Is Myocardial Infarction a Reasonable or Relevant Endpoint to Assess Carotid Intervention and Stroke Prevention Therapies in Clinical Practice and Trials?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- *Grant/Research Support*
  - *Federal Government*
- *Consulting Fees/Honoraria*
  - *Abbott*
  - *BARD*
  - *Boston Scientific*
  - *Gore*
  - *Medtronic*
  - *Terumo*

Should P-MI be an End Point in Carotid Revasculatization Trials?

- *Myocardial Infarction predicts short and long term mortality in cardiac and non-cardiac surgery as well as Endovascular procedures*
- *Heterogeneity in CAS trials is due to inadequate P-MI Ascertainment*
- *When deciding on revascularization strategy, MI risk is as important as stroke risk*

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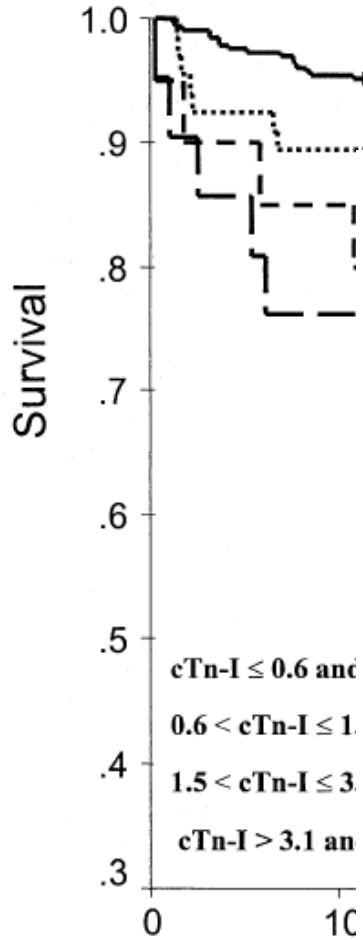

