*CTMC Webinar*

# Study Monitoring: Adverse Events, Independent Medical Monitors, and Data and Safety Monitoring Boards

Roger J. Lewis, MD, PhD
Department of Emergency Medicine
Harbor-UCLA Medical Center
David Geffen School of Medicine at UCLA
Berry Consultants, LLC

@RogerJLewis

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## Financial Disclosures

- Employee
  - County of Los Angeles, Department of Health Services, Harbor-UCLA Medical Center
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## Purpose of Monitoring

- The purposes of study monitoring during the conduct of clinical research, are to
  - Protect the patient from avoidable and often unforeseen risks of participation (requires real time monitoring)
  - Ensure research continues to be ethical, scientifically valid and worthwhile, and feasible over the entire time period of its conduct
  - Ensure that the trial is stopped as soon as a reliable conclusion can be drawn from the data

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## Philosophy

- The philosophy is that you must be prepared for unexpected events and effects
- The data and safety monitoring plan must be developed to address what could possibly happen, not what is expected or likely to happen
- This is a major paradigm shift for many investigators

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## Philosophy

- In designing a clinical trial you never know as much as you think you do!
- Study populations do not behave like general patient population (common to see lower event rates)
- Minor adverse events may be very important
- In drug development, many toxicities only appear late

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## Monitor versus DSMB/DMC

- A Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a group of independent experts who review accumulating data from an ongoing trial to determine whether the study should be continued, modified, or stopped
- A "Monitor" or "Independent Medical Monitor" (IMM) is a one-person DSMB

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## Other Use of the Word "Monitor"

- Industry sponsors of trials send "study monitors" to verify that information on CRFs can be validated with source documentation
- There is no relationship between the "monitoring" of CRFs and data and safety monitoring of a clinical trial

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## Goals of Safety Monitoring

- Detection of intervention-associated adverse events against background rates in population
- Identification of unanticipated intervention-associated adverse events
- Identification of subgroups at increased risk of adverse events
- Verification that expected adverse events are not occurring more often than expected

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## Adverse Events

- An adverse event (AE) is anything bad that happens to the patient while they are in the study, regardless of perceived causality
- An adverse drug experience is an AE that occurs after the patient is given a drug (21 CFR§312.32)
- An adverse device effect is an AE in a device trial (21 CFR§812.3)

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## Serious Adverse Events (SAEs)*

- An AE that results in "Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect."
- Other "important medical events" may also be SAEs, based on medical judgment
- No requirement for causation
- Death is always an SAE

*21 CFR§312.32

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## Unexpected Adverse Event (UAEs)*

- "Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere…"

*21 CFR§312.32

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## Adverse Events

- There may also be adverse events that can be anticipated and are particularly relevant for the drug or trial (e.g., coumadin and bleeding, suicide attempts in a trial of an antidepressant)
- These should be
  - Mentioned in investigator brochure
  - Disclosed as risks in the informed consent document
  - Specifically tracked in the data monitoring plan

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## Severity and Attribution

- Adverse events are further characterized by severity and attribution
  - Severity often uses a protocol specific grading scheme (don't use "serious")
  - Attribution is the investigator's judgment regarding causality
- If reporting is required, a description of the AE, along with assessment of severity and attribution, and follow up information is generally reported to the IRB and sponsor, and tabulated in reports provided to the DSMB (if any)

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## Requirements for Monitoring

- Intensity of monitoring (e.g., local safety officer, independent medical monitor, data and safety monitoring board) depends on complexity and risk of trial participation, stage of investigation, and sponsor requirements
- NIH requires a DSMB for
  - All phase III studies
  - Blinded phase I/II therapeutic studies
  - Any high risk phase I or II clinical trial
- NINDS requires that all clinical trials involving interventions that entail more than minimal risk to participants have a DSMB

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## Safety Officer

- In small, single-site studies, safety monitoring is often performed by a statistician in conjunction with a Safety Officer. The Safety Officer is:
  - Appointed by the grantee institution
  - Reviews adverse events (AEs) and Serious Adverse Events (SAEs) on an ongoing basis to determine action, if needed

