What clinical trials are needed next? - Prevention of non-CE stroke? High risk TIA?

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Disclosure Slide

- In the last 5 years:
  - I have been funded by CIHR, HSF Alberta/NWT/Nunavut, CSN, AHFMR (now AIHS), NINDS (NIH)
  - I have received speaker fees/honouraria from Hoffmann-La Roche Canada Ltd., Sanofi Canada, Boehringer-Ingelheim Canada, Novo-Nordisk Canada
  - I have been a paid advisor to NovoNordisk Canada, Genentech Ltd, Hoffmann-La Roche Canada Ltd., Stem Cell Therapeutics, Sanofi Canada, Portola Inc.
  - Hoffmann-La Roche Canada Ltd. Is providing drug for a thrombolytic stroke study – TEMPO trial
  - Covidien has provided a grant for the ESCAPE trial
  - I have been an unpaid advisor to Vernalis Group Ltd., NoNo Inc.
  - I hold no stock or direct investment in any pharmaceutical or device company (except those possibly in mutual funds

Outline – TIA and minor stroke

- Hyperacute phase

What do I do with this patient in the ED in front of me [no evidence of CE source]?

- Clinic / Subacute phase

What do I do with the patient in clinic in front of me [no evidence of CE source]?

Hyperacute
What are the Principles?

1. TIA and minor stroke are the same disease
   - TIA is a definition of hindsight
   - Imaging informs the clinical definition
2. Patients progress or recur, rarely both. These are two different ways to have a "recurrent stroke".
3. Image the vessels from arch to vertex
4. Image the brain with MR - DWI

General Approach FASTER study

	Risk difference (95% CI)	Risk ratio (95% CI)	p
Primary efficacy outcomes			
Clopidogrel vs placebo			
At the margins	−3·8% (−9·4 to 1·9)	0·7 (0·3–1·2)	0·19
Inside the table	−4·4% (−11·7 to 3·0)	0·5 (0·2–1·5)	0·24
Simvastatin vs placebo			
At the margins	3·3% (−2·3 to 8·9)	1·5 (0·8–2·8)	0·25
Inside the table	2·6% (−6·1 to 11·4)	1·3 (0·6–2·9)	0·55

