would comment on any differences. But it seemed to be different in medicine. Medical practitioners primarily tended to publish their own data; they often didn't compare their data with the data of other practitioners, even in their own field, let alone with the results of other types of treatments for the same condition."

Fortune, May 13, 1996

Institute of Medicine Definition of CER

- CER is the generation and synthesis of evidence comparing benefits & harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve delivery of care
- The purpose is to assist consumers, clinicians, purchasers, & policy makers to make informed decisions that will improve health at individual & population level

Characteristics of CER

- Compare 2 or more alternatives, each with real possibility of being best practice
  - Different drugs, devices, procedures, diagnostic and treatment strategies
  - More than just Drug A v. Drug B (and not placebo)
- Range of methods: RCTs, observational studies, registries, claims databases, systematic reviews, meta-analyses
- Measure outcomes important to patients
- Results at subgroup level
- Emphasis on informing real world decisions

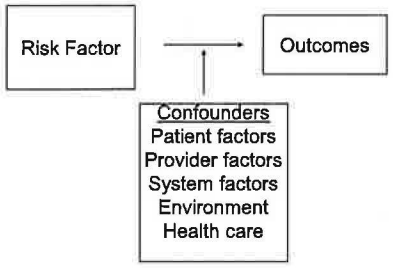
IOM Top 100 CER Priorities

- Cross cutting topics: health care delivery systems, disparities, disability
- Internal medicine topics: Cardiac, vascular, Endo/Metabolic, Heme/Onc, ID, Pulm, GI, Liver, Renal, Musculoskeletal, women's health, Geriatrics, palliative care
- Other topics: mental health, substance abuse, Neuro, Peds, birth/development, genetics
- Cite IOM CER report in your grant

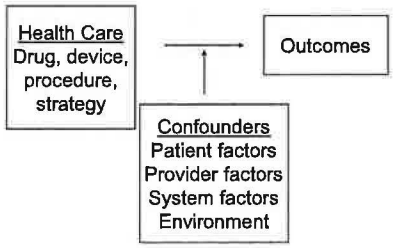
CER in Health Care Reform

- Increased research funding
  - ARRA dedicated $1.1 billion for CER
  - CER trust fund builds to $500 million/yr in 2013
- New Patient-Centered Outcomes Research Institute (PCORI)
  - Independent, non-profit, multi-stakeholder
  - Private-public funding: Medicare, health plans
  - Priority setting, methods standards, research, dissemination and implementation of findings

Traditional Clinical Research: Conceptual Model



Comparative Effectiveness & Health Services Research: Conceptual Model



Clinical Case A

- 70 year old man, HTN, ↑Chol
- CC: TIA 6 wks ago with right hand weakness & speech difficulty, now resolved
- Meds: ASA, ACEI, HCTZ, Statin
- Exam: 130/85, 80, bilateral carotid bruits
- Doppler Ultrasound:
  - 70% stenosis of Left ICA, 90% stenosis Right ICA
- Should he be referred for carotid surgery?
- Which artery would you fix, if any?

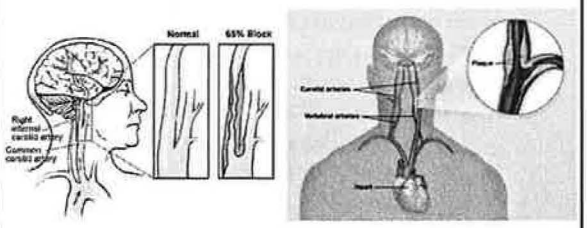
Clinical Case B

- 70 year old man, HTN, ↑Chol
- CC: No complaints, needs refills, forms
- Meds: ASA, ACEI, HCTZ, Statin
- Exam: 130/85, 80, bilateral carotid bruits
- Doppler Ultrasound:
  - 70% stenosis of Left ICA, 90% stenosis Right ICA
- Should he be referred for carotid surgery?
- Which artery would you fix, if any?