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## Independent Medical Reviewer

- For NINDS-sponsored studies which are likely to entail risks, an independent Medical Reviewer is often appointed by the Statistical (or Data Management) Coordinating Center to review serious adverse events in a "real time" manner

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## Data and Safety Monitoring Boards & Data Monitoring Committees

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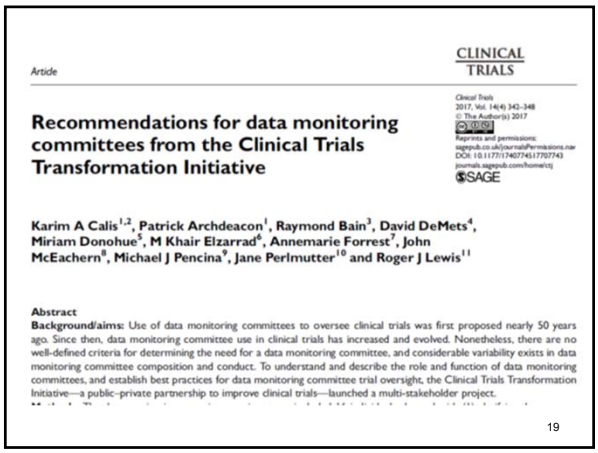

Article

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SAGE

**Recommendations for data monitoring committees from the Clinical Trials Transformation Initiative**

Karim A Calis[1,2], Patrick Archdeacon[1], Raymond Bain[3], David DeMets[4], Miriam Donohue[5], M Khair Elzarrad[6], Annemarie Forrest[7], John McEachern[8], Michael J Pencina[9], Jane Perlmutter[10] and Roger J Lewis[11]

**Abstract**

**Background/aims:** Use of data monitoring committees to oversee clinical trials was first proposed nearly 50 years ago. Since then, data monitoring committee use in clinical trials has increased and evolved. Nonetheless, there are no well-defined criteria for determining the need for a data monitoring committee, and considerable variability exists in data monitoring committee composition and conduct. To understand and describe the role and function of data monitoring committees, and establish best practices for data monitoring committee trial oversight, the Clinical Trials Transformation Initiative—a public–private partnership to improve clinical trials—launched a multi-stakeholder project.

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## Purposes of a DSMB

- Primary
  - To protect subjects from avoidable risk
  - To ensure trial integrity and validity
- Secondary
  - To provide an assurance that the trial is conducted in an unbiased manner
  - To enhance credibility and impact of trial results
- Tertiary
  - To operationalize sponsor's goals and values regarding continued product evaluation

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## DSMB Process

- The DSMB accomplishes its task by reviewing accumulating efficacy and safety data during the conduct of the trial (e.g., interim analyses)
- This informs recommendation for the continuation, modification, or termination of the ongoing trial
- The DSMB has both expertise and access to data that the IRB does not, giving the DSMB a unique and critical role

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## DSMB Basics

- Membership
  - Scope of expertise (medical domain, trial methodology and statistics, ethics, pharmacokinetics, regulatory requirements)
  - Balance of perspectives, ability to incorporate and yield to the expertise of others
- Charter
  - Defines structure for and rules under which the DSMB operates
  - Timing, content, and format of meetings, contents of reports, confidentiality and firewalls

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## DSMB Basics

- Open vs Closed vs Executive Sessions
  - Open: includes "interested parties" (e.g., sponsor, principal investigator, etc.); only aggregated and process data presented;
  - Closed: DSMB members and those preparing unblinded data (e.g., DCC statistician); and
  - Executive (rare): Only DSMB members
- Recommendations vs Decisions
  - DSMBs make recommendations
  - Most, but not all sponsors/PIs, follow them

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## DSMB Preparation and Education

- There is little training of DSMB members in general, let alone for an adaptive trial
- Greater time is required to understand an adaptive design
- DSMB should learn about the design from the team that designed it, ideally before first patient is enrolled

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## DSMB Preparation and Education

