TACIT:
Transatlantic Asymptomatic Carotid Intervention Trial

FDA Open Panel Session – October 2007

Sponsor:

Cooperative Alliance for Interventional Radiology Research

Society of Interventional Radiology Foundation

Cardiovascular & Interventional Radiology Society of Europe Foundation

TACIT Study Leadership

- Principal Investigator: John Rundback
- Study Chairs: Barry Katzen (US), Matthew Thompson (EU)
- Neurology Chairs: JP Mohr (US), Martin Brown (EU)
- Clinical Coordinating Center: CAIRR/SIR Foundation
- Data Coordinating Center: Roxanna Mehran, Cardiovascular Research Foundation
- Duplex Core Lab: Michael Jaff, VasCore
- Executive Cttee: Peter Gaines, Gary Roubin, Michael Jaff, Ken Ouriel, Rod Raabe, Marc Sapoval, Ken Rosenfield, Johannes Lammer, Bill Gray

TACIT Study Leadership

- Subcommittees / Sub-studies:
  - Medical Therapy and Risk Mgmt Intervention
    - Chairs – JP Mohr, Martin Brown
  - Stent Intervention
    - Chairs – Gerald Zemel, Klaus Mathias
  - Surgical Intervention
    - Chairs – Bruce Perler, Frans Moll
  - Site Selection
    - Chairs – Kenneth Rosenfield, Marc Sapoval
  - Economics and Quality of Life
    - Chairs – Jonathan Michaels
  - Neuropsychology
    - Chairs – Stan Newman, Robert Burr

Background (1)

- In U.S. there are 750,000 strokes annually; stroke is the leading cause of adult disability*
- Stroke costs the U.S. $30-50 billion annually and are estimated to top $2.2 trillion by 2050 (UPI)
- ¾ of patients treated with revascularization are asymptomatic (CAPTURE, CASES PMS)
- Early trials (1990's) demonstrated the benefit of carotid endarterectomy over [noncontemporary] medical therapy in reducing incidence of stroke.

* American Stroke Association

Background (2)

- Vascular protective medications like ***statins*** and antiplatelets have substantially improved the spectrum of optimal medical treatment – findings of previous studies with respect to optimal medical treatment are likely not representative of contemporary results
- Modern optimal medical therapy may stabilize the artherosclerotic plaque, while revascularization procedures resolve the carotid stenosis
- Result of trials have not resulted in consensus regarding the best treatment of patients with asymptomatic CAS (EVA3, SPACE).
- Currently in the U.S., the majority of patients with asymptomatic CAS are not offered revascularization.

Asymptomatic Trials

- ACAS (n=1,659)
  - 5 yr estimated ipsilateral stroke, perioperative stroke and death
  - 11% med, 5.1% CEA
- CASANOVA (n=410) no difference btwn medical Rx and CEA
- MACE (n=71, terminated)
- ACST (n=3120)
- CREST (n=2500, 1100 asymptomatic)
- ACT I (n=1540)
- TACIT (n=>2500)

ACST findings

- Endarterectomy reduced 3-year risk of all strokes and *perioperative* deaths from 11.8 to 6.7% compared to medical therapy alone.

ACST limitations

- Incomplete medical compliance
  - –17% of medical cohort on antilipemic medications from 1993-1996
  - –58% of medical cohort on antilipemic medications from 2000-2003
  - –70% of medical cohort on antilipemic medications at end of study
- No difference in comparison of ALL STROKES and ALL DEATHS
  - –Medical therapy 335/1560 @ 5 years = 21.5%
  - –CEA 309/1560 @ 5 years = 19.8%

Medical Trials of ASx Patients

Lower event rates than reported in Interventional Trials:

- CAPRIE (n=19,185) 1.9 yr stroke, MI, vasc death
  - 5.8% ASA, 5.3% Plavix
- 4S (n=4,444)
  - Simvistatin 2.7% stroke
  - Placebo 4.3% stroke
- Antiplatelets (ATP Trialists Grp) → 35% reduced stroke risk
- Antihypertensives (HOPE) → 40% reduced stroke risk