Stroke and Carotid Disease

- 750,000 strokes in US per year, 11% fatal
- Stroke is 3rd leading cause of death
- 240,000 TIAs in US/year
- Carotid disease causes about 10-15% of strokes
- Prevalence of moderate carotid stenosis (>50%):
  - <70 years: 5% men, 2% women
  - 70+ year: 12% men, 7% women
  - Incidence will grow as population ages (and no one goes un-imaged)

Carotid Artery Anatomy Made Ridiculously Simple



A Tale of Two Carotids: Symptomatic v. Asymptomatic Disease

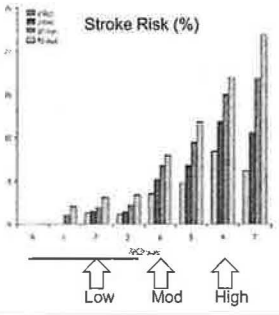
- Internal carotid artery supplies the retinal, anterior and middle cerebral artery
- Carotid distribution strokes and TIAs manifest as eye (amaurosis fugax), hand, arm, or leg symptoms or language/speech difficulties
- Symptomatic disease:
  - TIA or stroke in carotid distribution
  - Neurological symptoms in past 12 months
  - Not: dizziness, fatigue, the blahs
  - Unstable plaques: "ACS" of the internal carotid
  - Risk of stroke ↑ with ↑stenosis (90% > risk v. 50%)

Symptomatic Carotid Disease

- Recurrent Stroke:
  - 15-30% risk of 2nd stroke in 5 yrs
  - Highest in 1st yr after stroke (10%) then 4%/yr
- TIA as 'harbinger' of stroke: "ACS of brain"
  - 15% of ischemic strokes preceded by a TIA
  - Stroke after TIA: 5-7% at 7 days, 6-11% at 90 days
  - Half of strokes after TIA occur within 48 hrs of TIA
- TIAs should be taken very seriously
- ABCD2 prediction rule to stratify risk of impending stroke

Stroke Risk after TIA by ABCD2 Score

- **A** (Age); 1 pt for >60 yrs
- **B** (BP): 1 pt BP> 140/90
- **C** (Clinical features); 2 pts for focal weakness, 1 pt speech impairment without weakness
- **D** (Duration); 1 pt for 10-59 min of SX, 2 pts for ≥60 min
- **D** (Diabetes); 1 pt
- Score=Total # of points
- N=4800, 5 diff cohorts



Johnston et al. Lancet 2007

New Definition of TIA

- Old Definition: "Time-Based"
  - Transient neurological symptoms lasting < 24 hr
  - Not consistent with pathophysiology of brain ischemia/infarction or epidemiology of stroke risk
  - 33% of 'old defn' TIAs had infarction on imaging
- New Definition: "Tissue-Based"
  - Transient neurological dysfunction due to focal brain, spinal cord, or retinal ischemia
  - No brain imaging evidence of infarction
  - Typically lasting < 1 hr (at most a few hours)
  - MRI preferred test w/i 24 hrs of symptoms

AHA/ASA Council, Stroke 2009

Asymptomatic Carotid Disease

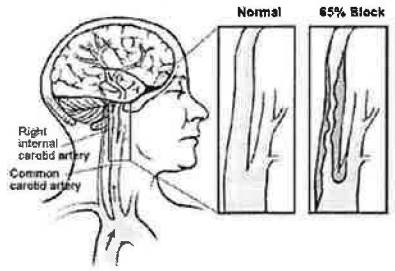
- Definition: No carotid symptoms in last 1 yr
- Silent atherosclerosis: detected inadvertently or via screening of uncertain rationale
- USPSTF does not recommend screening asymptomatic adults
- Risk of 'unheralded' stroke in ASX stenosis:
  - 1-2% per year older studies
  - 0.3% per year in recent data from post-statin era
- In ASX disease, risk of stroke does NOT increase with ↑ stenosis (60% = 90%).