- An early, face-to-face DSMB meeting is essential
  - Prior to final protocol and DSMB charter
  - Detailed explanation of design, rationale, and expected results
  - Principle efficacy and safety considerations
  - Expectations for committee member behavior and responsiveness

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## Cautionary Comments

- The DSMB works in isolation and can really screw up the trial
- The DSMB must understand what the trial is supposed to do so they can determine
  - If something is going wrong; or
  - If what the trial was designed to do is no longer the right thing to do; and
  - Recognize the potential impact on trial validity of making changes to the design after they've seen unblinded data

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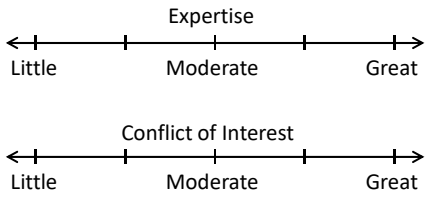
## Expertise and Conflicts of Interest

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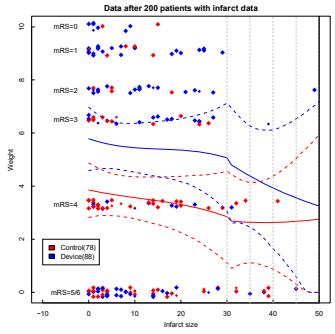
## DAWN Interim Analysis n=200

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## The DSMB Chair

- An effective chair must:
  - Have a working understanding of clinical, statistical, logistical, and regulatory considerations
  - Be able to facilitate deliberations incorporating all relevant expertise and perspectives
  - Be aware of regulatory considerations
  - Have the ability to "flex" substantial time to devote to DSMB activities

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## The Marketing/KOL Trap

- Sometimes sponsors choose KOLs for DSMBs, as a first marketing step
- Such choices can be problematic
  - Limited time for preparation and DSMB work
  - Pre-formed opinions regarding product
  - Authority that exceeds understanding of the trial design or the limits of sparse data
  - Lack of familiarity with considerations of trial integrity, preservation of designed operating characteristics, and regulatory issues

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## Conclusions

- The membership of a DSMB overseeing a clinical trial should include a variety of expertise
- DSMBs need to actively monitor
  - Efficacy, safety, futility
  - Fidelity to and appropriateness of the original design
- The DSMB members must understand the considerations surrounding the conduct and modification of a trial, including regulatory considerations
- Pre-trial education of the DSMB, and a detailed pre-trial meeting, is essential to protect trial validity

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## DSMB Examples

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NEUROLOGY/REVIEW ARTICLE

### Data and Safety Monitoring in Clinical Research: A National Institute of Neurologic Disorders and Stroke Perspective

**Robin A. Conwit, MD**
**Robert G. Hart, MD**
**Claudia S. Moy, PhD**
**John R. Marler, MD**

From the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Neuroscience Center, Bethesda, MD.

The National Institute of Neurologic Disorders and Stroke supports a broad spectrum of research in the diagnosis and treatment of neurologic disease. Emergency medicine is increasingly involved in clinical research for patients with neurologic emergencies. Independent data and safety monitoring are critical components of clinical trials to ensure the protection of patients and the scientific integrity of the research. We review National Institute of Neurologic Disorders and Stroke principles of data and safety monitoring and provide examples to illustrate key concepts. [Ann Emerg Med. 2005;45:388-392.]

doi:10.1016/j.annemergmed.2004.08.006

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**BENEFICIAL EFFECT OF CAROTID ENDARTERECTOMY IN SYMPTOMATIC PATIENTS WITH HIGH-GRADE CAROTID STENOSIS**

NORTH AMERICAN SYMPTOMATIC CAROTID ENDARTERECTOMY TRIAL COLLABORATORS*

**Abstract** *Background.* Without strong evidence of benefit, the use of carotid endarterectomy for prophylaxis against stroke rose dramatically until the mid-1980s, then declined. Our investigation sought to determine whether carotid endarterectomy reduces the risk of stroke among patients with a recent adverse cerebrovascular event and ipsilateral carotid stenosis.