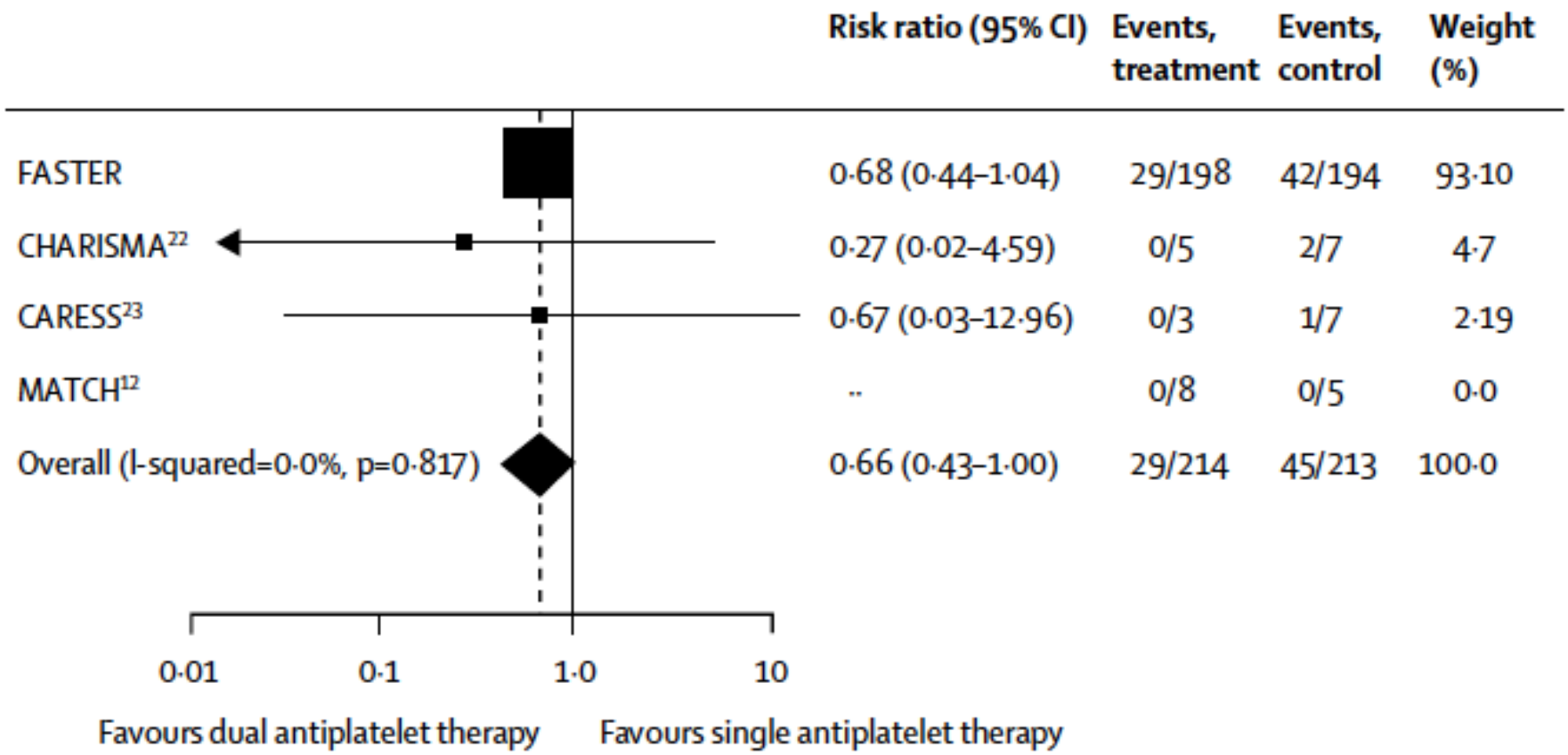