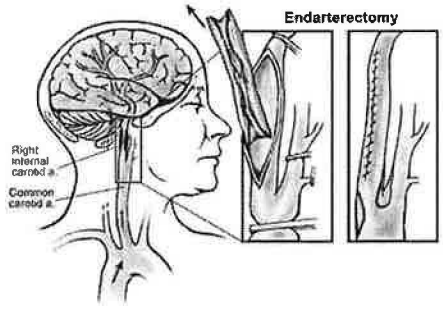
Medical Therapy in Asymptomatic Carotid Disease

- BP control ↓ stroke risk
- Aspirin:
  - ↓ risk of 1st stroke in women age 55 to 79 years, but not men (↓risk of MI in men, but not women)
  - Evidence of ASA-specific impact on carotid disease is not strong though AHA recommended
- Statins: Meta-analysis net benefit in ↓ stroke
- DM: tight control does not ↓risk of stroke
- Moderate exercise lowers stroke risk
- Smoking cessation

Carotid Endarterectomy (CEA) Made Ridiculously Simple

- CEA is surgery to prevent stroke by removing carotid plaque that can embolize, clot, or occlude
- Intermediate risk vascular procedure lasting 90 minutes (general or local anesthesia)
- Average 2 day LOS
- Performed by vascular, neuro, CT, and general surgeons





Natural History of CER Studies: Thru Lens of Carotid Surgery

- Innovation & Dissemination: "This new thing is great"
  - New procedure used without much evaluation
- 1st Generation Observational Studies: "This is terrible"
  - Outcomes of new procedure worse than expected, uncertainty about indications, high rates of inappropriateness
- RCTs: CEA v. medical therapy "Good for some, not all"
- 2nd Generation Observational Studies "Real world use"
  - Effectiveness v. efficacy: population-based studies of patterns of use, outcomes, appropriateness
- RCTs: CEA v. Stenting "Is the new mousetrap better?"
- Future Studies:
  - Personalized medicine: target Rx to Pt risk/benefits, shared decision making
  - Head to head comparison of all choices: CEA, CAS, meds

Early Use of Carotid Endarterectomy

- In the 1980s, carotid endarterectomy (CEA) was controversial
- Data on efficacy was lacking and complication rates were high
- RAND Medicare study of CEA in 1981:
  - Detailed chart review of 1500 CEAs from 3 states
  - 32% were for inappropriate indications
  - 75% were for symptomatic carotid stenosis (Strokes and TIAs)

Developing the Evidence Base: RCTs of CEA

- In response to these concerns, something amazing happened
- Several large RCTs were done to clarify who benefits from CEA, by how much, and under which circumstances
- Over 10,000 Pts randomized in North American and Europe
- Rare investment in RCTs of procedures

Symptomatic RCTs: Risks and Benefits of CEA v. Medical Therapy

Asymptomatic RCTs: Risks and Benefits of CEA v. Medical Therapy

Summary of RCTs: Risks and Benefits of CEA for Severe Stenosis

Summary of RCTs: Risks and Benefits of CEA for Severe Stenosis

Major Clinical Indications for CEA

- Symptomatic: more to gain
  - Stroke and Carotid TIAs
  - "ACS of the brain"
  - Unstable plaques
- Asymptomatic: less to gain
  - No carotid distribution symptoms
  - Plaque on imaging
    - Time bomb or incidentaloma?

Did Evidence Influence the Use of Carotid Endarterectomy?

ACAS: ASX

NASCET: SX

Did Evidence Change Appropriate Use of CEA?

- New York Carotid Artery Surgery Study (NYCAS)
- Define appropriateness of CEA use
- Assess the appropriateness and use of CEA among unselected, population-based cohort of Medicare Pts treated since RCTs
- Examine outcomes of CEA in real world practice

Defining Appropriateness: RAND Group Judgment Methodology

- Multidisciplinary, national expert panel to rate, discuss, and re-rate appropriateness of 1557 indications for CEA
- Indication is clinical scenario in which CEA might be considered
- Appropriateness rating for each clinical scenario:
  - Inappropriate: risks > benefits
  - Uncertain: benefits = risks
  - Appropriate: benefits > risks

