

**Medicare Evidence Development and  
Coverage Advisory Committee  
January 25, 2012  
Management of Carotid  
Atherosclerosis** 

American Association of Neurological  
Surgeons/ Congress of Neurological Surgeons  
Comments regarding research topics

1. How confident are you that there is adequate evidence to determine if: *persons in the Medicare population who are asymptomatic for carotid atherosclerosis can be identified as being at high risk for stroke in either cerebral hemisphere?*

- Increasing Degree of Stenosis (risk of ipsilateral CVA = 3-12% @ 5 years depending on degree and medical tx)
  - Medical (ASA) Arm of ACST (1023 pts)/ACAS (547 pts) 1990s
    - >60% stenosis
    - 11%-12% @ 2-3 years mean FU
  - Oxford Vascular Study (n=101 patients)
    - > 50% stenosis
    - 0% major stroke @ 3-year mean FU
  - *Nicolaides et al JVS (52:1486, 2010)*
    - 1121 pts @ 2-year mean FU (2.5% - 4.8% - 7.7%) for <70, 70-90, >90%
- Data Autoregulatory Reserve
  - Loss of Autoregulatory Reserve more at risk [[J Neurol](#), 2008 Aug;255(8):1182-9; [JAMA](#), 2000 Apr 26;283(16):2122-7.]
- Data on Plaque Morphology
  - More plaque volume more at risk [*Nicolaides et al JVS (52:1486, 2010)*]
- Data on Gender
  - Men more at Risk [ACST/ACAS]
- Inflammatory Biomarkers
  - Inflammation more at risk [[Eur J Vasc Endovasc Surg](#), 2003 Nov;26(5):523-8.]
- Data on DWI lesions
  - Presence of DWI lesions more at risk [*Nicolaides et al JVS (52:1486, 2010)*]
- Data on Contralateral CVA/TIA
  - Prior TIA/CVA more at risk [*Nicolaides et al JVS (52:1486, 2010)*]

## ANSWER:

• HIGH IF ASPIRIN ALONE AS MEDICAL THERAPY

• INTERMEDIATE IF ANTI-PLATELET PLUS STATIN PLUS ACE-INHIBITOR/BETA-BLOCKER

## **2. How confident are you that there is *adequate evidence to determine if persons in the Medicare population, who are considering carotid revascularization, can be identified as being at high risk for adverse events from CEA?***

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- **“ High risk patients” have been defined by the ineligibility criteria from NASCET and ACAS trials**
  - This higher risk group trends towards (a nonsignificant) higher neurological morbidity, but the risks are still comparable with NASCET/ACAS results, and as such, such de novo classification as high risk may not indeed be justified. (Lepore et al., 2001).
- **Smaller studies do suggest that ‘high risk’ criteria may have higher complications**
  - ie: HTN showed a trend toward increasing the risk of TIAs and stroke after carotid operation. Diabetes and clinically evident CAD reduced survival rates in post carotid patients. (Hallett et al., 2002).
- **Recent studies which may validate “high risk patients” as a group include: CREST and SAPPHIRE**
  - Both studies examine the putative higher-risk group and found higher risks of stroke and death
  - SAPPHIRE is a RCT that demonstrated rates of stroke and death greater than deemed acceptable by analysis of NASCET and ACAS
  - Studies suggest carotid endarterectomy (CEA) in high risk patients can be performed with reasonable morbidity and mortality in this patient group (Lepore et al, 2001; Mozes et al, 2004))
- **Confidence level: 3 -While much is known about the natural history of carotid disease, there is conflicting data with regard to identification of patients at high risk for adverse events from CEA.**
  - Validation of ‘high risk patients’ as a group based largely on retrospective reviews as well as post hoc analysis of prospective studies such as SAPPHIRE

3.b. Is there adequate evidence to determine whether either CAS or CEA is the favored treatment strategy, as compared to BMT alone, to decrease stroke or death in the Medicare population?