*Methods.* We conducted a randomized trial at 50 clinical centers throughout the United States and Canada, in patients in two predetermined strata based on the severity of carotid stenosis — 30 to 69 percent and 70 to 99 percent. We report here the results in the 659 patients in the latter stratum, who had had a hemispheric or retinal transient ischemic attack or a nondisabling stroke within the 120 days before entry and had stenosis of 70 to 99 percent in the symptomatic carotid artery. All patients received optimal medical care, including antiplatelet therapy. Those assigned to surgical treatment underwent carotid endarterectomy performed by neurosurgeons or vascular surgeons. All patients were examined by neurologists 1, 3, 6, 9, and 12 months after entry and then every 4 months. End points were assessed by blinded, independent case review. No patient was lost to follow-up.

*Results.* Life-table estimates of the cumulative risk of any ipsilateral stroke at two years were 26 percent in the 331 medical patients and 9 percent in the 328 surgical patients — an absolute risk reduction (±SE) of 17±3.5 percent (P<0.001). For a major or fatal ipsilateral stroke, the corresponding estimates were 13.1 percent and 2.5 percent — an absolute risk reduction of 10.6±2.6 percent (P<0.001). Carotid endarterectomy was still found to be beneficial when all strokes and deaths were included in the analysis (P<0.001).

*Conclusions.* Carotid endarterectomy is highly beneficial to patients with recent hemispheric and retinal transient ischemic attacks or nondisabling strokes and ipsilateral high-grade stenosis (70 to 99 percent) of the internal carotid artery. (N Engl J Med 1991; 325:445-53.)

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## North American Symptomatic Carotid Endarterectomy Trial

- Powered to detect a 50% reduction in patients with high-grade stenosis with planned n= 600 and 5 years of follow up
- Stopping rule: P < .001 for 6 months and results deemed unambiguous and clinically important
- Included a futility rule as well
- Early stopping recommended with about 1.5 years follow up among the 659 participants
- A clinical alert was quickly circulated to physicians regarding the benefits of endarterectomy

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### A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis

M.E. Cudkowicz, MD, MSc; J.M. Shefner, MD, PhD; D.A. Schoenfeld, PhD; R.H. Brown, Jr., DPhil, MD; H. Johnson, BS, MPH; M. Qureshi, MD, MPH; M. Jacobs, MPH; J.D. Rothstein, MD, PhD; S.H. Appel, MD; R.M. Pascuzzi, MD; T.D. Heiman-Patterson, MD; P.D. Donofrio, MD; W.S. David, MD, PhD; J.A. Russell, DO; R. Tandan, MD, FRCP; E.P. Pioro, MD, PhD; K.J. Felice, DO; J. Rosenfeld, MD, PhD; R.N. Mandler, MD; G.M. Sachs, MD; W.G. Bradley, DM, FRCP; E.M. Raynor, MD; G.D. Baquis, MD; J.M. Belsh, MD; S. Novella, MS; J. Goldstein, MD; and J. Hulihan, MD, for the Northeast ALS Consortium*

**Abstract**—*Objective:* To determine if long-term topiramate therapy is safe and slows disease progression in patients with ALS. *Methods:* A double-blind, placebo-controlled, multicenter randomized clinical trial was conducted. Participants with ALS (n = 296) were randomized (2:1) to receive topiramate (maximum tolerated dose up to 800 mg/day) or placebo for 12 months. The primary outcome measure was the rate of change in upper extremity motor function as measured by the maximum voluntary isometric contraction (MVIC) strength of eight arm muscle groups. Secondary endpoints included safety and the rate of decline of forced vital capacity (FVC), grip strength, ALS functional rating scale (ALSFRS), and survival. *Results:* Patients treated with topiramate showed a faster decrease in arm strength (33.3%) during 12 months (0.0997 vs 0.0748 unit decline/month, $p = 0.012$). Topiramate did not significantly alter the decline in FVC and ALSFRS or affect survival. Topiramate was associated with an increased frequency of anorexia, depression, diarrhea, ecchymosis, nausea, kidney calculus, paresthesia, taste perversion, thinking abnormalities, weight loss, and abnormal blood clotting (pulmonary embolism and deep venous thrombosis). *Conclusions:* At the dose studied, topiramate did not have a beneficial effect for patients with ALS. High-dose topiramate treatment was associated with a faster rate of decline in muscle strength as measured by MVIC and with an increased risk for several adverse events in patients with ALS. Given the lack of efficacy and large number of adverse effects, further studies of topiramate at a dose of 800 mg or maximum tolerated dose up to 800 mg/day are not warranted.