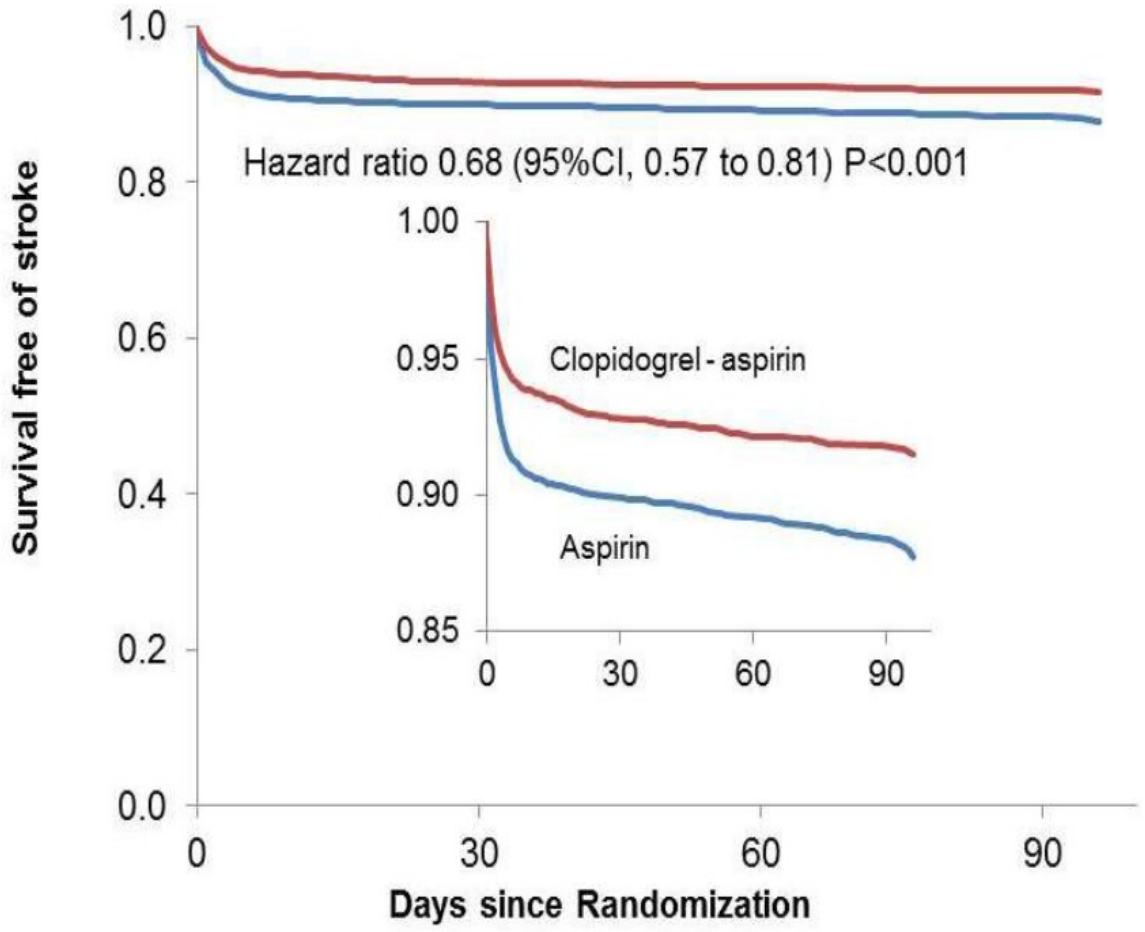


