

Multimodal outcome prediction in alteplase therapy

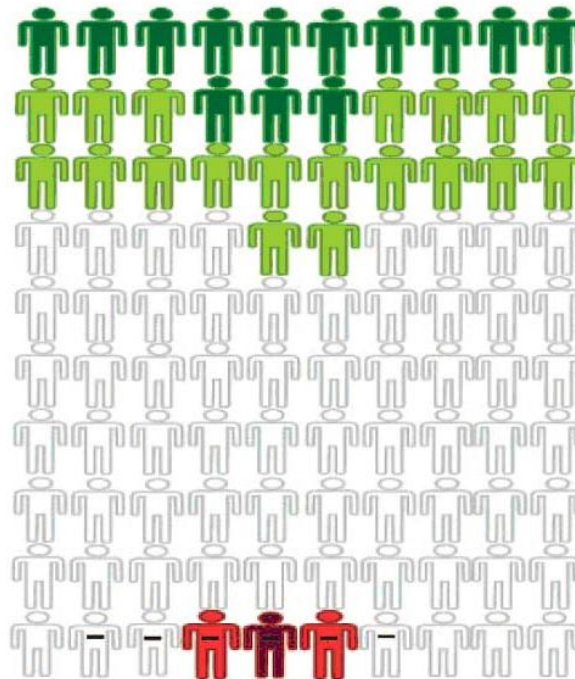
Christopher Levi

Director

PRIORITY RESEARCH CENTRE
TRANSLATIONAL NEUROSCIENCE AND MENTAL HEALTH
Hunter Medical Research Institute
University of Newcastle

The challenges faced by the acute stroke physician

TPA for Cerebral Ischemia within 3 Hours of Onset-Changes in Outcome Due to Treatment



Changes in final outcome as a result of treatment:

- Green: Normal or nearly normal
- Light Green: Better
- White: No major change
- Red: Worse
- Dark Red: Severely disabled or dead

Early course:

- White: No early worsening with brain bleeding
- Dark Red: Early worsening with brain bleeding



ENTERING EXPERT TERRAIN

BEYOND THIS GATE IS SOME OF THE MOST DIFFICULT TERRAIN AT ALTA. THERE ARE UNMARKED OBSTACLES SUCH AS ROCKS, CLIFFS, STUMPS AND FRACTURE LINES. SKI WITHIN YOUR ABILITIES AND IN CONTROL SO YOU CAN AVOID ALL OBSTACLES.

WEATHER AND SNOW CONDITIONS CAN CHANGE AT ANY TIME.

DO NOT PROCEED UNLESS YOU ACCEPT RESPONSIBILITY FOR YOUR OWN SAFETY AND ARE WILLING TO CONFRONT ALL CONDITIONS AND RISKS, INCLUDING UNMARKED OBSTACLES, PRESENTED BY SKIING THIS TERRAIN.



Outline

- Endophenotypes of potential genetic interest in thrombolysis
- “Intermediate” outcomes under potential genetic influence in thrombolysis
 - Reperfusion
 - Recanalization
 - Haemorrhagic transformation
- Current NHMRC grant (Holliday, Maguire, Attia, Levi et al) – the current Australian Stroke Genetics Collaborative major project – tPA treated patients – genes and biomarkers influencing major clinical outcomes
 - Haemorrhagic transformation
 - (Reperfusion)
 - (Recanalization)
 - (Early clinical outcome)
 - Long-term functional outcome

Activation markers of coagulation and fibrinolysis in twins: heritability of the prethrombotic state

Lancet 2002; **359**: 667–71

	h^2	e^2
Prothrombin	0.57 (0.37–0.71)	0.43 (0.29–0.63)
F1+2	0.45 (0.28–0.60)	0.43 (0.30–0.61)
TAT	0.40 (0.18–0.57)	0.60 (0.43–0.82)
D-dimer	0.65 (0.50–0.75)	0.35 (0.25–0.50)
TAFI	0.82 (0.73–0.88)	0.18 (0.12–0.27)

Values expressed as point estimate (95% CI). F1+2=prothrombin fragment 1+2; TAT=thrombin–antithrombin complex; TAFI=thrombin-activatable fibrinolysis inhibitor. Effect of common environment was not significant for any of the measurements.