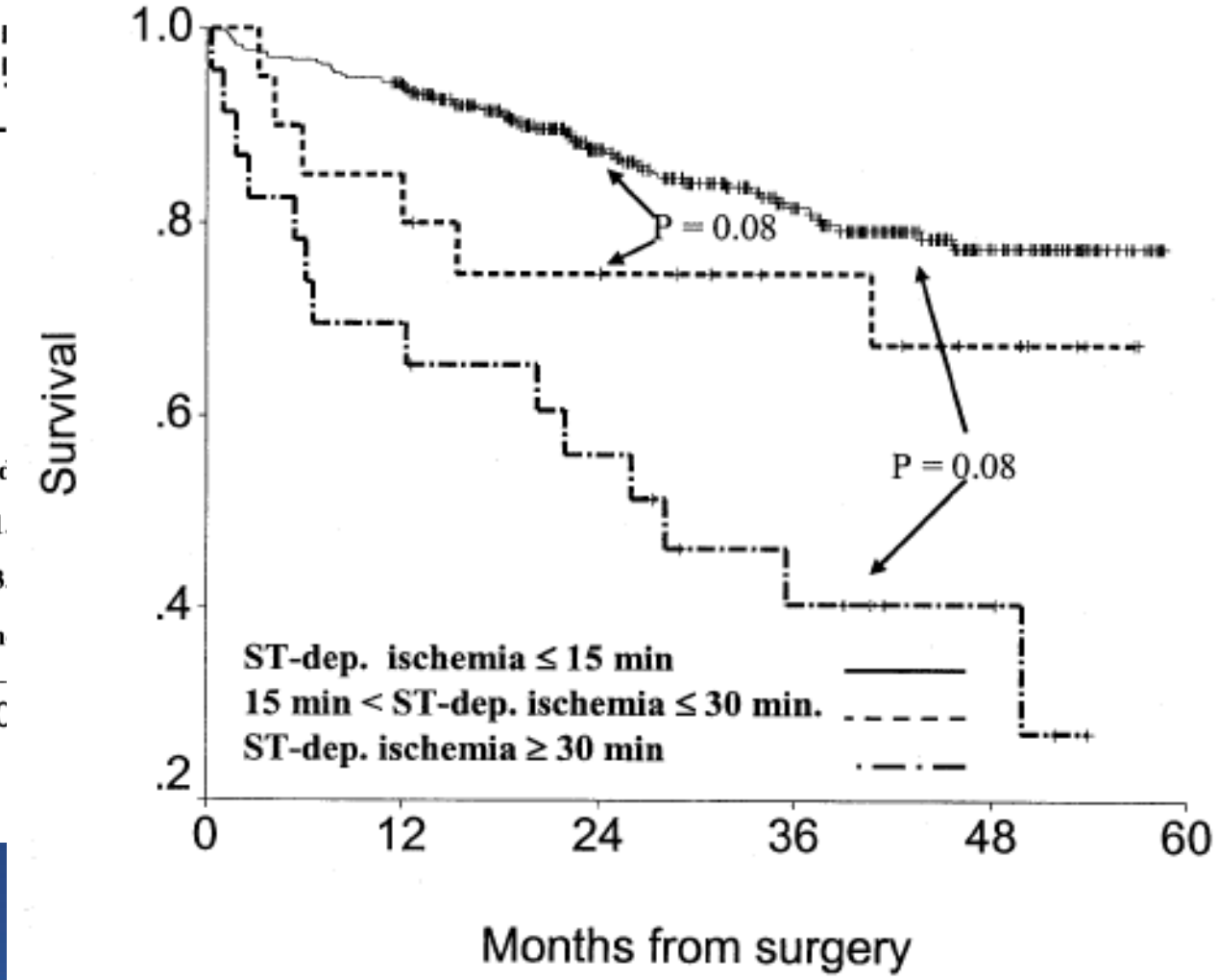

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