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CEA - Level 5, high confidence

- Previous RCTs (NASCET, ACAS, CREST) show strong evidence that both CEA and CAS can decrease stroke or death over BMT
- Strong benefit in symptomatic patients that is proportional to the degree of stenosis
- Benefit achieved early on in treatment course

CAS – Level 3 Intermediate confidence

- CREST addressed question of differential benefit between CEA and CAS
- Primary endpoint of peri-procedural stroke, death or MI and 4 year ipsilateral stroke was equivalent
- CEA statistically significant reduction in risk of any peri-procedural stroke or death or post-procedural ipsilateral stroke (2% absolute risk reduction, HR 1.90, P value 0.005)

BMT – Level 1 Low confidence

3. Is there adequate evidence to determine whether either CAS or CEA is the favored treatment strategy, as compared to BMT alone, to decrease stroke or death in the Medicare population?

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## **Patient age, gender and racial/ethnic background**

- CREST – pre-specified secondary analysis showed significant (Pvalue 0.02) effect of age on treatment efficacy, CEA showed greater efficacy at older ages, CAS showed greater efficacy at younger ages with the crossover occurring at around age 70.
- This lends further support to the superiority of CEA over CAS in the Medicare population for prevention of stroke or death

## **Time to treatment**

- NASCET clearly demonstrated an effect of time to treatment from onset of symptoms.
- Patients randomized to BMT had the highest risk of further events immediately after onset of symptoms, gradually dropping over a two to three year period to approx. 3%
- CEA patients saw a marked drop in stroke rate by 10 days post-op to approx 2%

## 4. a. Asymptomatic Carotid Atherosclerosis & Carotid Narrowing, Not a High Risk for CEA

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**Intermediate Confidence 3 that there is adequate evidence that either CAS or CEA should be favored over BMT.**

- Previous RCTs demonstrated superiority of CEA over BMT for prevention of stroke and death (ACAS, ACST). However, these studies are outdated and do not compare CEA to current BMT.
- There is evidence to suggest that current BMT has reduced the natural history risks of stroke (Abbott et al, *Stroke* 2005; 36:1128-1133, Goessens et al, *Stroke* 2007; 38:1470-1475, Marquardt et al, *Stroke* 2010; 41:e11-e17, SAMMPRIS).
- There are no RCTs comparing CAS to current BMT.

## 4. Asymptomatic Carotid Atherosclerosis & Carotid Narrowing, Not a High Risk for CEA

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- 4b.i. CAS favored - Low confidence (1)
  - no PRCT comparing CAS to current BMT
- 4b.ii. CEA favored - Intermediate confidence (3)
  - ACAS and ACST
- 4b.iii BMT favored - Low confidence (1)
  - no recent PRCT in asymptomatic patients that includes BMT arm

## 5. Asymptomatic Carotid Stenosis

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- Observational studies only include patients with significant stenosis with annual stroke risks ranging from 0.34 – 3.1%
- The three large asymptomatic carotid trials report annual stroke risks of 2.2 (ACAS), 2.36 (ACST) and 2.35% (VA)
- Patients with less than 50-60% stenosis likely have a lower annual risk of stroke and medical therapy has improved since the era of these trials.
- Asymptomatic patients who are not at high risk for stroke should not be offered revascularization with either endarterectomy or stenting.

## 6. Carotid artery screening to prevent stroke

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- 6.a. Intermediate evidence to determine benefit of screening in the general Medicare population.
- 6. b. Low evidence that screening decreases risk of stroke or death in the general Medicare population.
- four different positions statements since 2006 have unanimously dissuaded routine screening in the general population  $\geq 65$  years without accepted risk factors (hypertension, hyperlipidemia, current smoking, coronary artery disease).
- screening with ultrasonography has moderate sensitivity and specificity, but screening of the general population would result in false-positives, leading to interventions or invasive angiography testing that would result in more frequent adverse events than in prevention of stroke.
- over 4300 patients would need to be screened to prevent one stroke, and over 8600 patients would need to be screened to prevent one disabling stroke, assuming a 1% prevalence rate of carotid stenosis (60-99%) in the Medicare population.