TACIT population at risk

- 20-30% of >700K annual strokes dues to CAS (17% of LFL pts with mod/hi risk)
  - Stroke is the most common initial presentation of asymptomatic CAS (90%) **→ 125K – 200K individuals per year**
- ¾ of all CEA's for asymptomatic dx
- CREST enrollment increased due to asx pts

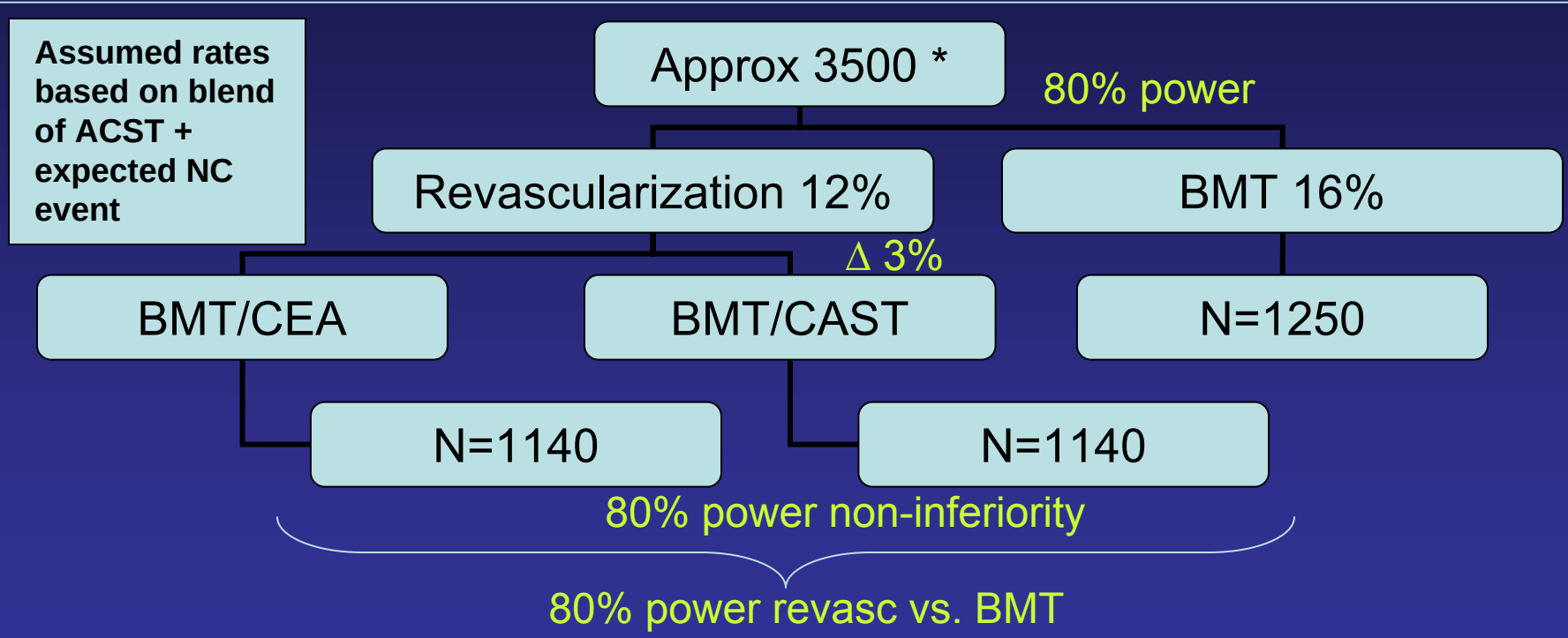
TACIT

- Primary study aim: Can optimized medical therapy, with or without revascularization by carotid endarterectomy or stenting, reduce the risk perioperative mortality and 5 year all strokes and neurocognitive decline? (** 5-yr primary endpt)

- Study Design: TACIT is a prospective multi-center, collaborative U.S. and EU unblinded, three-arm, randomized trial comparing three treatment strategies in patients with duplex evidence of ≥60% carotid stenosis:
  - 1. optimal medical therapy alone;
  - 2. medical therapy with carotid artery stenting (CAST);
  - 3. medical therapy with carotid endarterectomy.