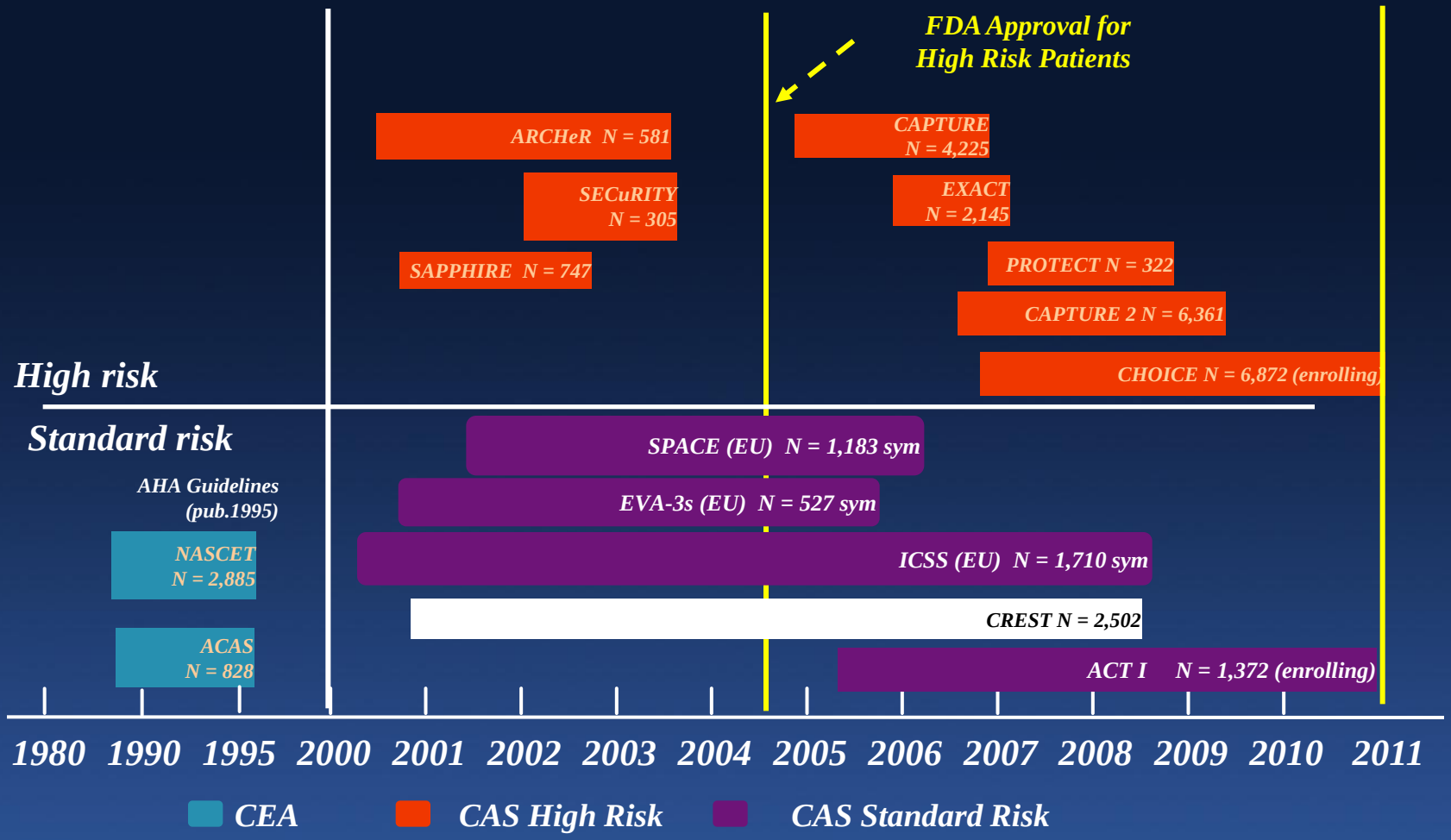
Heterogeneity in CAS trials is due to inadequate P-MI Ascertainment