Figure 2: **Fixed-effects meta-analysis of 90-day risk of tertiary efficacy outcome**

Tertiary outcome was combined outcome of stroke, transient ischaemic attack, acute coronary syndrome, and all-cause death in patients enrolled within 24 h of onset of stroke or transient ischaemic attack. Note that x-axis is a logarithmic scale.

Primary outcome: stroke



No. at Risk

Aspirin	2586	2307	2287	1906
Clopidogrel - aspirin	2584	2376	2361	1989

POINT [NINDS]
NCT00991029

- Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke
  - TIA or minor stroke with NIHSS ≤ 3
  - ABCD2 score ≥ 4
  - Randomized 1:1 to clopidogrel v. control (ASA) for 90 days
- Trial is ongoing
- DSMB evaluation of the trial given results of CHANCE in May 2013

SOCRATES [Astra-Zeneca]

- TIA / minor stroke patients
- 24 h time window

- Randomized to ticagrelor vs. ASA

[Study design being reviewed given the results of the CHANCE study]

DATAS [Academic] [NCT01769707]

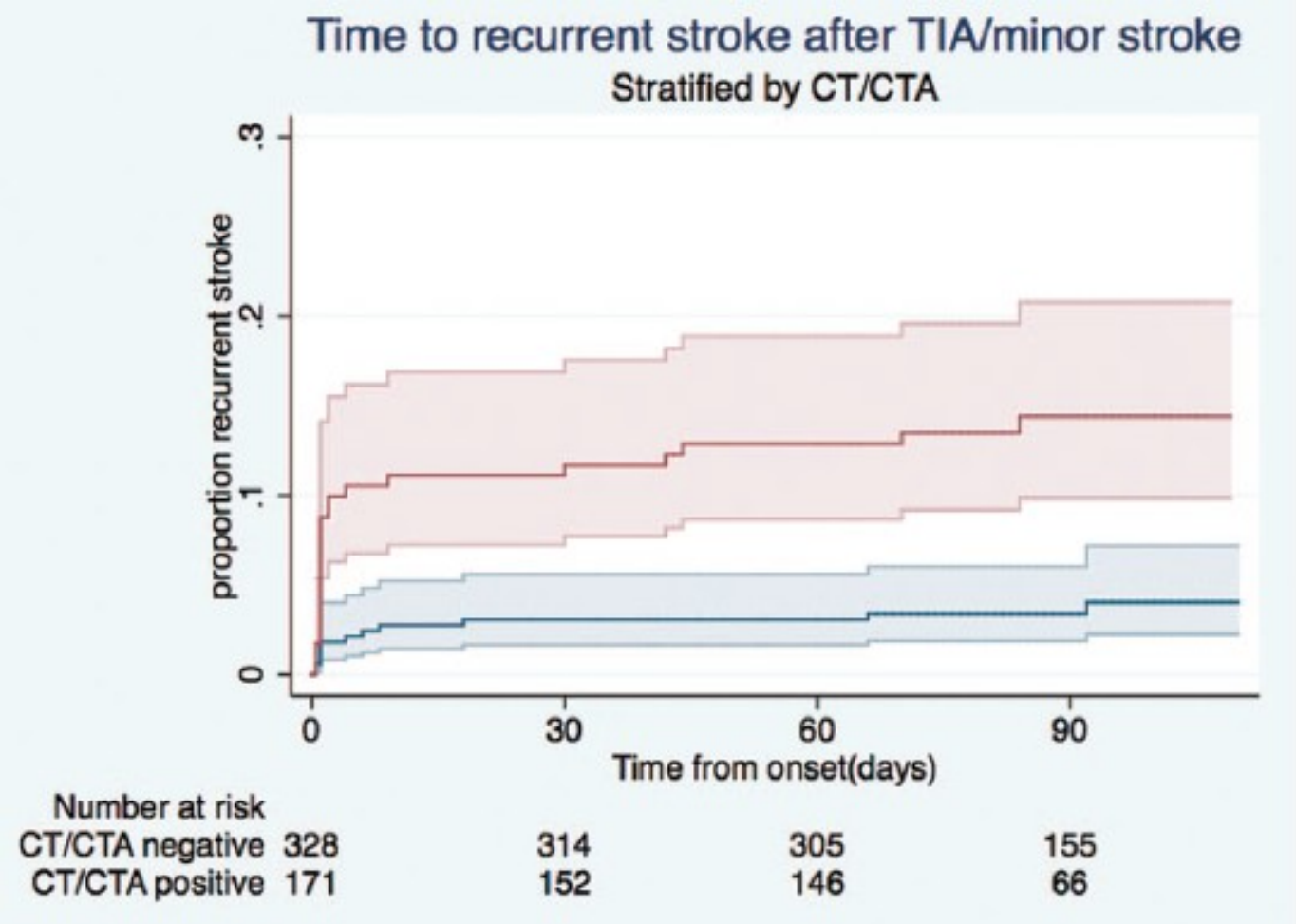
- Dabigatran Treatment following TIA and minor stroke

- Open label single arm safety study

Aggressive Approach PRISMS [P. Khatri]

- Phase III, randomized, IV tPA v.control
- Minor stroke: NIHSS </=5 and deficit not clearly disabling.
- 950 subjects, 60 sites.
- We are in the process of a formal feasibility and regulatory assessment.
- 113 interested sites at this point.
- Genentech-sponsored

CATCH study



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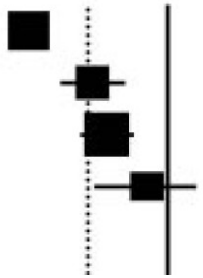
TEMPO [M. Hill, S. Coutts]

- Phase 2, dose-escalation safety cohort study of TNK-tPA for minor stroke
- NIHSS ≤ 5
- Proven intracranial occlusion on CTA
- TNK-tPA within 12 hours of symptom onset
- 2 dose tiers (0.1mg/kg and 0.25mg/kg)
- CTA outcome at 2-8h and 90d clinical outcome

Are there any remaining Q for Symptomatic Carotid Revascularization?

Subgroup	Events/Patients Surgical	Medical	RR	95% CI
Time since last event				
<2 weeks	30 / 284	80 / 269	0.35	0.31 - 0.40
2-4 weeks	29 / 233	41 / 193	0.57	0.45 - 0.73
4-12 weeks	56 / 512	76 / 450	0.63	0.52 - 0.78
>12 weeks	36 / 297	30 / 218	0.85	0.58 - 1.26



Rothwell PM et al. Stroke 2004;35:2855-2861.