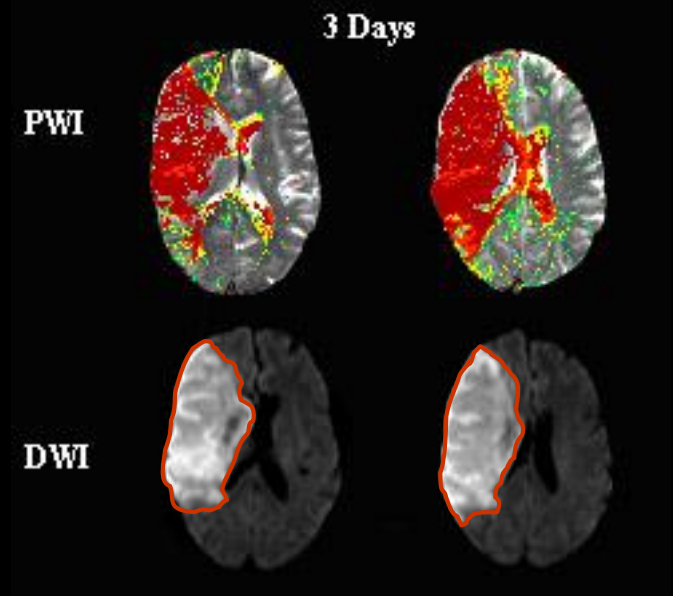
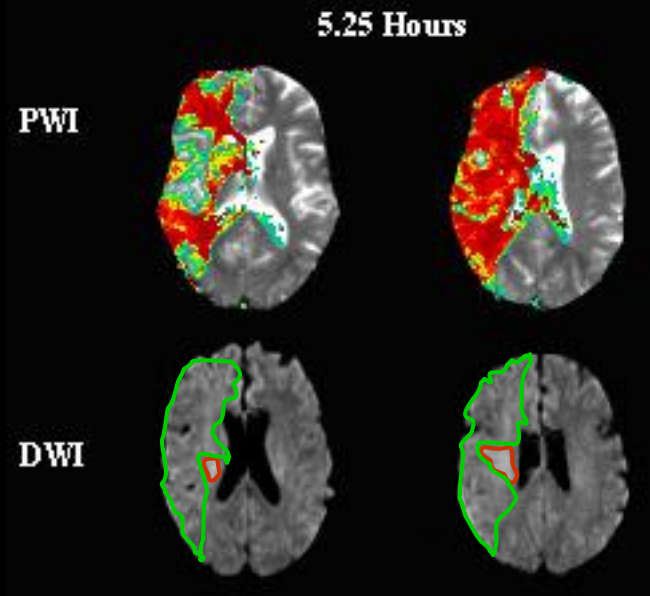
Estimates of heritability (h^2) and unique environment (e^2) from best fitting models

Endophenotypes & alterplase therapy outcomes?

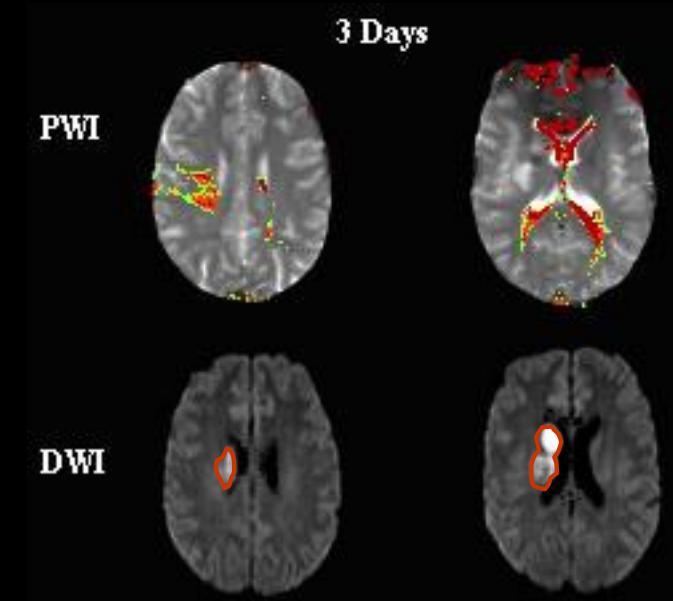
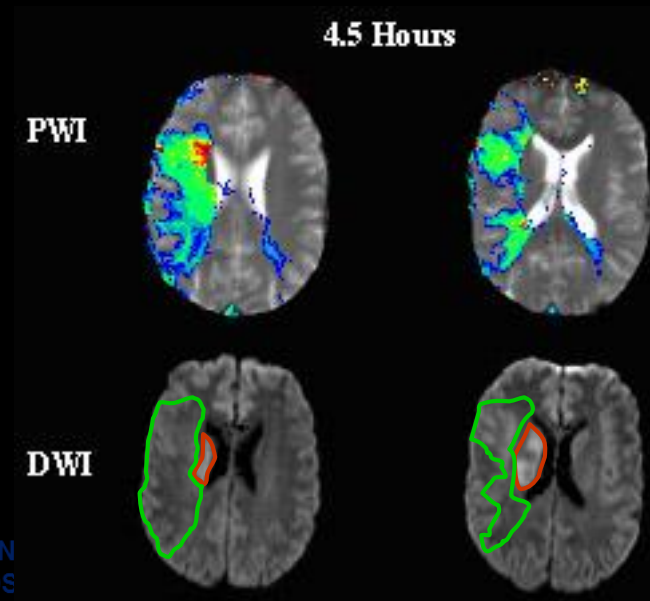