TACIT Design

Primary Endpoint: periproced mortality and 5-yr all strokes and neurocognitive function



* Need to add patients for anticipated attrition (5%)

BMT = Best Medical Treatment, CAST = Carotid stenting, CEA = endarterectomy

Medical / Risk Plan

- There will be strict monitoring of medical compliance and cardiovascular risk factors.

Medical / Risk plan

- All patients on statins and antiplatelet
  - Vytorin 10/40 or equivalent in all patients
  - ASA 325 for life, periprocedural plavix
- Enforced therapeutic targets:
  - Two LDL Entry Groups – (NCEP/ATPIII guidelines)
    - Baseline LDL-C 130-160 →LDL-C target ≤ 100
    - Baseline LDL-C <130 →LDL-C ≤ 70
  - BP < 140/90 (JNC VII guidelines)
  - Hgb A1C < 6.5
  - Not smoking

BP mgmt

- First line ACE/ARB (HOPE trial)
- Early Diuretic
- Additional agents in systematic fashion
  - Calcium channel blockers
  - Beta blockers
  - Alpha antagonists

Inclusion/Exclusion

- Inclusion Criteria
  - Duplex ICA stenosis >= 60% (ICA PSV >125 cm/sec) with second confirmatory imaging test (to assure stenting candidacy)
  - Asymptomatic – no prior event attributable to the target lesion within 6 months prior to enrollment

Exclusion Criteria

1. General study exclusions:
   a. Unable to provide informed consent
   b. Unable or unwilling to comply with study protocol or procedures
   c. Participation in another drug or device trial during the study period
2. Fibromuscular dysplasia or congenital carotid artery stenosis
3. Pregnancy or unknown pregnancy status
4. Age <18
5. History of any prior stroke or documented TIA within 6 months of study enrollment
6. High anticipated non-carotid stroke risk
   a. Hospitalization for heart failure within 3 months
   b. Known ejection fraction <30%
   c. Atrial fibrillation or digoxin therapy
7. Allergy to aspirin, clopidogrel, or intravascular contrast, not amenable to pre-treatment

Exclusion Criteria

8. Comorbid status with life expectancy < 5 years
    a. Any major surgery, major trauma, revascularization procedure, unstable angina, or myocardial infarction less than 3 months prior to study enrollment
    b. Anticipated coronary intervention
    c. Known untreated aneurysm of the abdominal aorta >4.0 cm
    d. Serum Cr >3.0 mg/dl or Cockcroft-Gault estimated CFR < 50 cc/min
    e. Intracranial aneurysm > 5 mm in diameter
9. Previous carotid angioplasty or stent intervention
10. Vascular disease of the upper or lower extremity precluding access for stenting

– Presence of carotid stenosis or carotid artery that demonstrates anatomic features indicating tha stenting will carry increased procedural risk.
    a. String sign (“trickle flow”) in target vessel
    b. Intraluminal thrombus
    c. Moderate or severe tortuosity and/or calcification

12. Surgically inaccessible lesion or high surgical risk – tracheostoma, prior neck dissection or irradiation

Crossovers

- Putative mechanism of medical therapy is plaque stabilization. Therefore, crossovers allowed from medical therapy to revascularization for:
  - ICA stenosis progression from <80% to >80% (ICA PSV >250)
  - Progression from <80% to "trickle flow"
  - Documented TIA or stroke in evolution
- TACIT will evaluate "strategies" of initial medical therapy vs. initial revascularization, while maintaining clinical equipoise.
- A separate per protocol analysis will be done

Major Secondary Endpoints:

I. Neurocognitive function testing
   a. Limited cognitive testing on all pts
   b. Comprehensive battery on 400

II. Health Economic Analysis

III. Plaque characteristics substudy
   a. Duplex evaluation
   b. de novo risk in medical arm
   c. Procedural risk

NP testing

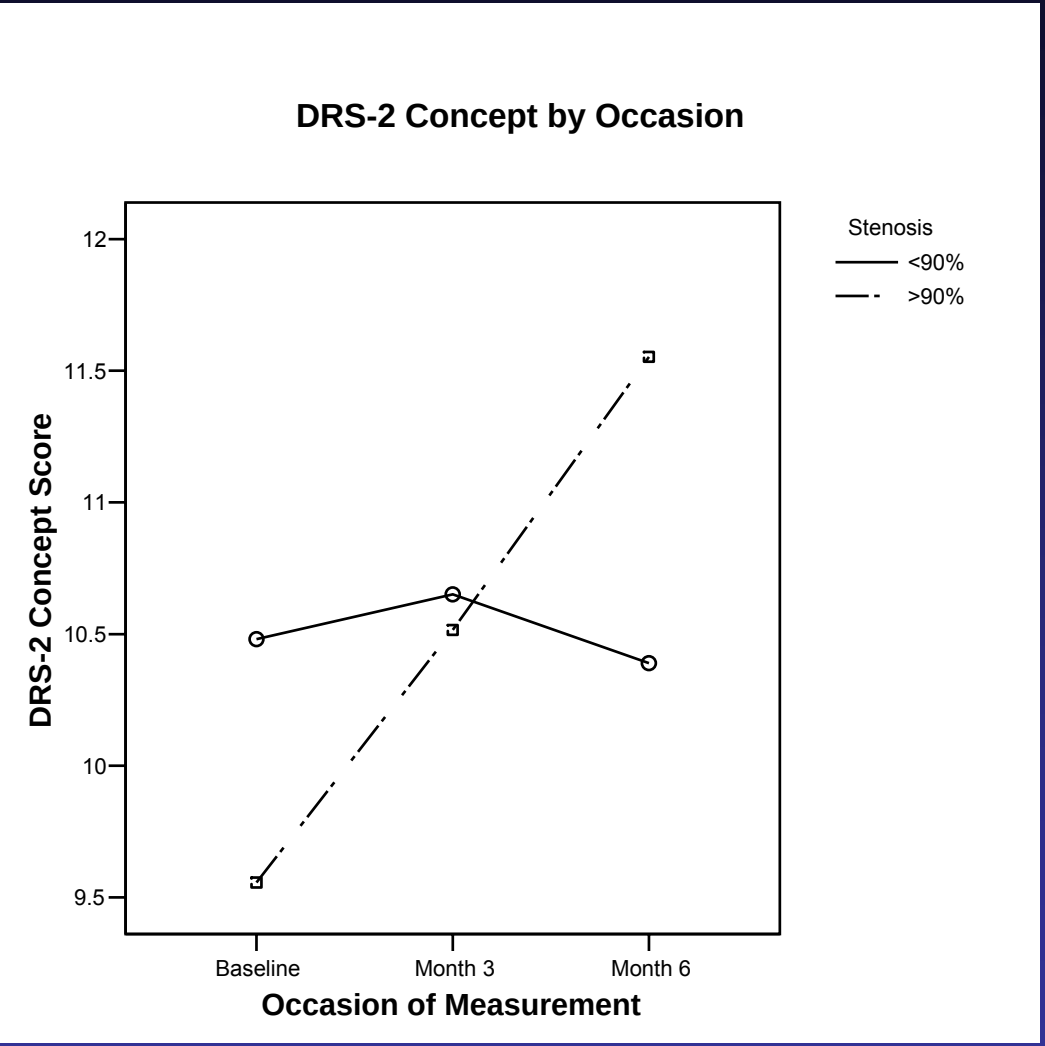
Entire TACIT group will undergo NP testing:

- Trail Making Tests A & B (Reitan & Wolfson, 1993) –
  - Change in Trail Making test performance has been found in dementia, stroke, trauma.
  - Its sensitivity to cognitive function change makes it one of the most widely used tests.
- Symbol Digit Modalities Test [SDMT] (Smith, 1982) –
  - sensitive at detecting acute or chronic organic cerebral dysfunction like might be seen in stroke (Smith)
  - found to be the best discriminator of dementia (Pfeffer)

- The tests selected have been used in stroke and consequently there is data to perform the requisite power calculations
- The tests are widely used and have been established to detect minor brain dysfunction.

