point QUARTERLY
The Newsletter of the POINT Trial

Volume I, Issue I | Third Quarter 2010

Welcome

Welcome *to the Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial.*

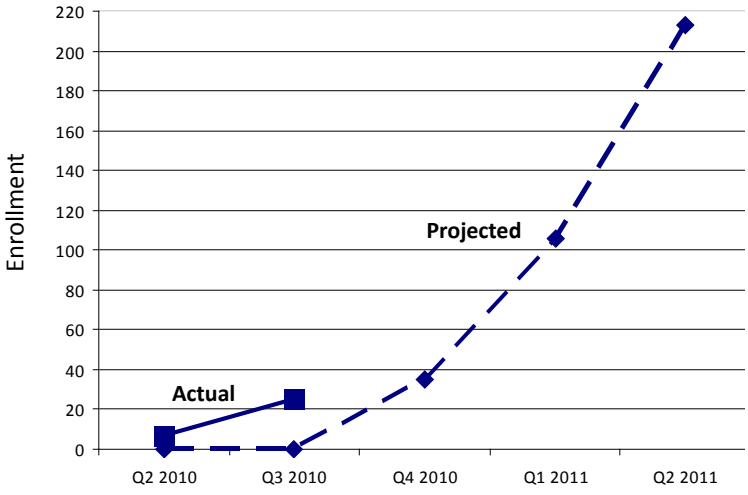
After 10 years of grant revisions, lobbying, and false starts, we are finally underway, addressing a question that has become more pressing: How do we reduce the high stroke risk after TIA and minor stroke?

As of August 31, 2010, 25 of our planned 150 sites are up and running, with many more in progress. The University of Maryland entered the first patient on May 28, 2010, and at the end of August, Guilford Neurological in Greensboro, SC, already had 12 patients enrolled. Some of you just have a few forms to fill out before we can get you started.

We plan to send out a newsletter quarterly to keep everyone informed about issues, such as the FDA's recent black box warning on clopidogrel. The newsletter will also help to track our progress, showing our projected and actual recruitment (Figure 1) and featuring the secrets of success for rapidly enrolling sites.

Once again, welcome! —Clay Johnston

Figure 1: POINT Cumulative Enrollment



Total Enrollment as of August 31, 2010=27

Send your feedback and suggestions for future newsletters to Mary.Farrant@ucsfmedctr.org

POINT Partners

The University of California, San Francisco, Clinical Coordinating Center (CCC) has partnered with the EMMES Clinical Research Collaboration (known as the POINT CRC) and the Neurologic Emergencies Treatment Trials Clinical Coordinating Center (NETT-CCC) to conduct the POINT Trial.

The UCSF CCC offers expertise in study design, epidemiology, biostatistics, and study coordination. It has coordinated multicenter observational studies and clinical trials for the past decade.

EMMES has provided biostatistical, epidemiological, data management, computer systems development and support for clinical research programs for 30 years.

The NETT-CCC at the University of Michigan and NETT Statistical and Data Management Center (SDMC) at Medical University of South Carolina (MUSC) make up the NETT Network.

POINT Enrollment Update: Total=27

Top Enrollers† (as of August 31, 2010)

Site (Hub)	City	State	#
Guilford Neurological (CRC)	Greensboro	NC	12
Henry Ford (HFHS)	Detroit	MI	3
U. of Maryland (Maryland)	Baltimore	MD	3
Memorial Hermann (Texas)	Houston	TX	3
Hennepin Cty. MC (Minnesota)	Minneapolis	MN	2

† Includes sites with at least 2 subjects enrolled.

Completed Readiness Calls (as of August 31, 2010, listed alphabetically)

Site (Hub)	City	State
Augusta Health (CRC)‡	*Fishersville*	*VA*
Colorado Neuro Inst. (CRC)	Englewood	CO
Diablo/Concord (CRC)	Concord	CA
Diablo/Walnut Creek (CRC)	Walnut Creek	CA
El Camino (Stanford)	Mt. View	CA
Fairview Southdale (Minnesota)	Edina	MN
Hospital of UPenn (UPenn)	Philadelphia	PA
Mercy Hospital (CRC)	Chicago	IL
Mills-Peninsula (Stanford)	Burlingame	CA
NYP Cornell (NYP)‡	*New York*	*NY*
Providence Sacred Heart (CRC)	Spokane	WA
Stanford (Stanford)	Stanford	CA
Temple U. Hospital (Temple)	Philadelphia	PA
UMMC, Fairview (Minnesota)	Minneapolis	MN
University Hospital (Cincinnati)‡	*Cincinnati*	*OH*
U. of Arizona MC (Arizona)	Tucson	AZ
U. of Kentucky (Kentucky)	Lexington	KY
VCU/MCV (VCU)	Richmond	VA
West Bloomfield (HFHS)‡	*Detroit*	*MI*

‡ Has 1 enrollment as of August 31, 2010

Cytochrome P-450 Polymorphisms and Clopidogrel

Much is being written about genetic variability altering clopidogrel metabolism, which in turn affects inhibition of platelet function. Clopidogrel is a *prodrug* that requires conversion to its active metabolite by liver cytochrome P 450 enzymes, particularly cytochrome P450 2C19 (CYP2C19). The active molecule then binds to the platelet P2Y12 adenosine receptor resulting in inhibition of platelet aggregation.