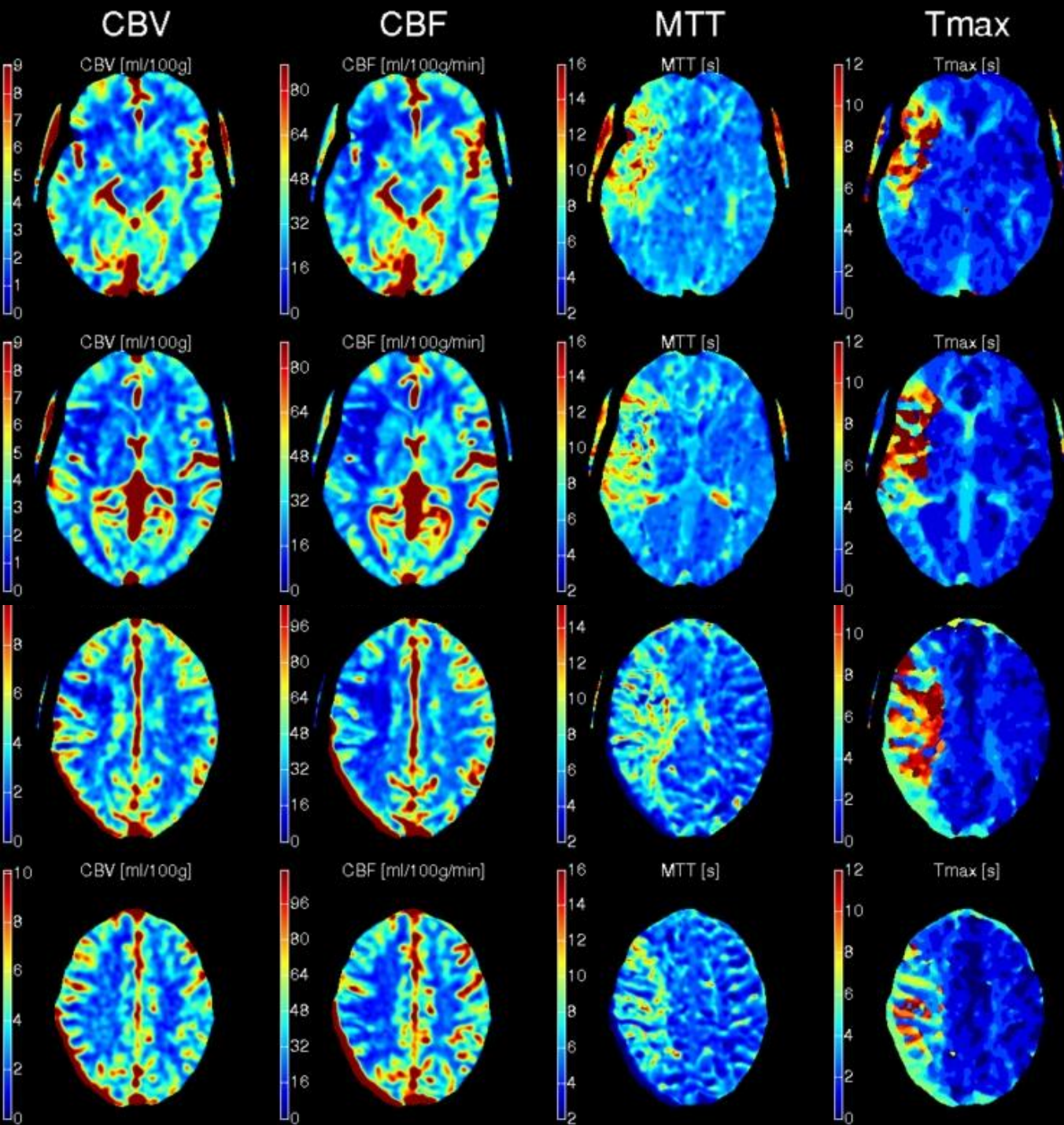
Infarct Core & Penumbra

Placebo



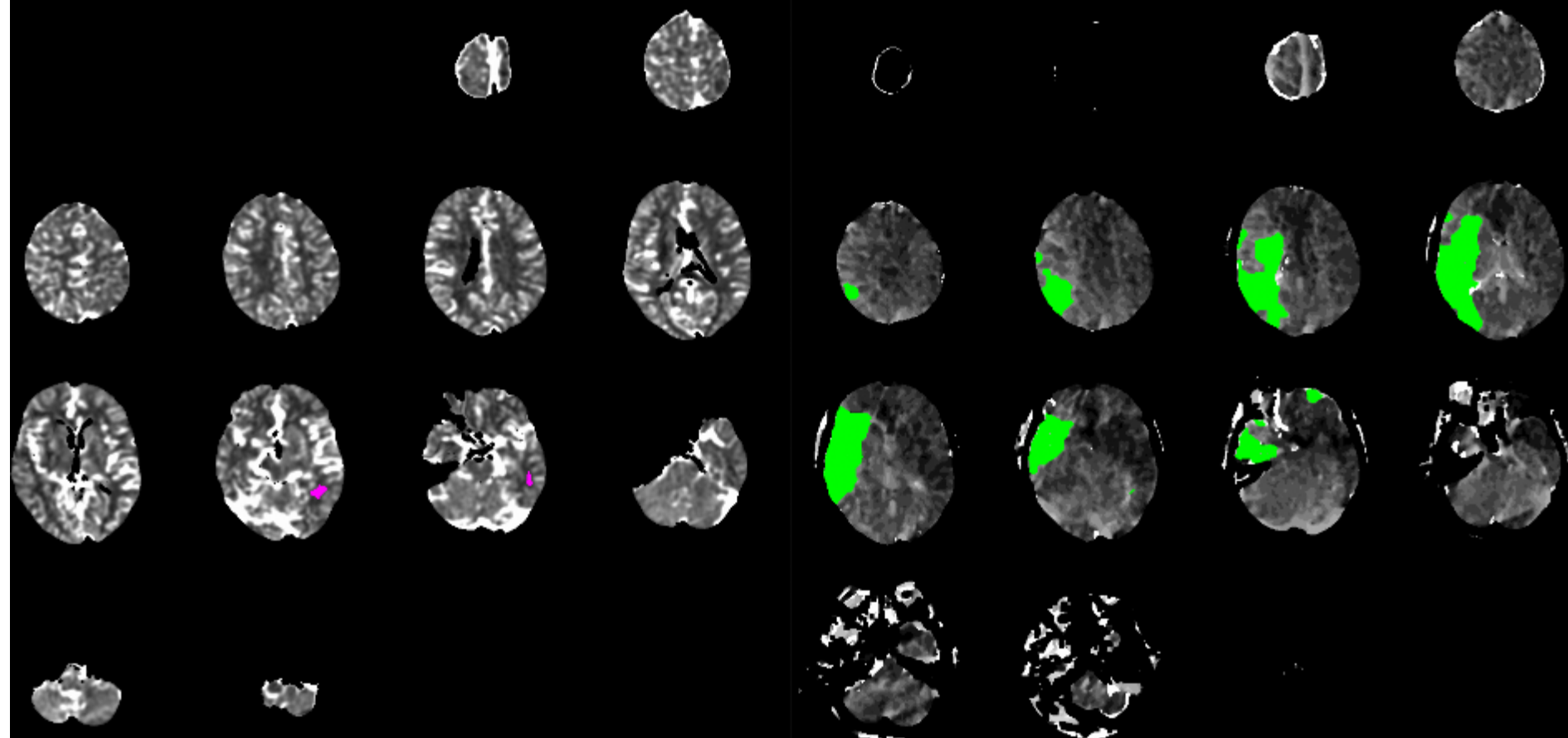