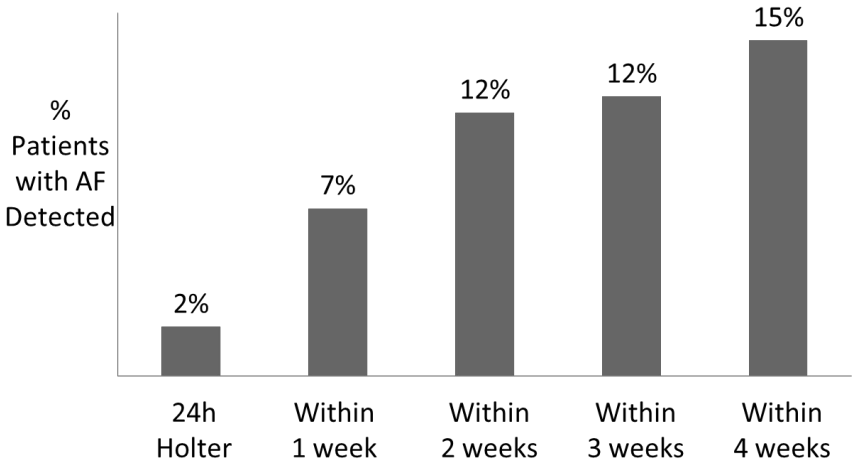
- Speed of surgery – 48h vs. 10-14d
- Can stenting technology improve to reduce stroke rate?

Subacute – Clinic - Principles

- Identify the mechanism of stroke – <u>speciate the stroke</u>
  - usually this means imaging
- Treat the cause
- Treat other risk factors – holistically

Look hard for A.FIB…. EMBRACE trial

	Repeat Holter (n=285)	30-day Monitor (n=287)	p-value	Absolute Detection Difference (95% CI)	NNS
Primary Outcome					
AF ≥30 seconds (within 90 days)	3%	16%	<0.001	13% (9%-18%)	8



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AF Detection According to Age EMBRACE trials

	Repeat Holter (n=285)	30-day Monitor (n=287)	Absolute Detection Difference (95% CI)	NNS
Age >75 years	4%	20%	16%	6
Age <75 years	1%	13%	12%	8

ESUS

- Embolic Stroke of Undetermined Source
  - Can we get rid of the term “cryptogenic stroke”?
  - Is this AFIB? 16% in a selected population in EMBRACE
  - Other causes?
  - RCT of NOACs?
  - Role of ILRs……

Carotid Disease – from the clinic

- Abandon US for carotid disease

- Remaining questions –
  - Asymptomatic disease v. medical [CREST2, SPACE2, ICSS2]
  - Technology – can stenting become safer for the brain?

ICAD

- SAMPRISS

- Medical therapy? What kind?
- Long term outcomes?
- Can procedures be made safer? Bio-absorbable stents?