Clinical Indication Structure

- Neurologic symptoms: type, severity, recency, frequency, disability
- Degree of carotid stenosis (ipsi and contra)
- Type of operation: CEA v. CEA/CABG, operating ipsi v. contralateral to symptoms
- Comorbidity/perioperative risk:
  - Revised Cardiac Risk Index (Lee et al.)
  - High comorbidity: 3+ risk factors
  - CAD, CHF, CVD, DM on Insulin, Creat > 2.0

New York Carotid Artery Surgery (NYCAS) Study Population

- Retrospective cohort of all CEAs in Medicare Pts in NY State January 1998 thru June 1999
- Included FFS and managed care cases
- Partnered with Medicare, NY QIO/PRO
- Research RNs abstracted detailed clinical info from charts on history, neuro exam, imaging
- N=9588 (94% of eligible cases)
- 166 hospitals, 488 surgeons

Patient Characteristics (N=9588)

Sociodemographics	(%)
Mean age*	75 yrs (40-98)
Male	56%
White	93%
Black	2.5%
Hispanic	2.2%
Other	2.4%
FFS	91%
Managed care	9%

*RCTs mean age: 65-67 years

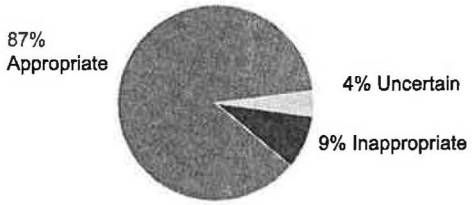
Comorbid Conditions (N=9588)

Comorbidity	(%)
Hypertension	78
CAD	62
Past stroke/TIA	44
Diabetes	30
CHF	9
Severe disability	3

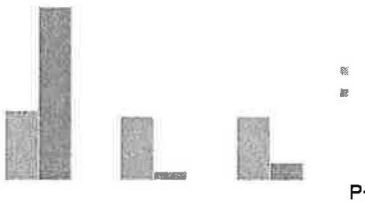
Indications for Surgery (%)

Carotid TIA	18	
Crescendo carotid TIA	<1	
Stroke-in-evolution	<1	
Minor stroke	8	
Major stroke	2	
Vertebrobasilar TIA	<1	72
Asymptomatic	69	
Asymptomatic CEA/CABG	3	

Appropriateness of CEA in NYCAS: 1998-1999



Changing Appropriateness Over Time: RAND v. NYCAS



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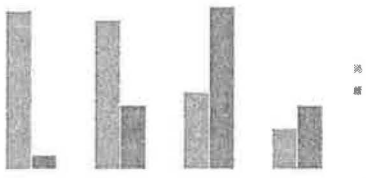
Halm et al. Neurology 2007

Changing Use of CEA Over Time: RAND v. NYCAS



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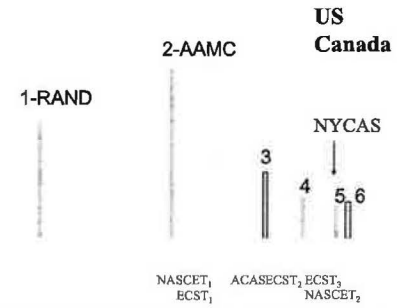
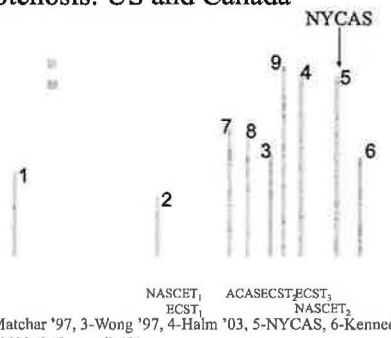
Halm et al. Neurology 2007

Decreasing Inappropriateness of CEA in US and Canada



1-Winslow '88, 2-Matchar '97, 3-Wong '97, 4-Halm '03, 5-NYCAS, 6-Kennedy '04

Increasing Use CEA for Asymptomatic Stenosis: US and Canada



1-Winslow '88, 2-Matchar '97, 3-Wong '97, 4-Halm '03, 5-NYCAS, 6-Kennedy '04
7-Karp '98, 8-Cebul '98, 9-Kresowik '01

Efficacy v. Effectiveness: 30 Day Stroke/Death Rates (%)

	NYCAS	RCT/Benchmark
CEA Alone		
Symptomatic	6.4	≤ 6
Asymptomatic	3.0	≤ 3
CEA/CABG		
Asymptomatic	11.1	???