tPA





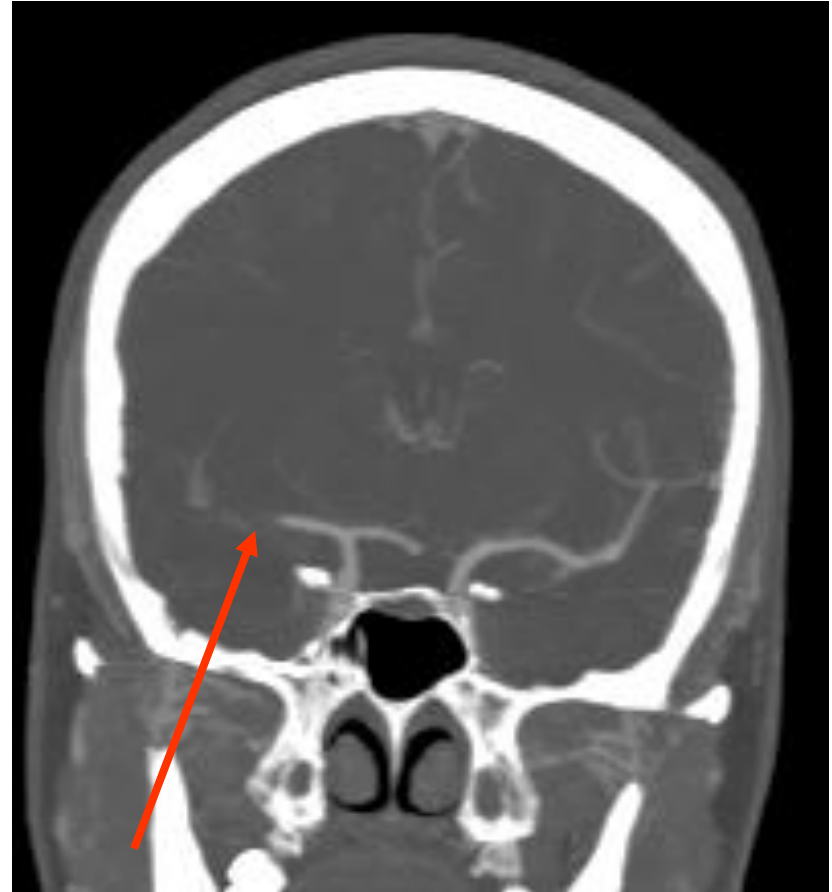
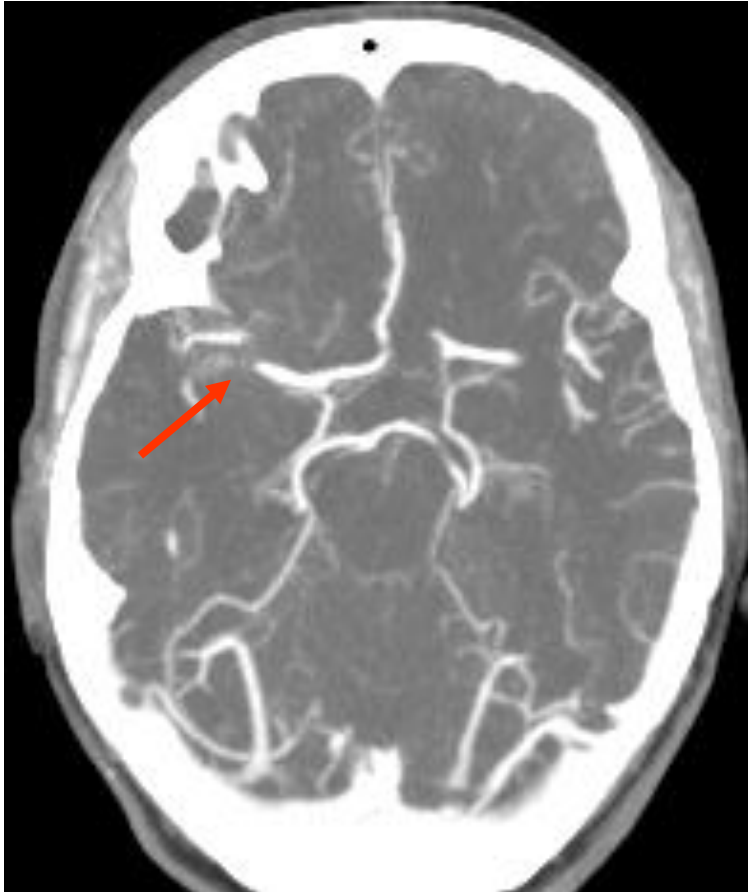
CBF-based Core