## 7.a. FUTURE STROKE PREVENTION TRIALS

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### **Should be powered to evaluate only asymptomatic patients:**

- Symptomatic: Meaningful and significant reductions in stroke risk with carotid intervention well established by randomized studies (NASCET, ECST)
- Asymptomatic: Controversy exists regarding the benefit of treatment for asymptomatic disease in the era of modern medical management, despite prior randomized studies (ACAS, ACST)

### **Should be powered to draw conclusions about gender:**

- Randomized studies of asymptomatic patients have largely failed to demonstrate benefit of treatment in women, and/or have shown higher periprocedural risks (ACAS, ACST, CREST)

### **Should evaluate outcomes for racially/ethnically diverse populations:**

- Racial/ethnic disparities in the diagnosis, use, and outcomes of treatment for carotid disease have been reported, which justify recruitment of diverse populations and evaluation of outcomes relative to race and ethnicity

## 7.b.TOOLS FOR IDENTIFICATION OF HIGH RISK PATIENTS

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Prospective multi-center study data (ACES, ACSRS studies) and meta-analyses have shown risk stratification based on:

- Plaque echogenicity
- TCD microemboli detection
- Silent stroke
- Hemodynamic reserve

Prior to further interventional trials, prospective observational natural history studies of asymptomatic patients needed:

To develop stroke predictive models using a combination of

- Clinical features (e.g. age, h/o contralateral stroke/TIA)
- Imaging tools: Degree of stenosis; Stenosis progression; Plaque morphology; Microemboli detection; Hemodynamic assessment; Silent stroke

To look at broader outcomes

- Stroke
- Cognitive function
- QOL measures

# Recent trials

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The recent large randomized trials focused on symptomatic carotid stenosis favor CEA over stenting:

peri-procedural risk significantly higher with CAS

- EVA            stroke/death            9.6% vs 3.9%    p=0.01
- ICSS           stroke/death/MI    8.5% vs. 5.2%   p=0.0006