NP testing

- CV Health cognition study → 13% onset of vascular dementia over 5.7 yrs
- Ann Intern Med 2004 (n=4006) → Asx LICA stenosis associated with cognitive impairment and decline (OR 6.7 [95% CI, 2.4 to 18.1])
- Tromso study 2004 (n=6885) → subjects with CAS had significantly lower performance for attention, psychomotor speed, attention, memory and motor function
- CAST associated with improved NP function and vascular depression *in subset of pts*



Burr & Raabe et. al., in process

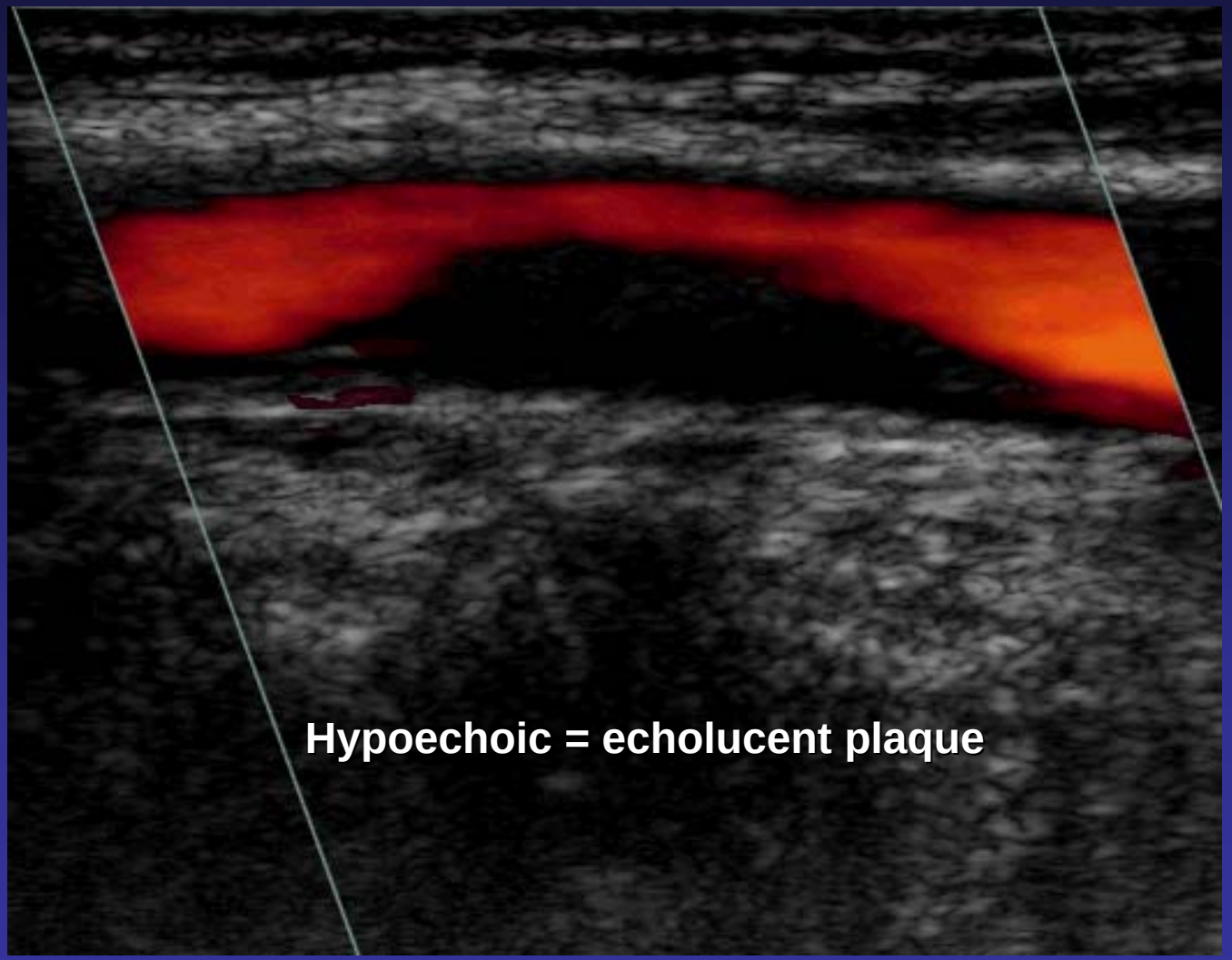
Health Economic Analysis (Jonathan Michaels)