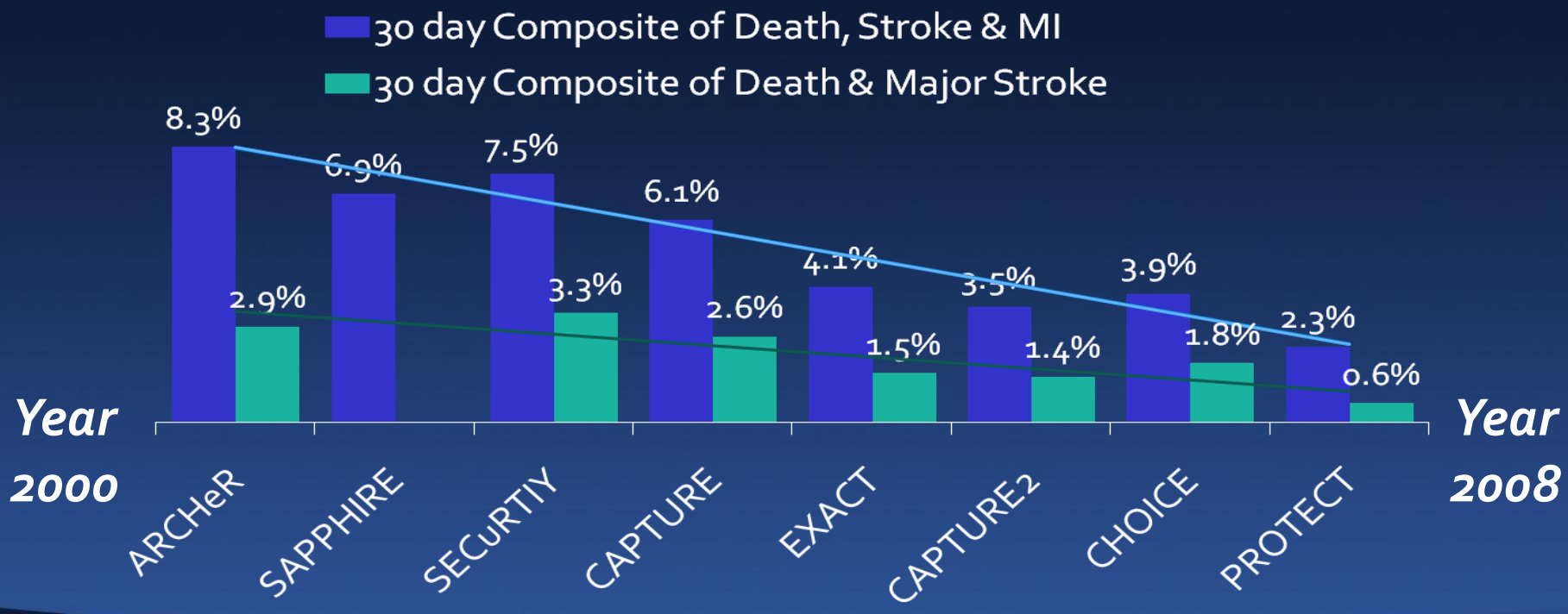
Timeline of Clinical Trials

Evaluating CAS Treatment



Outcomes of CAS Trials Over Time

- ***CAS results have vastly improved over time due to: (1) more experienced operators; (2) better patient selection and; (3) a wider spectrum of technology***
- ***CAS outcomes have evolved over time similarly to CEA***



Multicenter Randomized Trials of CAS vs. CEA

Trial	30-Day Outcome (Death/Stroke)		
EVA-3S (30 days)	*CEA: 3.9%*	*CAS: 9.6%*	*p=0.01*
SPACE (30 days)	*CEA: 6.3%*	*CAS: 6.8%*	*p=0.09*
ICSS (120 days)	*CEA: 4.7%*	*CAS: 8.5%*	*p=0.001*
CREST (Symptomatic Only)	*CEA: 5.4%*	*CAS: 6.7%*	*p=0.30*

Summary of Critical Trial Attributes

Trial	EPD Use	MI Ascertainment	Operator Experience
EVA-3S	+	0	0
SPACE	½+	0	++
ICSS	+	0	0
CREST	++	++	++

P-MI In Carotid Revascularization Trials

Study (Year)	***n***	***PMI as Endpoint***	***Per Protocol PMI Ascertainment***	***PMI CAS %***	***PMI CEA%***
NASCET (1991)	*1415*	*Neither*	*No*	*Not reported*	*Not reported*
ACAS (1995)	*1659*	*Secondary*	*No*	*Not reported*	*Not reported*
SPACE (2006)	*1214*	*Neither*	*No*	*0*	*0*
EVA-3S (2004)	*527*	*Secondary*	*No*	*0.4*	*0.8*
SAPPHIRE (2004)	*334*	*Primary*	*Yes*	*2.4*	*6.1*
ICSS (2010 interim)	*1713*	*Secondary*	*No*	*0.4*	*0.6*
CREST PMA (2010)	*2502*	*Primary*	*Yes*	*2.0*	*3.4*

When deciding on revascularization strategy, MI risk is as important as stroke risk

Death, Stroke and MI within 30 Days

Per protocol	CAS N = 1,131	CEA N = 1,176	Difference	Unadjusted p-value*
All Death, Stroke, or MI	5.8% (65)	5.1% (60)	0.7%	0.5200
Death	0.53% (6)	0.26% (3)	0.27%	0.3335
Any Stroke	4.1% (46)	1.9% (22)	2.2%	0.0019
Major Stroke	0.9% (10)	0.4% (5)	0.5%	0.2005
Minor Stroke	3.2% (36)	1.5% (18)	1.7%	0.0088
MI	2.0% (22)	3.4% (40)	-1.5%	0.0387