or failed to establish non-inferiority

- SPACE        stroke/death            7.5% vs 6.2%    p= NS

# Recent trials

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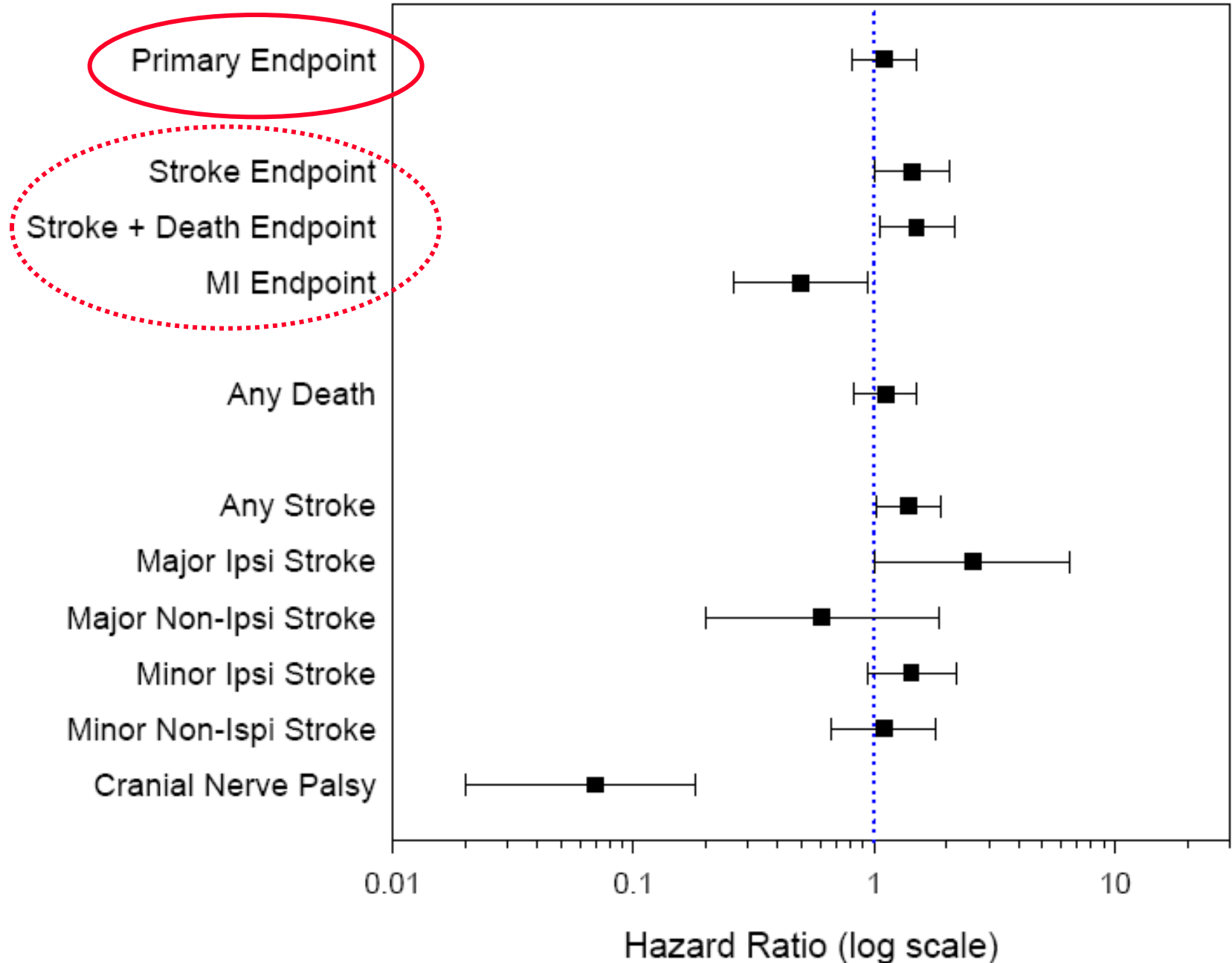
CREST: large randomized trials looking at symptomatic and asymptomatic carotid stenosis

Primary Endpoint – stroke, MI or all cause death during periprocedural period (30 days) or any ipsilateral stroke within 4 years after randomization