NEUROLOGY 2003;61:456–464

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## Topiramate in Amyotrophic Lateral Sclerosis

- After the randomized trial of 198 subjects, 122 patients elected to participate in an open-label continuation phase
- At the end of the randomized component, the DSMB recommended immediate termination of the open-label phase, based on
  - Faster decline in strength (primary endpoint)
  - Excess number of cases of thromboembolism (12 cases [6%] vs 1 case [1%]), P=.07

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**A RANDOMIZED TRIAL COMPARING TICLOPIDINE HYDROCHLORIDE WITH ASPIRIN FOR THE PREVENTION OF STROKE IN HIGH-RISK PATIENTS**

WILLIAM K. HASS, M.D., J. DONALD EASTON, M.D., HAROLD P. ADAMS, JR., M.D., WILLIAM PRYSE-PHILLIPS, M.D., BASIL A. MOLONY, M.D., SHARON ANDERSON, PH.D., AND BARBARA KAMM, M.A., FOR THE TICLOPIDINE ASPIRIN STROKE STUDY GROUP

**Abstract** We report the results of the Ticlopidine Aspirin Stroke Study, a blinded trial at 56 North American centers that compared the effects of ticlopidine hydrochloride (500 mg daily) with those of aspirin (1300 mg daily) on the risk of stroke or death. The medications were randomly assigned to 3069 patients with recent transient or mild persistent focal cerebral or retinal ischemia. Follow-up lasted for two to six years.

The three-year event rate for nonfatal stroke or death from any cause was 17 percent for ticlopidine and 19 percent for aspirin — a 12 percent risk reduction (95 percent confidence interval, −2 to 26 percent) with ticlopidine (P = 0.048 for cumulative Kaplan–Meier estimates). The rates of fatal and nonfatal stroke at three years were 10 percent for ticlopidine and 13 percent for aspirin — a 21 percent risk reduction (95 percent confidence interval, 4 to 38 percent) with ticlopidine (P = 0.024 for cumulative Kaplan–Meier estimates). Ticlopidine was more effective than aspirin in both sexes.

The adverse effects of aspirin included diarrhea (10 percent), rash (5.5 percent), peptic ulceration (3 percent), gastritis (2 percent), and gastrointestinal bleeding (1 percent). With ticlopidine, diarrhea (20 percent), skin rash (14 percent), and severe but reversible neutropenia (<1 percent) were noted. The mean increase in total cholesterol level was 9 percent with ticlopidine and 2 percent with aspirin (P<0.01). The ratios of high-density lipoprotein and low-density lipoprotein to total cholesterol were similar in both treatment groups.

We conclude that ticlopidine was somewhat more effective than aspirin in preventing strokes in this population, although the risks of side effects were greater. (N Engl J Med 1989; 321:501-7.)

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## The efficacy and safety of ticlopidine and aspirin in non-whites:

### Analysis of a patient subgroup from the Ticlopidine Aspirin Stroke Study

Leon A. Weisberg, MD, for the Ticlopidine Aspirin Stroke Study Group

**Article abstract**—We analyzed the efficacy of ticlopidine and aspirin in the non-white subgroup of patients from the Ticlopidine Aspirin Stroke Study. In this double-blind, randomized, multicenter study, patients received either ticlopidine 250 mg (312 non-white patients) or aspirin 650 mg (291 non-white patients) twice a day. The 1-year cumulative event rate per 100 patients for nonfatal stroke or death from any cause was 5.5 for ticlopidine and 10.6 for aspirin—an apparent 48.1% reduction in risk with ticlopidine relative to aspirin. The 1-year cumulative event rate for fatal or nonfatal stroke was 3.7 for ticlopidine and 9.4 for aspirin—an apparent 60.8% reduction in risk with ticlopidine relative to aspirin. The cumulative event rates for both endpoints also were lower in ticlopidine-treated patients after the 2nd and 3rd years. These reductions were not significantly different between treatment groups, but were of the same order of magnitude as previously found for the total series, which did attain statistical significance ($p = 0.048$), and the frequency of adverse events was not significantly different between the two treatment groups. Severe neutropenia, the most serious adverse event associated with ticlopidine use, did not occur in non-white patients. These results suggest that ticlopidine is superior to aspirin for stroke prevention in non-whites.

NEUROLOGY 1993;43:27-31

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## Aspirin and Ticlopidine for Prevention of Recurrent Stroke in Black Patients

### A Randomized Trial

Philip B. Gorelick, MD, MPH
DeJuran Richardson, PhD
Michael Kelly, MD
Sean Sulland, DO
Elena Hung, MS
Yvonne Harris, MPA, CCRA
Steven Kittner, MD, MPH
Sue Lesrgana, PhD
for the African American Antiplatelet Stroke Prevention Study (AAASPS) Investigators

**Context** Blacks are disproportionately affected by stroke, and they are about 2 times more likely than most other individuals in the United States to die of or experience stroke.

**Objective** To determine the efficacy and safety of aspirin and ticlopidine to prevent recurrent stroke in black patients.

**Design, Setting, and Patients** Randomized, double-blind, investigator-initiated, multicenter trial of 1809 black men and women who recently had a noncardioembolic ischemic stroke and who were recruited between December 1992 and October 2001 from 62 academic and community hospitals in the United States and followed up for up to 2 years.

**Intervention** A total of 902 patients received 500 mg/d of ticlopidine and 907 received 650 mg/d of aspirin.

**Main Outcome Measures** Recurrent stroke, myocardial infarction, or vascular death was the composite primary end point (according to intention-to-treat analysis). The secondary outcome was fatal or nonfatal stroke.

**Results** The blinded phase of the study was halted after about 6.5 years when futility analyses revealed a less than 1% probability of ticlopidine being shown superior to aspirin in the prevention of the primary outcome end point. The primary outcome of recurrent stroke, myocardial infarction, or vascular death was reached by 133 (14.7%) of 902 patients assigned to ticlopidine and 112 (12.3%) of 907 patients assigned to aspirin (hazard ratio, 1.22; 95% confidence interval, 0.94-1.57). Kaplan-Meier curves for time to event for the primary outcome did not differ significantly ($P = .14$ by log-rank test). Kaplan-Meier curves for time to the secondary outcome of fatal or nonfatal stroke approached a statistically significant reduction favoring aspirin over ticlopidine ($P = .08$ by log-rank test). The frequency of laboratory-determined serious neutropenia was 3.4% for patients receiving ticlopidine vs 2.2% for patients receiving aspirin ($P = .12$) and 0.3% vs 0.2% for thrombocytopenia, respectively ($P = .69$). One ticlopidine-treated patient developed thrombocytopenia, which was thought to be a case of possible thrombotic thrombocytopenia purpura, and recovered after therapy with plasmapheresis.

**Conclusions** During a 2-year follow-up, we found no statistically significant difference between ticlopidine and aspirin in the prevention of recurrent stroke, myocardial infarction, or vascular death. However, there was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group. Based on these data and the risk of serious adverse events with ticlopidine, we regard aspirin as a better treatment for aspirin-tolerant black patients with noncardioembolic ischemic stroke.

JAMA. 2003;289:2947-2957 www.jama.com

HR=1.22

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## African-American Antiplatelet Stroke Prevention Study

- As part of interim DSMB monitoring, futility analyses were performed
- After ~80% of the planned number of events, there was < 1% chance that ticlopidine would be shown to be superior to aspirin (and a 50% chance that aspirin would be shown to be better)
- The DSMB recommended termination of follow-up based on the cost, dosing, and potential adverse effects of ticlopidine, since proving the superiority of aspirin was not deemed relevant

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