BOXED WARNING—On March 12, 2010, the FDA announced it is estimated that 2–14% of the population are poor metabolizers of Plavix and that a *Boxed Warning* has been added to the prescribing information for Plavix®. The warning includes information to caution about reduced effectiveness in patients who are poor metabolizers of Plavix, to inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function, and to advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers. This warning will not affect the POINT Trial as there are no guidelines specific to hyper-acute TIA or minor stroke patients and the Class I, Level of Evidence A "AHA/ASA Recommendations for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack" do not recommend other antiplatelet drugs over aspirin. All subjects in POINT will receive aspirin.

PPIs—Proton-pump inhibitors (PPIs) also are metabolized by CYP2C19 and when taken concomitantly with clopidogrel can decrease the antiplatelet effectiveness of clopidogrel. Enzymes other than CYP2C19 can metabolize one of the PPIs, pantoprazole. For these reasons, POINT recommends that H2 antagonists be used when possible in subjects requiring gastroesophageal protection and for those not controlled with H2 antagonists and deemed to require a PPI, pantoprazole may be the best choice.

GENOTYPING—More recently some writers have advocated genotyping patients prior to initiating clopidogrel therapy to determine if they carry a reduced-function gene variant (primarily the CYP2C19*2 polymorphism) because these carriers appear to have an excess risk of cardiovascular events and mortality on clopidogrel. Studies do not address cerebrovascular disease. This issue remains controversial and caused the American College of Cardiology Foundation/American Heart Association on June 28, 2010 to issue a Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning" stating, "Overall, however, the evidence is insufficient to recommend routine genetic or platelet-function testing at the present." One of the authors is our own Dana Leifer at NY Presbyterian Hospital-Weill Cornell Medical Center. [Holmes DR, Jr., et al., ACCF/AHA Clopidogrel clinical alert: approaches to the FDA "boxed warning". Circulation 2010; 122:537-57.]

In an important study regarding this matter, it was concluded that CYP2C19 loss-of-function variants do not modify the efficacy and safety of clopidogrel. [Paré G, et al., Effects of CYP2C19 Genotype on Outcomes of Clopidogrel Treatment. N Engl J Med online.]

Undoubtably more will be written about this subject as new data accumulate.

POINT Frequently Asked Questions (FAQs)

Q. *The protocol states, "A trained licensed physician investigator will be required to confirm the diagnosis of TIA or minor ischemic stroke and to calculate the ABCD² score and NIH Stroke Scale score." Does this have to be the PI or co-PI, or can it be a sub-investigator? Is an MD required?*

A. A physician, Physician's Assistant (PA) or Nurse Practitioner (NP) investigator must confirm eligibility and review the calculation of the NIHSS and the ABCD² score either in person or by phone with properly trained and certified non-physician study personnel prior to randomization into the study. The protocol will be modified to reflect this change.

Q. *The POINT Manual of Procedures (MOP) states the initial (loading) dose of study drug must be taken in the presence of the PI or study team member. If it's not possible for ANY member of the team to actually witness the subject take the initial dose, may a nurse in the hospital witness the subject take the study drug and note this in the patient's hospital record?*

A. As the time to treatment, rather than time to randomization, is the crucial element of POINT, the subject should take the first eight pills of the study drug (loading dose) while the study investigator or other study team member is present. The investigator must facilitate dispensing the medication and ensure it is taken within the 12-hour treatment window, recording the date and time of the dose in WebDCU™. The time between randomization and treatment should be minimized: drug treatment should be considered STAT, administered in the first hour following randomization.

(More FAQs at https://webdcu.musc.edu/NETT/index.asp)

Recovery After Acute Ischemia

POINT is interested in determining whether subjects being enrolled with minor stroke had 1) no recovery, 2) modest recovery, or 3) substantial recovery. A few years ago, Johnston and Easton hypothesized that substantial recovery immediately after acute ischemia may be an indicator of greater instability and greater likelihood of early deterioration (Johnston SC, Easton JD. Stroke. 2003;34:2446-2452). This has been demonstrated to be the case for both TIA and minor stroke subsequently. These are the patients we want to enroll in POINT. It is less clear if minor stroke without substantial early recovery carries a similar high risk for early deterioration.

This is the rationale for the following question on the Randomization Case Report Form (CRF-10):

From the maximum ischemic deficit to the time of randomization, how much did the patient recover?

- ☐ None
- ☐ Modestly (estimated 1-49% improvement in NIHSS if it could have been measured)
- ☐ Substantially (estimated ≥50% improvement in NIHSS if it could have been measured)

The answers will be a best clinical estimate rather than a precise quantitative assessment, and will allow the DSMB to monitor event rates by degree of recovery, which could be helpful if event rates are lower than expected.