* Fisher's exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

	Adjudicated MI (n=42)	Adjudicated Biomarker+ Only (n=20)	No MI or Biomarker+ Only (n=2440)	*P* for Difference Between MI, Biomarker+ Only, and No MI or Biomarker+ Only
Age, y	72.3±8.0	72.3±8.8	69.0±8.9	0.01
Male sex, %	66.7	65.0	65.1	0.98
White race, %	85.7	90.0	93.4	0.13
Symptomatic carotid stenosis, %	52.4	60.0	52.8	0.81
Randomized to CEA, n	28	12	1200	
Randomized to CAS, n	14	8	1240	
Hypertension, %	95.2	85.0	85.8	0.21
Diabetes mellitus, %	40.5	35.0	30.3	0.33
Dyslipidemia, %	92.9	80.0	84.3	0.27
On cholesterol-lowering medication, %*	88.6	93.8	91.8	0.76
Current smoker, %	22.0	10.0	26.5	0.20
Previous cardiovascular disease, %	65.8	50.0	43.3	0.02
Previous CEA, %	9.5	0.0	4.8	0.22
Previous coronary artery bypass, %	31.0	35.0	20.4	0.07
Systolic blood pressure, mm Hg	143.9±23.6	143.0±22.3	141.4±20.3	0.68
Diastolic blood pressure, mm Hg	74.3±9.9	71.9±14.8	74.0±11.5	0.70
Stenosis ≥70%, %	83.3	95.0	86.0	0.45
Median time from randomization to treatment, d	6.0	5.0	7.0	0.42
Creatinine clearance, mL/min†				
<30	5.1	10.0	1.9	0.02
30–59	35.9	35.0	26.8	
≥60	59.0	55.0	71.3	
Transfusion required, %	7.1	5.0	1.3	0.003
Procedural hypertension, %	7.1	0	3.1	0.002
Procedural hypotension, %	11.9	5.0	2.7	0.23

MI indicates myocardial infarction; biomarker+, biomarker positivity; CEA, carotid endarterectomy; and CAS, carotid artery stenting.

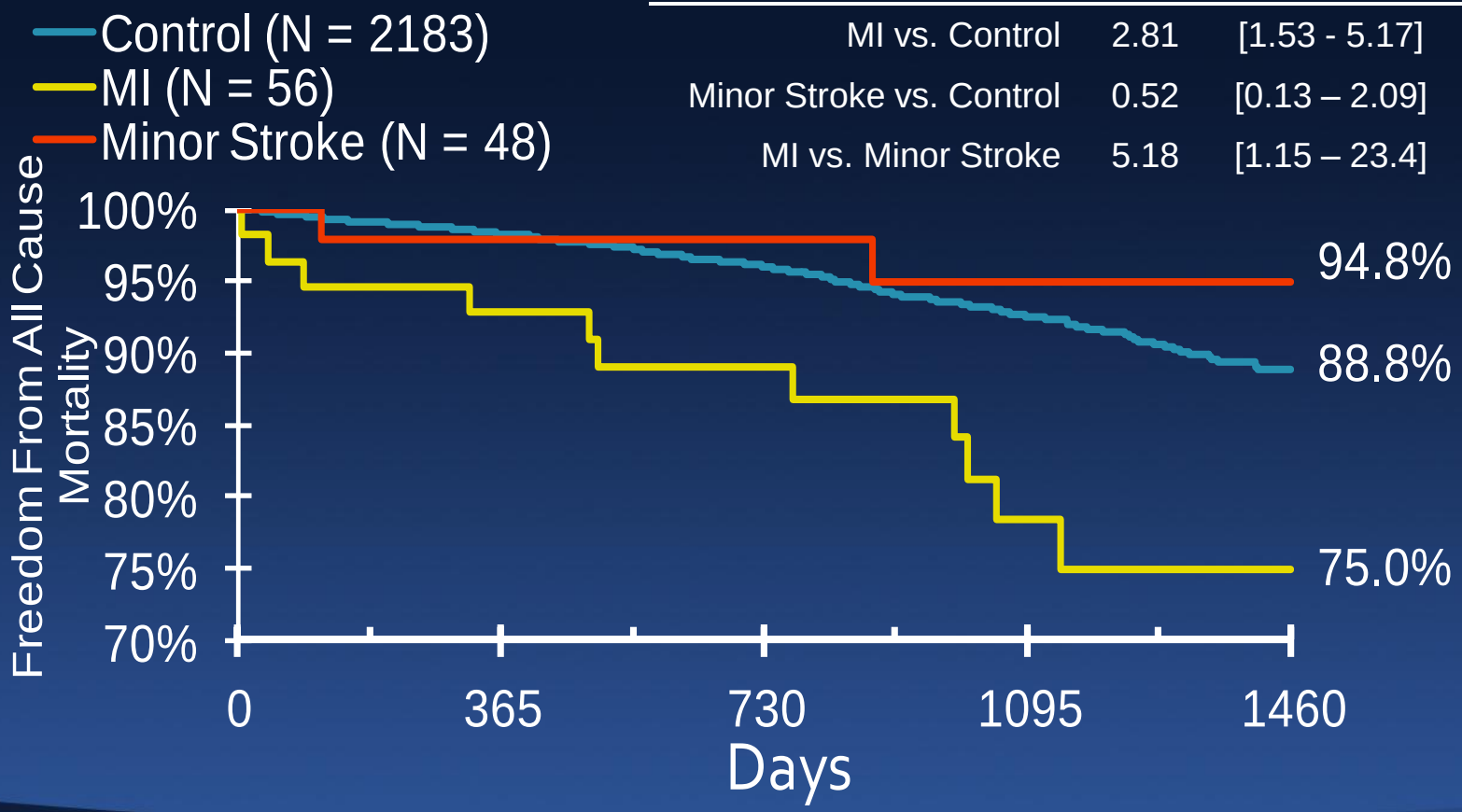
*Use of cholesterol medication was recorded only in those who answered affirmatively to dyslipidemia.