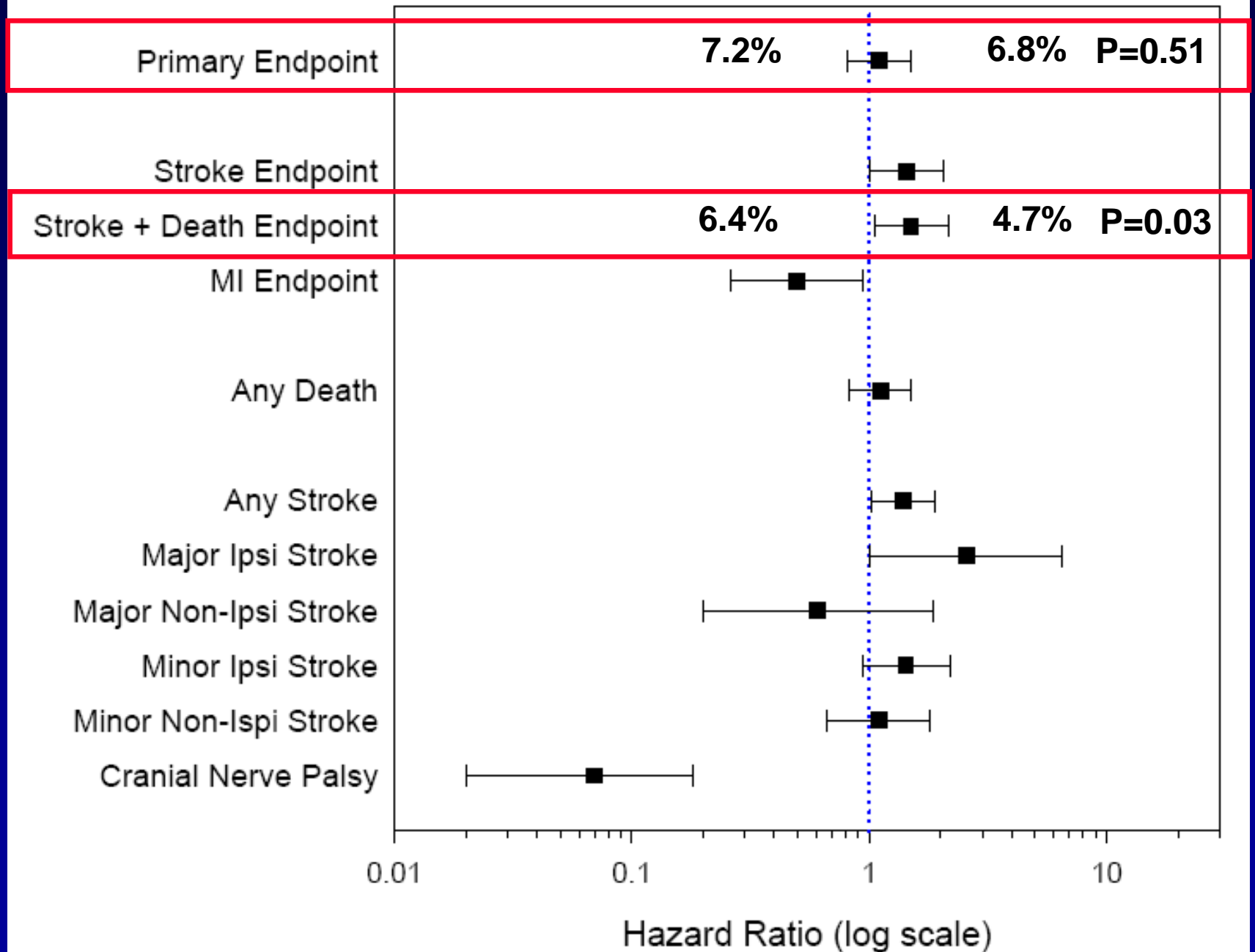
Primary endpoint:

**7.2% CAS vs. 6.8% CEA (P=0.51)**

← CAS Superior | CEA Superior →

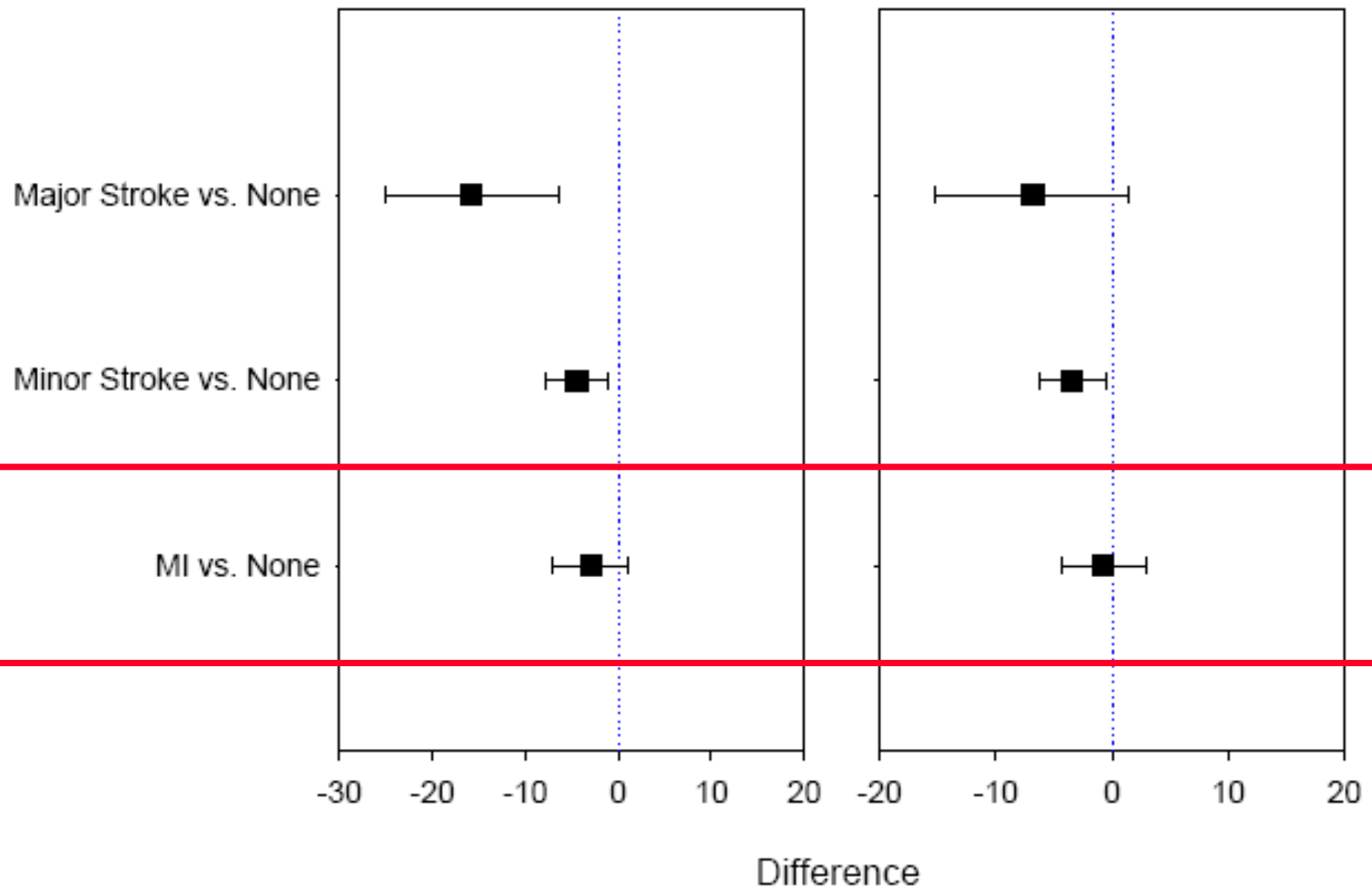


← CAS Superior | CEA Superior →



Physical Component Scale

Mental Component Scale



**MI – no effect on physical or mental health at one year**

# CREST results- critique

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## The important numbers

- Stroke periprocedural:  
4.1% CAS vs 2.3% CEA (p=0.01)

## ALTHOUGH

- Major stroke  
0.9% CAS vs 0.6% CEA (p=0.52)