Tmax



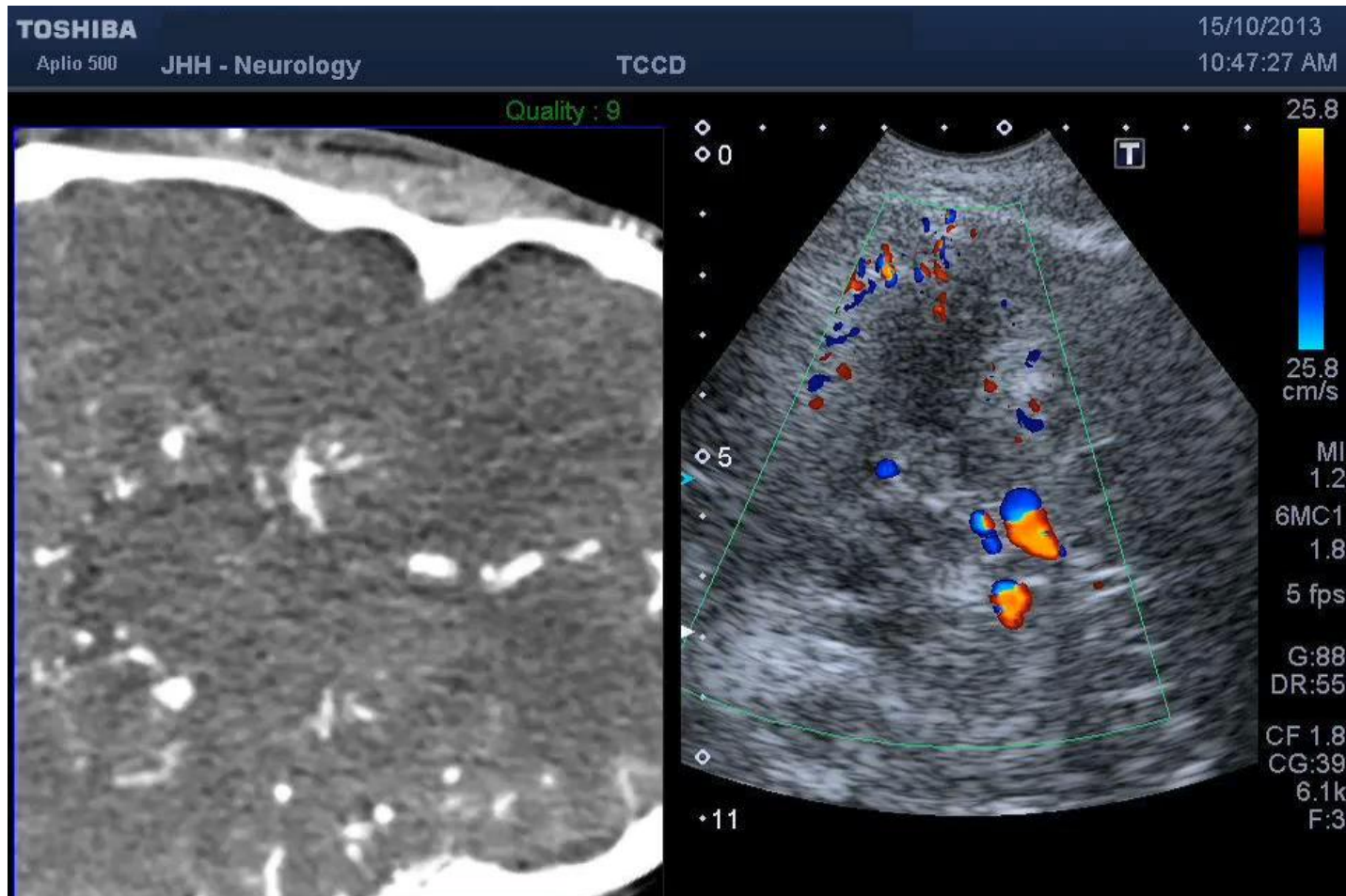
Infarct Core: 2 ml PWI (Tmax>6s) lesion: 133 ml
 Mismatch ratio: 66.7 Absolute Mismatch Difference: 131 ml
 Mismatch > 1.2: YES
 Absolute mismatch > 10 ml: YES
 Infarct Core < 70 ml: YES
 Randomize patient: YES