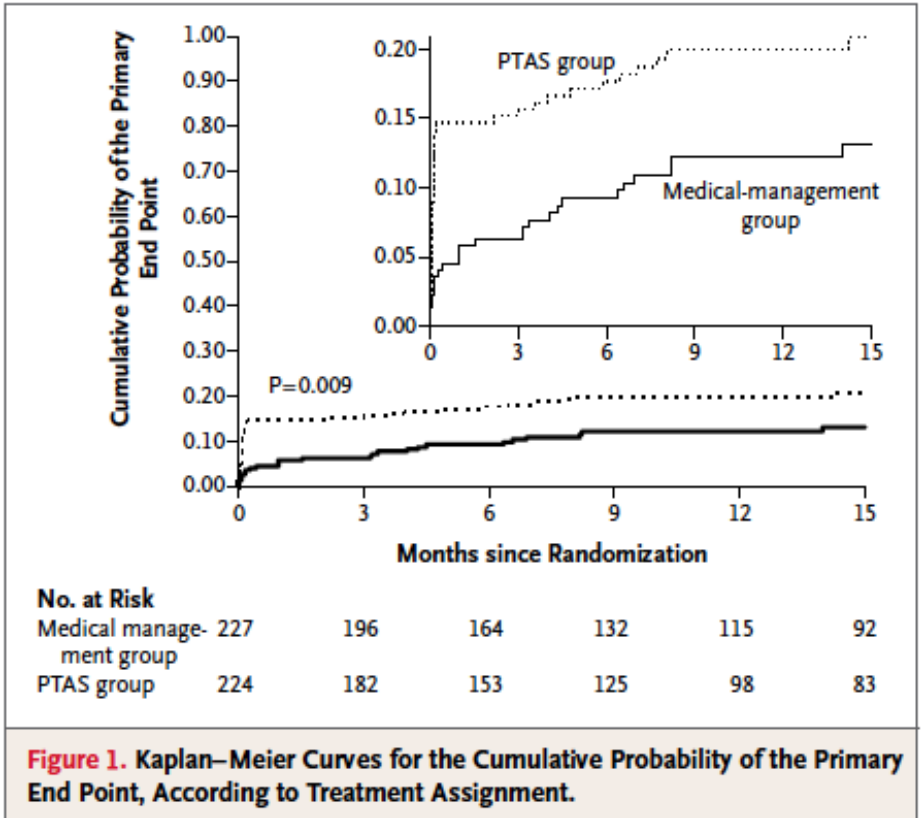

Figure 1. Kaplan–Meier Curves for the Cumulative Probability of the Primary End Point, According to Treatment Assignment.

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Lacunar disease – SPS3
A challenge to the STIR group

- We need a way to image the small penetrating arteries and observe what is going on before we make progress in this area
- Multiple pathologies
  - Lipohyalinosis
  - Microatheroma
  - Embolism (cardioembolic, arteroembolic)