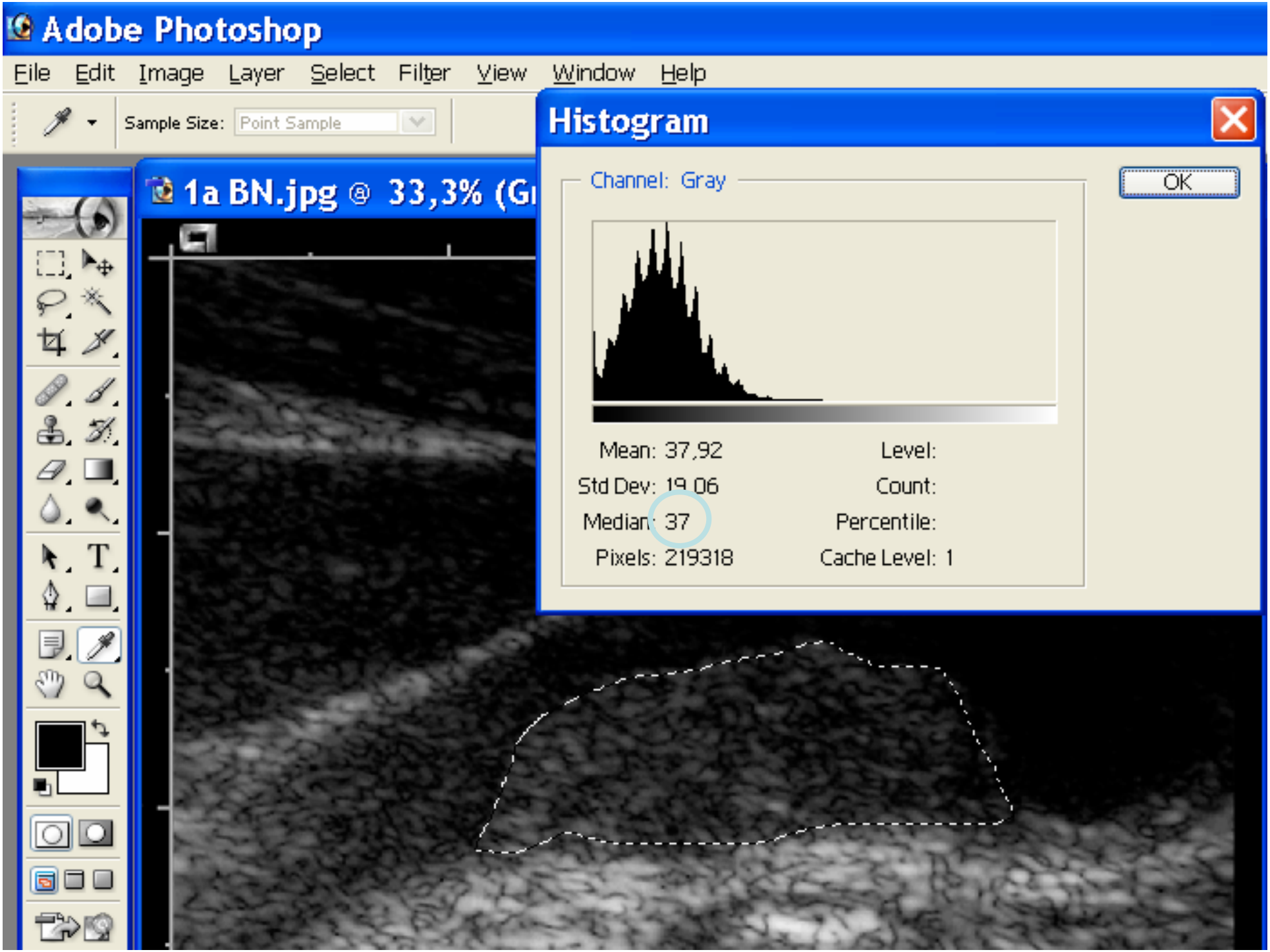
- Incremental CER
  - Resource Use Form (RUF): medical, direct non-medical, and indirect costs associated with BMT, CAST and CEA will be collected through a survey instrument designed specifically for this purpose
  - the average cost per patient under each treatment and the total benefit will be calculated and the treatments considered in order of ascending cost
  - The two more costly treatments will be compared to the least costly and to each other, to calculate relevant ICER's
  - expressed in terms of cost per additional Quality Adjusted Life Year (EuroQOL utility measure)