†Creatinine clearance was calculated with the Cockcroft-Gault formula: GFR=(140−age)(weight in kg)(0.85 if female)/(72)(creatinine in mg/dL), where GFR

CREST

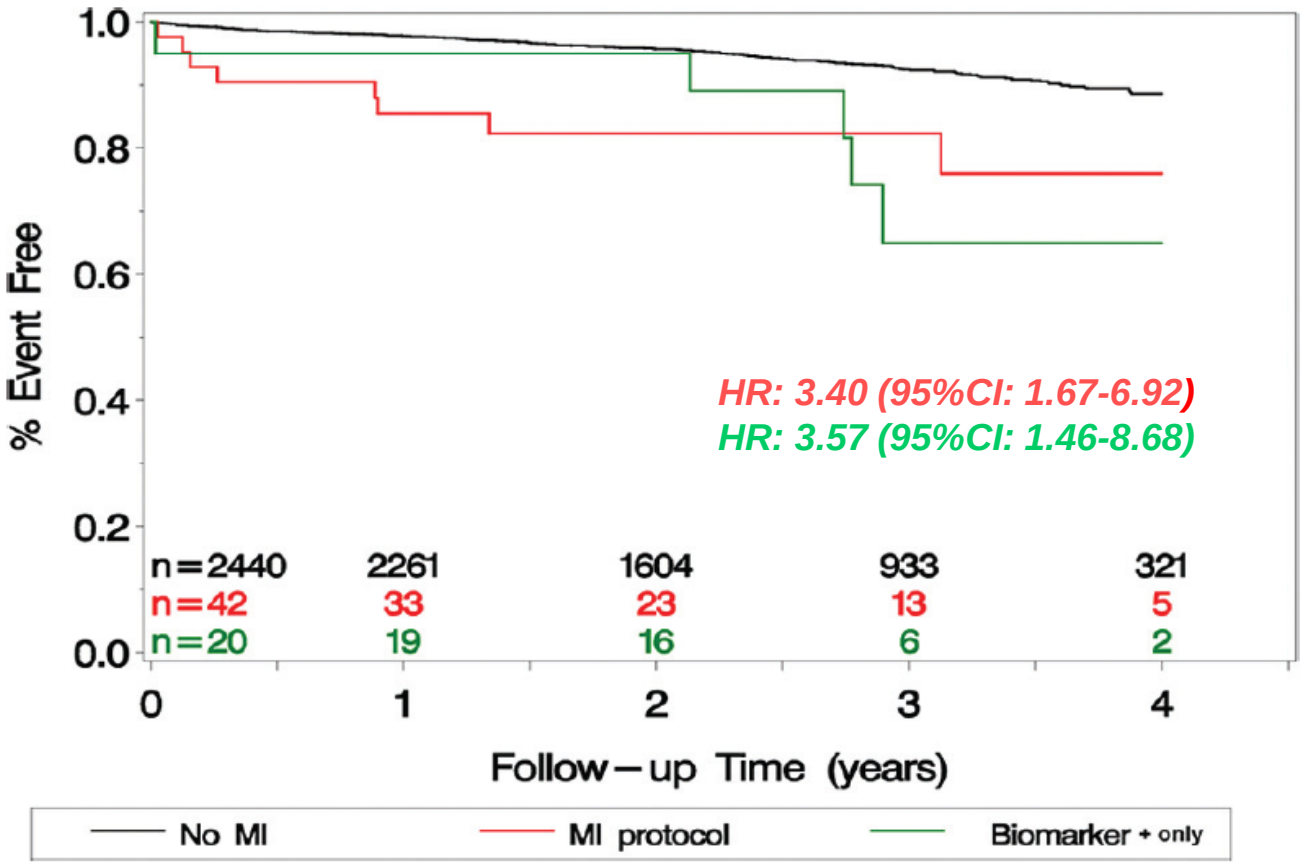
Lack of Association of Minor Stroke with Long Term Mortality