**Does minor stroke matter?**

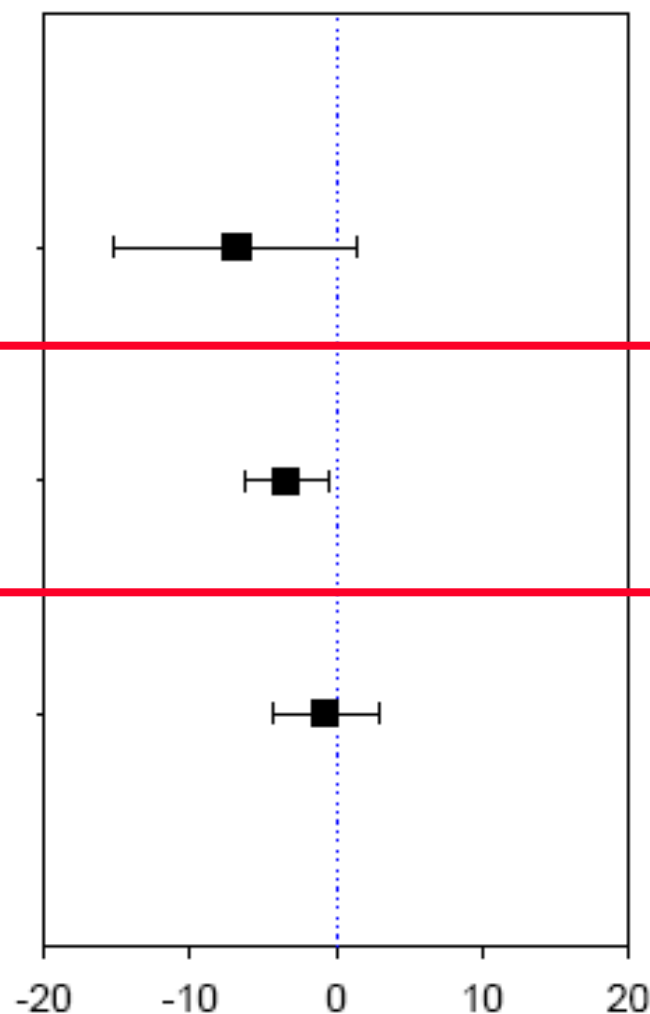
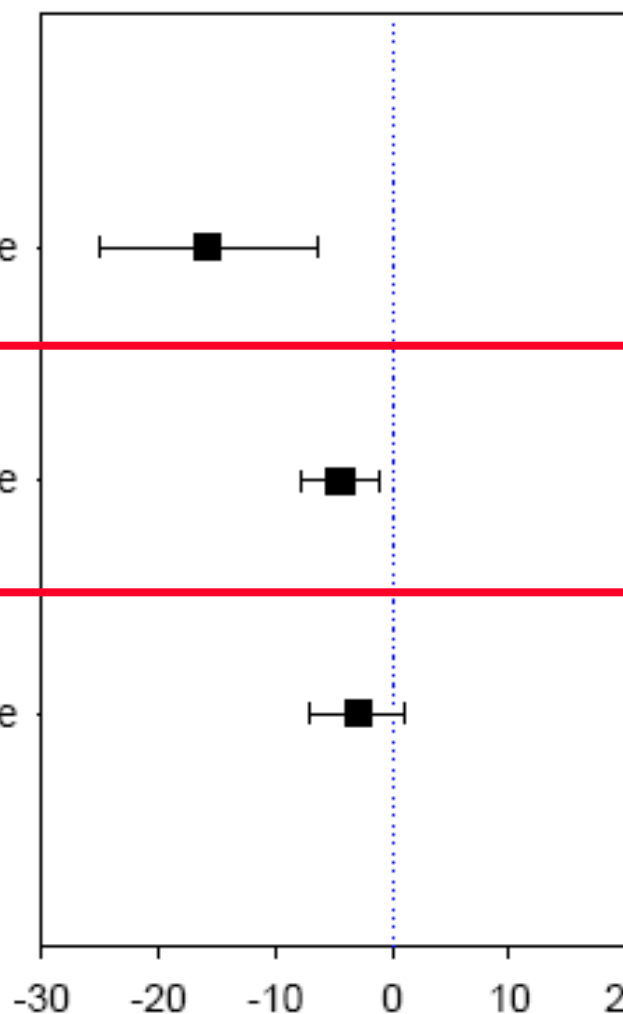
Physical Component Scale