Clot & Collaterals

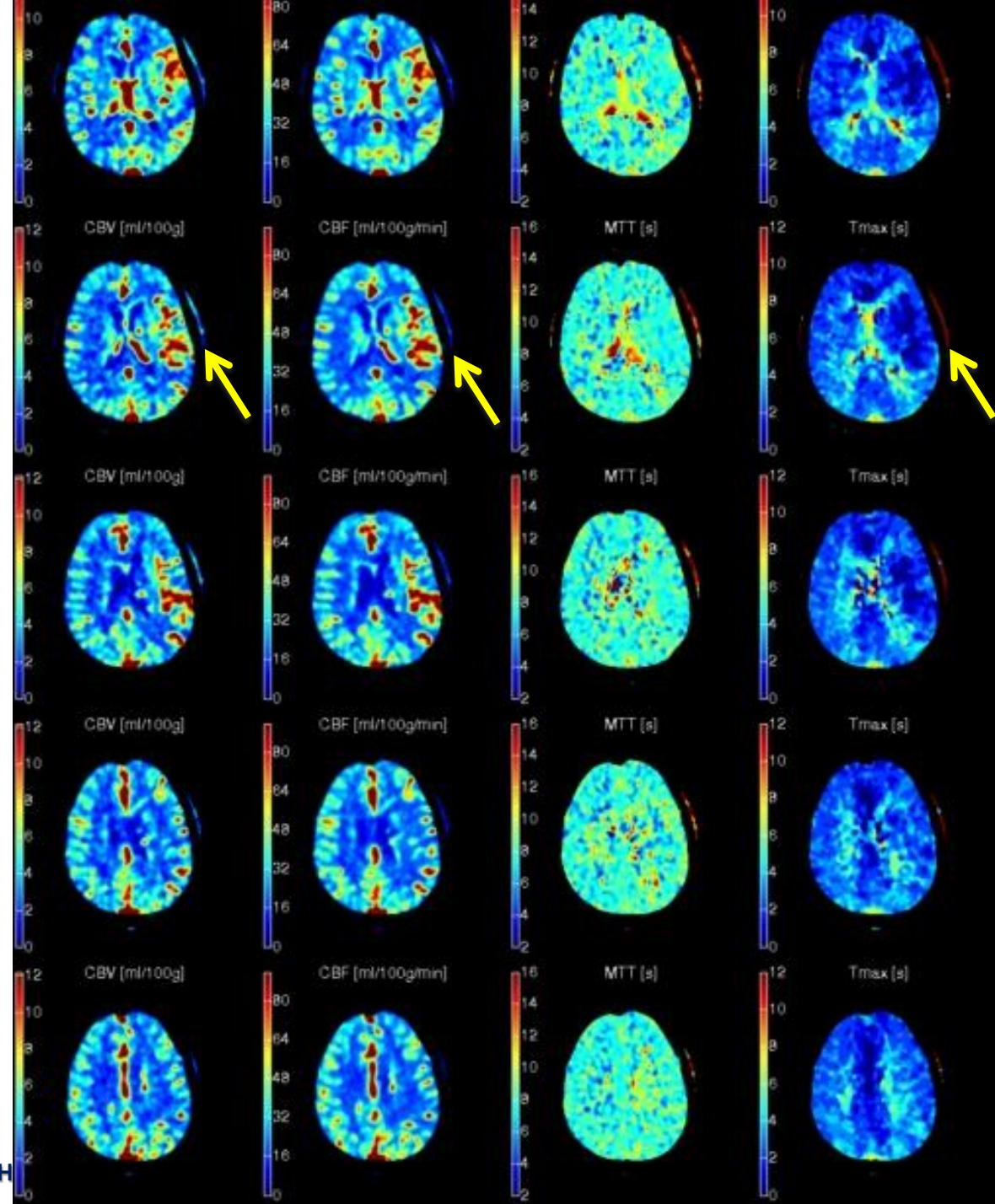




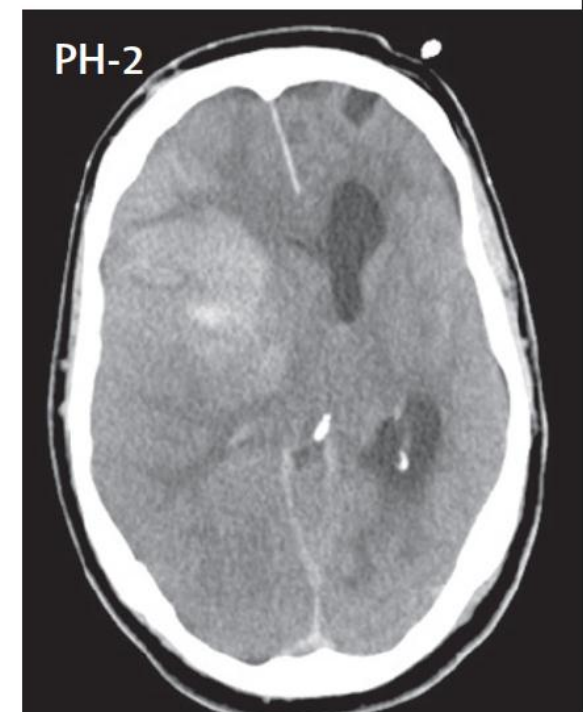
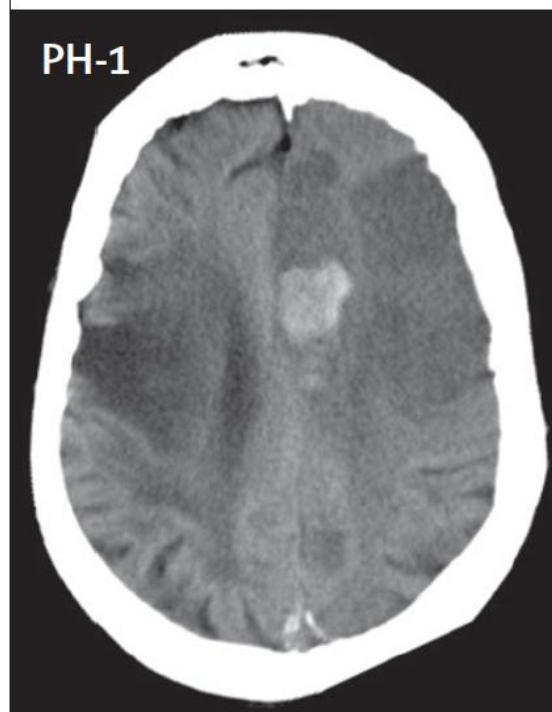
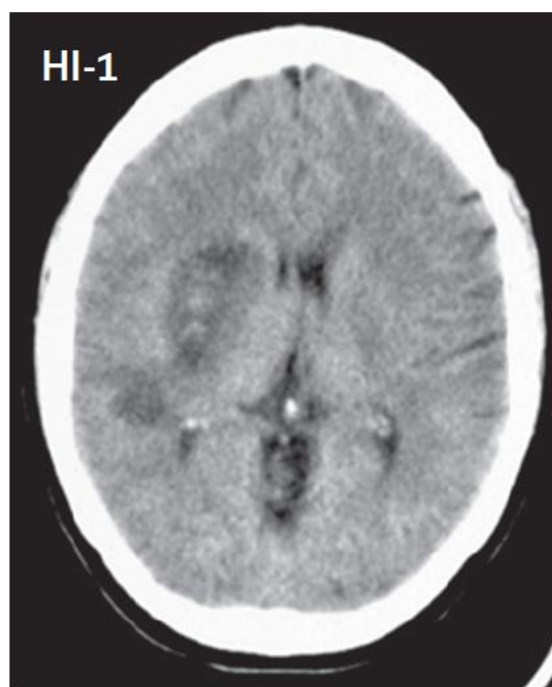
Recanalization



REPERFUSION



Haemorrhagic Transformation







HELPING STROKE PHYSICIANS CHOOSE WHO TO THROMBOLYSE – THE “TARGETING OPTIMAL THROMBOLYSIS OUTCOMES” (TOTO) STUDY

NHMRC \$ year Project Grant application 2015-2018

CI A Elizabeth Holiday

AIMS

Aim 1: To develop a set of clinical decision rules to guide decisions in targeting ischaemic stroke patients for thrombolysis. These rules will be developed in a prospective cohort of Australian ischaemic stroke patients treated with intravenous alteplase, incorporating a combination of clinical, basic radiological, advanced radiological and biomarker measures. Primary outcomes will comprise good and poor 90 day functional outcome, and the adverse event of brain haemorrhage.