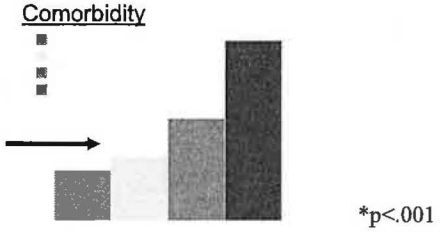
NYCAS Conclusions

- Since large investment in RCTs of CEA:
- Good news: Triumph of evidence based medicine
  - ↓ Inappropriateness (32% to 9%)
  - Complication rates in unselected practice similar to RCTs
- Not so good news:
  - 1 in 11 still inappropriate
  - Extrapolates to 12,000 unneeded CEAs/yr in US
- Bad news:
  - Shift from high benefit symptomatic Pts to lower benefit asymptomatic Pts (25% to 72%)

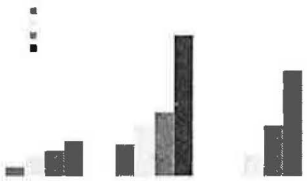
Reasons for Inappropriate Indications in NYCAS (N=826)

Reason	%
High comorbidity in ASX	62
Major recent/disabling stroke	14
Minimal stenosis	10
Operating contralateral to SX	8
Occluded artery	2

Comorbidity and 30 Day Rate of Death/Stroke: Asymptomatic Pts



Differential Outcomes by Comorbidity: Asymptomatic Patients



*p<.05

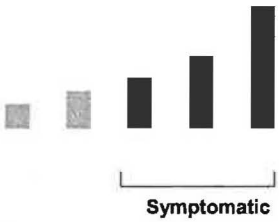
Personalizing Risk Info: Practicing Smarter than RCTs?

- RCTs focused on symptomatic v. asymptomatic
- Several other important risk factors likely influence risk of complications (& benefits)
  - Neurological acuity/disease severity
  - Comorbid conditions
  - Socioeconomic factors
  - Provider factors (MD, hospital)

Thinking Beyond the RCTs: Asymptomatic v. Symptomatic

Halm et al, Stroke, 2008

Risk of Complications after CEA by "Neurological Acuity"



Halm et al, Stroke, 2009

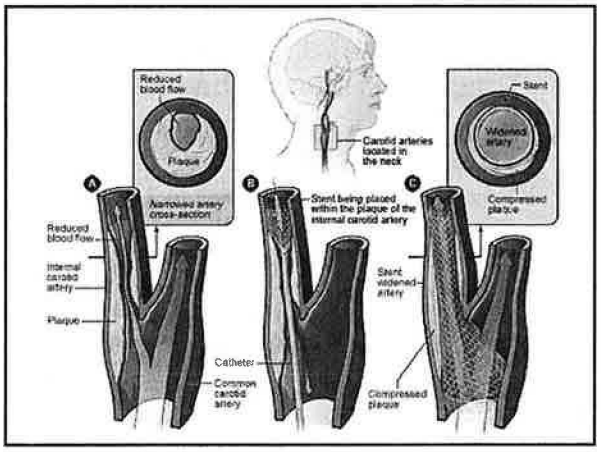
Multivariable Risk Factors for 30-Day Death or Stroke