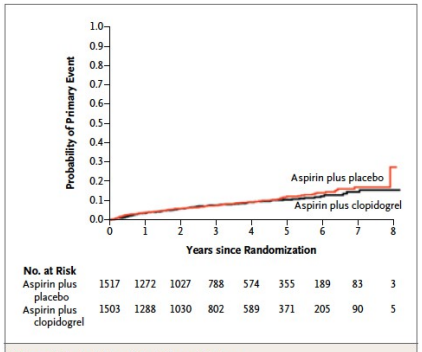
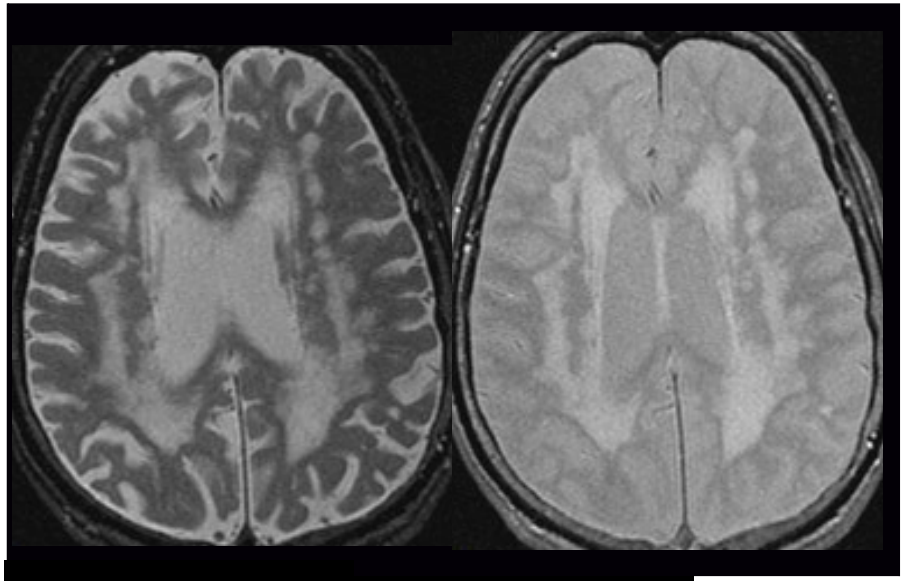
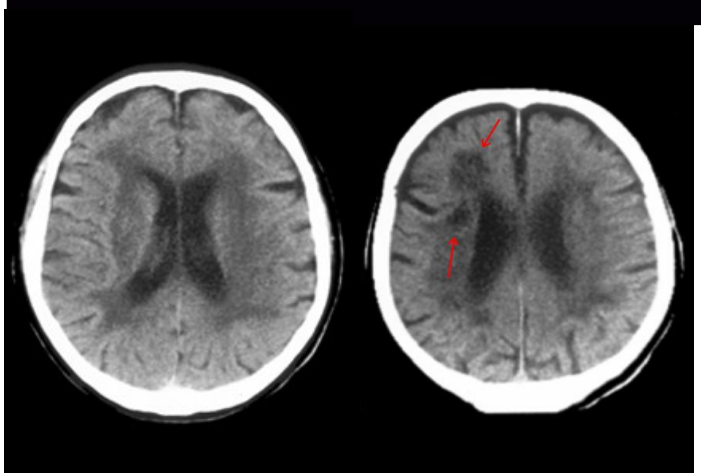
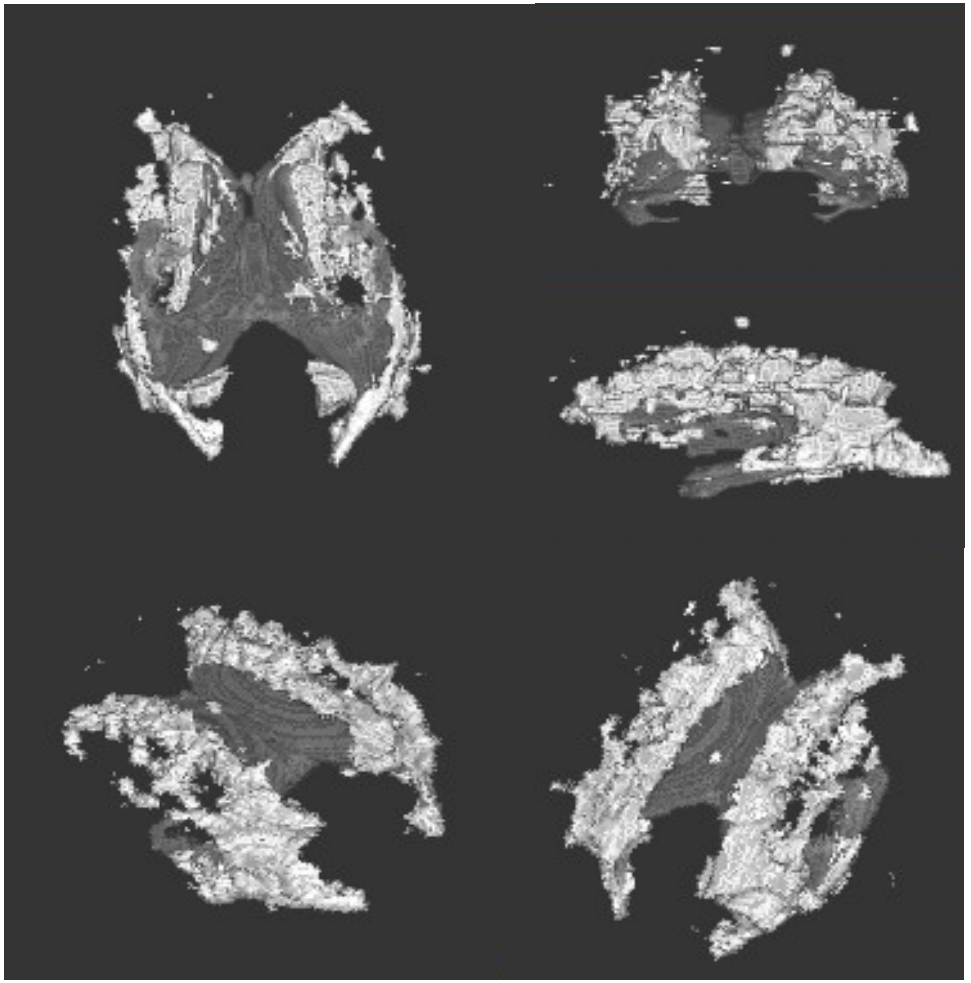


Figure 1. Probability of the Primary Outcome.
The hazard ratio for the primary outcome, recurrent stroke, was 0.92 (95% CI, 0.72 to 1.2).

Subcortical Ischemic Vascular Disease







Future Trials

Hyperacute TIA/minor stroke

- Thrombolyse the occlusion?
- Antiplatelet therapy?
- CEA in 48h or wait and let the plaque “cool off”

- Sub-acute/Clinic
  - CEA vs. medical
  - Look hard for a.fib – ILRs?
  - ESUS – NOACs?
  - New approaches to ICAD? New technology? Better medicine.
  - Lacunes – development or imaging