Comparison	HR	HR Confidence Interval	Log Rank P-value
MI vs. Control	2.81	[1.53 - 5.17]	0.0005
Minor Stroke vs. Control	0.52	[0.13 – 2.09]	0.34
MI vs. Minor Stroke	5.18	[1.15 – 23.4]	0.02



CREST

Biomarker-Only MI Carries Significant Long-Term Mortality



Source: Circulation June 7, 2011: 2571-2575

Table 2. Results of Multivariable Analysis of Risk Factors for Periprocedural Myocardial Infarction

Variable	HR	95% CI	*P*
MI model*			
Age*	1.03	0.99–1.08	0.19
Prior cardiovascular disease or CABG*	2.22	1.13–4.35	0.02
Diabetes mellitus*	1.60	0.84–3.07	0.16
Creatinine clearance, mL/min*			
<30	2.16	0.47–10.02	0.33
30–59	1.21	0.57–2.61	0.62
≥60	Reference	Reference	Reference
MI or Biomarker+ only model†			
Age†	1.03	0.96–1.07	0.10
Prior cardiovascular disease or CABG†	1.73	1.02–2.95	0.04
Diabetes mellitus†	1.44	0.85–2.46	0.18
Creatinine clearance, mL/min†			
<30	2.97	0.97–9.05	0.06
30–59	1.23	0.66–2.29	0.52
≥60	Reference	Reference	Reference

Blackshear et al. Circulation 2011;123:2571

CREST MI rate in Octogenarians

	Octogenarian			Non-octogenarian		
Per Protocol	CAS N = 106	CEA N = 103	Difference [95% CI][1]	CAS N = 1025	CEA N = 1073	Difference [95% CI][1]
MI[2]	1.9%	6.8%	-4.9% ANM	2.0%	3.1%	-1.1% [-2.5%, 0.2%]

Conclusions

- *MI in carotid revascularization is clearly linked to morbidity/mortality*
- *Even biomarker only MI is a key safety endpoint in CAS/CEA trials and must be assessed*
- *When deciding on revascularization strategy, assess patients for MI risk*
- *Decreasing periprocedural MI will make CAS and CEA safer*