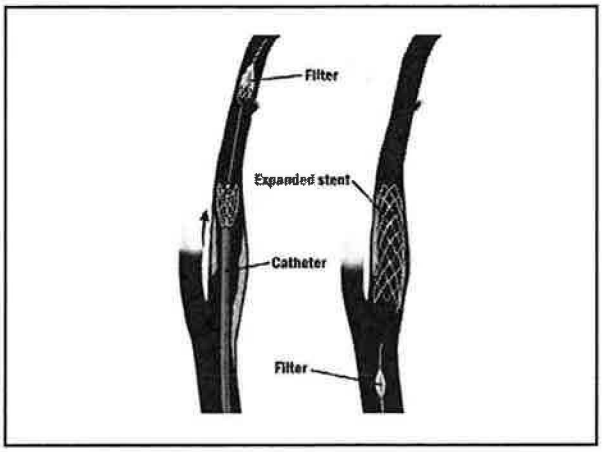
Risk Factor	Odds Ratio	Domain
Age ≥80 yrs	1.3	
Non-White	1.8	SES
ASX: Distant Hx TIA/CVA	1.4	
TIA as indication for CEA	1.8	Neurologic Acuity
CVA as indication for CEA	2.4	
Acute syndrome	3.6	
Contralateral stenosis >50%	1.4	Disease severity
Deep carotid plaque ulcer	2.1	
Admitted from ED	1.9	
Severe disability	2.9	
CAD	1.5	Comorbidity
DM on insulin	1.6	

Halm Stroke 2009

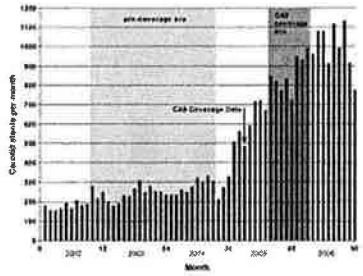
Carotid Stenting: A Better, Less-Invasive Mousetrap?

- Angioplasty & stenting of internal carotid
- Done by surgeons, cardiologists, radiologists
- Pros:
  - Less invasive, no incision or anesthesia risk
  - Could revascularize Pts too risky for surgery
- Cons:
  - Risk of distal embolization
  - Evidence of short-term efficacy is mixed
  - Sparse long-term outcomes data





Growth in Carotid Stenting Over Time



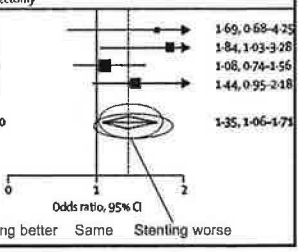
Groeneveld J Vasc Surg 2009

Geographic Variations in Carotid Artery Stenting: 2005-2006

Groeneveld J Vasc Surg 2009

Meta-Analysis of Carotid Stenting v. Surgery: Early RCTs

Trial	Median follow-up (years)	Stroke or procedural death: Endovascular	Stroke or procedural death: Endarterectomy	Odds ratio, 95% CI
SAPPHIRE[3]	3	16/50	10/46	1·69, 0·68–4·25
EVA-3S[4]	3·5	35/265	20/262	1·84, 1·03–3·28
SPACE[5]	2	65/607	59/589	1·08, 0·74–1·56
CAVATAS[1]	5	67/251	51/253	1·44, 0·95–2·18
Subtotal		183/1173	140/1150	1·35, 1·06–1·71
Heterogenity p=0·42				
Significance p=0·02				



Rothwell Lancet Oct 2009 Stenting better Same Stenting worse

RCTs of Carotid Stenting v. CEA

- Unacceptably high periop complication risk in age >75, >80 yrs
  - SPACE: 75+ yrs 11% v. 7%
  - CREST: 80+: 13% in CAS Pts, stopped enrolling
    - 75+ yrs: 11% CAS, 7.5% CEA
- Short term rates of death/stroke in both stenting & CEA arms higher than what natl guidelines considered acceptable complication rate
- SX stent trials: 1 yr D/S rates was 14%, nearly half-way to 31% 5 yr D/S rate in SX CEA RCTs
- ASX stent trials: 1 yr D/S rates 14%, half-way to 5 yr D/S rate in ASX CEA RCT

New ICSS Trial Results: CEA v. CAS

- European RCT (N=1710)
- Screening and approval of stenters
- Carotid stenosis > 70%, mean age 60 years
- All Symptomatic