Health Economic Analysis (Jonathan Michaels)

- HRQoL Evaluation scales
  - EuroQOL health status instrument (EQ-5D)
  - 36-Item Short-Form Health Survey
  - Side Effects and Symptom Distress Index
  - SF-6D health utility index derived from SF-36

Plaque Characterization




Adobe Photoshop
File Edit Image Layer Select Filter View Window Help
Sample Size: Point Sample
1a BN.jpg @ 33,3% (Gr
Histogram
Channel: Gray
OK
Mean: 37,92
Std Dev: 19,06
Median: 37
Pixels: 219318
Level:
Count:
Percentile:
Cache Level: 1

ICAROS: Results

GSM value in uncomplicated vs. complicated patients (Stroke)

20.80±17.43 vs. 35.07±19.60, p=0.0036

Additional Secondary Endpoints:

IV. Adjudicated clinical outcomes assessed at 30-days:

- all deaths
- all strokes
- ipsilateral strokes
- fatal stroke
- myocardial infarction (q-wave & enzymes: CK-MB > 2x nl)
- All procedural complications
- Quality of life

V. Adjudicated clinical outcomes assessed at 5-years:

- All deaths
- All strokes
- ipsilateral strokes
- fatal stroke
- myocardial infarction
- Quality of life
- Cost effectiveness

VI. Duplex analyses of restenosis:

- Residual stenosis at 30-days
- Progression of stenosis in non-revascularized patients
- Restenosis in revascularized pts at 6 mths, 1-, 2-, 3- yrs

Tertiary/Exploratory Endpoints:

I. Subgroup interaction in critical subgroups
II. Comparing clinical evaluation tools
III. Outcomes by treatment characteristics
IV. Outcomes by Disease/lesion characteristics
V. Duplex prognostic characteristics
VI. Biochemical prognostic characteristics

Enrollment targets

- Total 3700 patients / 125 sites / 18 mth enrolled

mths	0-6	6-12	12-18	18-24	24-7yrs
# sites enrolling	Activation	50	75	100	f/u
# pts/mth		2	2	2	
Mthly enrollment	NO ROLL-INS	100	150	200	
Annual enrollment		600	1800	1200	
Total n		600	2400	3600 +	

TACIT distinction

1. Contemporary data regarding the salutary effects of medical therapies including statin medications and antiplatelets, not present at the time of other trial design, have been used to construct a cohort of patients treated without revascularization.
2. TACIT will be the only trial to date that directly compares outcomes in patients undergoing CAST with optimized medical therapy alone.
3. All risk patients rather than just high surgical risk patients will be studied in TACIT.

TACIT distinction

4. this trial will evaluate numerous other critical intermediary and mechanistic outcomes never before studied, and which may have a substantial impact on therapeutic decisions –

(a) neurocognitive assessments to determine progression of overtly subclinical neurological or functional declines related to carotid disease treatment;

(b) plaque characterization impact on events and procedural complications

(c) relationship of stenosis progression and clinical events in revascularized versus non-revascularized subjects;