Mental Component Scale

Major Stroke vs. None

Minor Stroke vs. None

MI vs. None



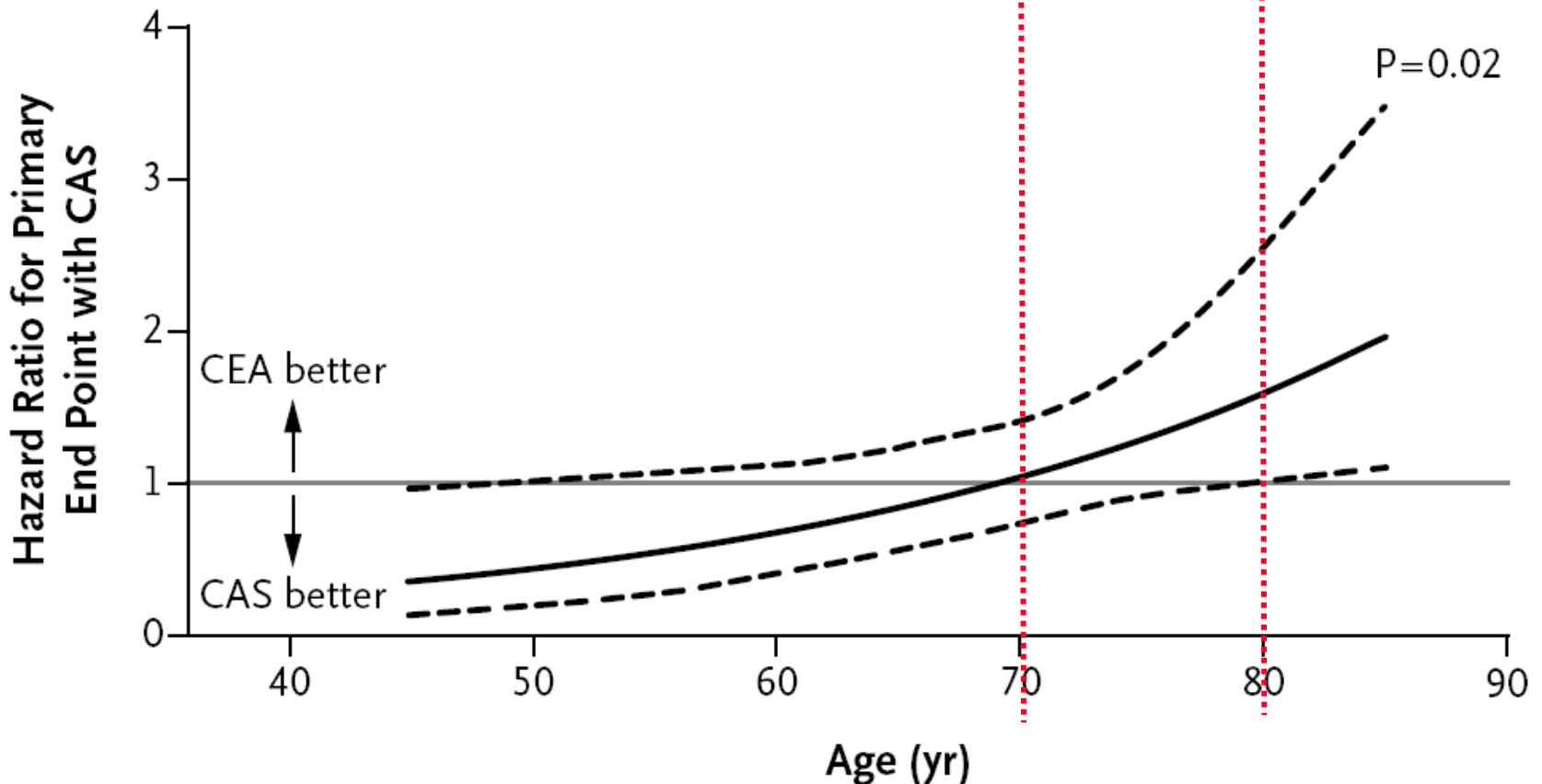
Difference

**Minor stroke does affect function at one year**

# CREST results - age

Other important numbers

The age effect



# Symptomatic Carotid Disease

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- Aggregate of multiple randomized studies do not favor CAS; CEA remains treatment of choice
- However CREST data indicate use in young patients (age <70) may be favorable
- Expansion of coverage to allow CAS as an alternative to CEA in young symptomatic patients (<70 y.o.) is reasonable

# CREST results - asymptomatic

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Asymptomatic disease

CAS and CEA both very safe for asymptomatic carotid stenosis:

- **CAS 2.5%** vs **CEA 1.4%** periprocedural stroke/death

**BUT**

**Considerable evidence has accumulated that modern medical therapy has more than halved the risk of stroke with carotid stenosis** (Marquardt et al, Stroke 2010 41:e11-e17)

# Asymptomatic Carotid Disease

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- Only one randomized study subgroup indicates non-inferiority of CAS
- Expansion of coverage beyond current high risk indications is not necessary
- Expansion of coverage for asymptomatic disease may increase intervention beyond what is beneficial for the prevention of stroke and death given current medical therapy