	Periop MI + Death or Any Stroke at 120 days	
• CEA (Surgery)	5.2%	
• CAS (Stenting)	8.5%	P=.006

- Stenting significantly worse in Age > 70 years

*ICSS Lancet Mar 2010

New CREST Trial Results: CEA v. CAS*

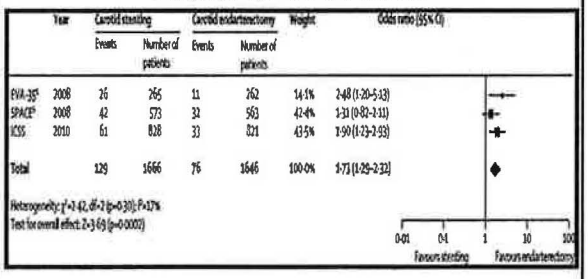
- North American NIH-funded RCT (N=2522)
- Intense training, approval of stenters
- Carotid stenosis > 70%, mean age 60 years
- Symptomatic (53%), Asymptomatic (47%)

	30-day death/stroke/MI + ipsilateral strokes in 2.5 yr	
• CEA (Surgery)	6.8%	
• CAS (Stenting)	7.2%	P=NS

- Stenting significantly worse in Age > 70 yrs

*NY Times Journal of Medicine Feb 2010, AHA Internatl Stroke conference

Meta-Analysis of Symptomatic Trials: CEA v. CAS



ICSS Lancet 2010

Editorials: "Time for Moratorium on Carotid Stenting"

- "The routine use of stenting in patients with recent symptoms of carotid stenosis who are suitable for endarterectomy can no longer be justified…the use of vague and non-evidence-based categorizations, such as 'high risk for surgery', has been systematically misused to justify uncontrolled use of stenting. Most patients who had stenting for symptomatic carotid stenosis outside of RCTs would have met the eligibility criteria for CAVATAS, EVA-3S, SPACE, and ICSS trials, and would have faced a greater procedural risk of stroke, a greater risk of severe restenosis, and a worse long-term outcome than if they had had CEA."

Rothwell Lancet Neuro Aug 2009

What is Next for Stenting?

- What to make of discordant findings?
  - Different endpoints, follow-up duration, technique
  - ICSS was symptomatic only, CREST-mixed
- Detailed CREST results not yet published
  - Need outcomes stratified by SX v. ASX
- Both trials found stenting worse for >70 yrs
- Avg age in RCTs 69 yr, Avg age Medicare 74
- Strong market pressure for stenting because done by many (cards, IR, surgery)
- Mission creep: 70-80% of stenting in ASX

Clinical Implications

- *Mortality* at *1 year* for both procedures was greater or equal to the *combined* outcomes in the RCTs at *2.5 and 5 years* and not much better than medical therapy in the asymptomatic trials
- Risk reduction with current medical therapy with high potency statins better than trials, with lower expected stroke risk 0.3% v. 1-2%/yr
- *Medical therapy* may be superior to CEA OR stenting in many patients because higher peri-procedural complication rates, advanced age and multiple comorbidities may greatly reduce or eliminate the potential long term benefits of revascularization, especially among asymptomatic patients

Need to Improve Informed Decision Making: Voice of Pts

- Middleton 2006: 133 CEA patients
  - Half did not know risk of stroke DUE to the surgery
  - More likely to recall MD talking about risk of stroke if NO CEA
- Focus Group of asymptomatic patients with carotid disease
  - Phillip: 80 "Risk was 5%, but if no CEA 'drop dead, no choice' "
  - Hardy: 91 yr. "Call from MD on Mon saying CEA scheduled Thurs. MD says, "Do you want to live or die?"
  - Mary: 88 yr. "I've never operated on anyone your age. But if I don't, you could have a stroke in 2 years...He had the best bedside manner"

Fostering Evidence-Based Informed Decision Making About Asymptomatic Carotid Disease

- Physician strategy:
  - Help physicians characterize an individual patient's risks and benefits of revascularization
  - Develop an individual risk calculator
- Patient strategy:
  - Engage patients in making a shared, informed decision about which option is right for them
  - Develop a multimedia, interactive decision aid

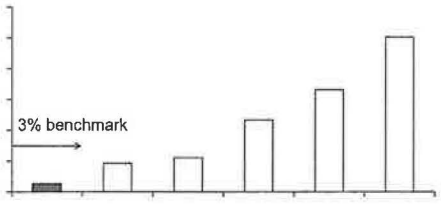
Personalized Medicine: Predicting 30-Day Risk of CEA: Asymptomatic Patients

- NYCAS Medicare cohort study
- N=6553
- Mean age=74 years, 62% with CAD
- Avg 30-day death/stroke rate=3.0%
- Developed multivariable logistic regression model of adverse outcomes

Multivariate Predictors of 30-day Death or Stroke: Asymptomatic

Risk Factor	Adjusted OR	Risk Score Points
Female	1.5	1
Non-White	1.8	1
Distant stroke or TIA	1.5	1
Non-operated stenosis $\geq$ 50%	1.8	1
Severe disability	3.7	2
Congestive heart failure	1.6	1
Coronary artery disease	1.6	1
Valvular heart disease	1.5	1

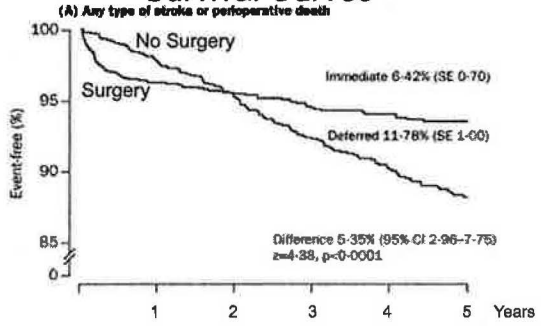
30-Day Death/Stroke Risk by CEA-8 Risk Score



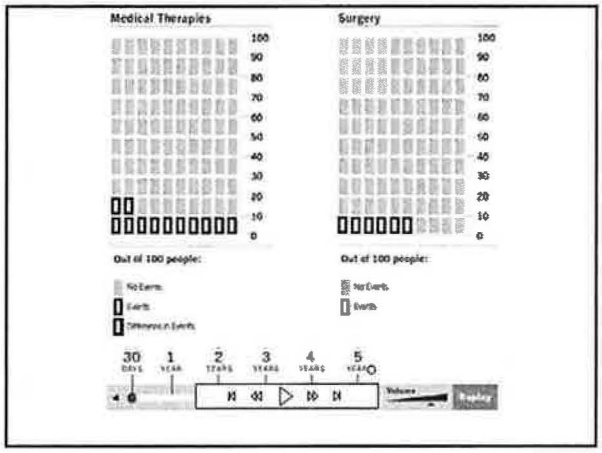
Decision Aid for Managing Asymptomatic Carotid Disease

- Developing a multimedia, interactive, web-based, patient education program
- Explains carotid disease, treatment options
- Outlines pros/cons of CEA v. med. therapy
- Personalized risk information
- Video testimonials of MDs and Pts
- Highlights gist of 'time-trade off' decision

Displaying Time Trade-Off With Survival Curves



"Surgery is a riskier roller coaster ride at first but the ride lasts longer"



Natural History of CER Studies: Thru Lens of Carotid Surgery

- Innovation & Dissemination: "This new thing is great"
  - New procedure used without much evaluation
- 1st Generation Observational Studies: "This is terrible"
  - Outcomes of new procedure worse than expected, uncertainty about indications, high rates of inappropriateness
- RCTs: CEA v. medical therapy "Good for some, not all"
- 2nd Generation Observational Studies "Real world use"
  - Effectiveness v. efficacy: population-based studies of patterns of use, outcomes, appropriateness
- RCTs: CEA v. Stenting "Is the new mousetrap better?"
- Future Studies:
  - Personalized medicine: target Rx to Pt risk/benefits, shared decision making
- Head to head comparison of all choices: CEA, CAS, meds