Aim 2: To validate prediction models in independent cohorts from our international collaborative network.

Background

1. Alteplase has variable efficacy in opening blocked cerebral arteries, producing marked variation in clinical outcome for otherwise clinically similar cases. Using standard clinical and radiological measures, treatment response cannot be reliably predicted. In cases where alteplase therapy is futile, more effective approaches such as endovascular treatments may be delayed.

2. Alteplase can cause serious harm or death due to drug-induced brain haemorrhage. The likelihood of this adverse event cannot be predicted using standard clinical and radiological measures. This is a major disincentive to many stroke physicians who, despite recognising an average net population benefit, remain risk-averse. Recent extension of the approved time window from 3 to 4.5 hours after stroke onset leaves a relatively narrow margin of benefit, and symptomatic bleeding generally results in complete loss of treatment benefit.

Research plan

- Alteplase treated acute ischaemic stroke cohort
 - Blood collection pre-therapy – post-therapy consent proxy or patient
 - Standard clinico-radiological eligibility
 - Advanced multimodal CT or MRI DWI/PWI where “standard”
- 24 h clinical outcome
 - NIHSS
 - NCCT or MRI
 - If “standard” – reperfusion and recanalization imaging with CTP, MR or TCD
- 90 day outcome
 - mRS
- Candidate gene/GWAS/ELISA
- Univariate and multivariate logistic models and AUROC curve analyses

Preliminary data – clinico-radiological

- 300 John Hunter Hospital alteplase treated cases with advanced imaging at baseline and 3m functional outcome 2010-2013
- “Standard” clinico-radiological predictors
 - Favourable outcome – DRAGON (*Dense Artery, Rankin Score>1, Age>80, Glucose, Onset to Treatment Time>90m, NIHSS>15*)
 - HT – SEDAN (*Sugar, Early Infarct Signs, Dense Artery, Age>75, NIHSS>10*)
- Then – addition of “advanced” imaging predictors
 - Infarct core >50ml; <5 ml
 - Collateral status – good/moderate/poor
- Univariate and multivariate logistic models and AUROC curve analyses

Advanced imaging based selection – potential for improvement in alteplase effectiveness

Multivariate prediction models – Good 90 day outcome (mRS ≤ 2)

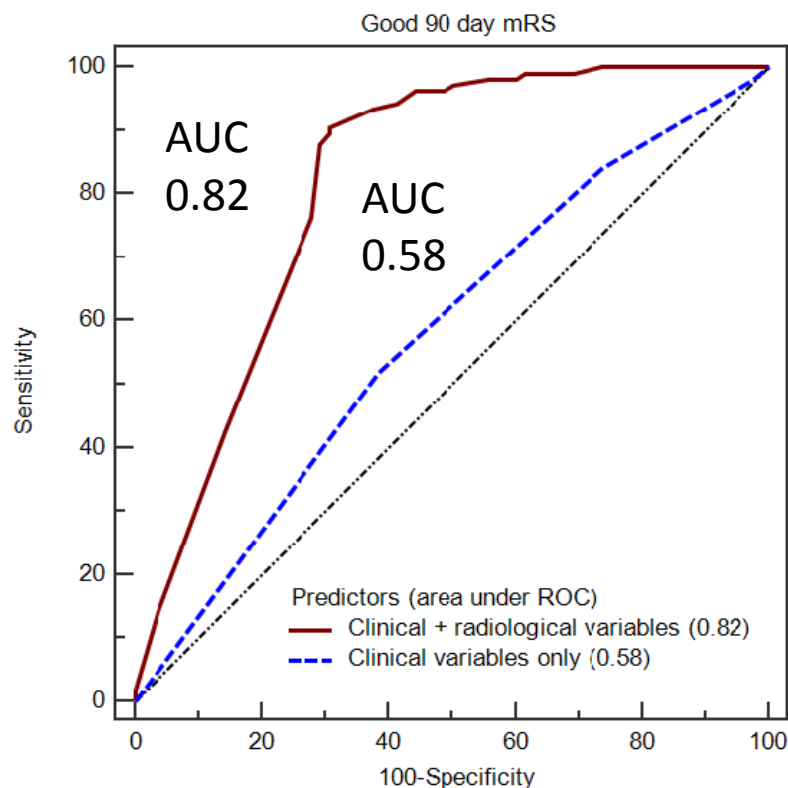


Figure 1. ROC curves for good outcome

Table 1. Odds Ratios and P-values

Predictor	OR (95% CI)	P-val
DRAGON	1.04 (0.75, 1.44)	0.83
Large core	0.07 (0.02, 0.32)	1×10^{-3}
Collateral circ. (ref Poor)		
Moderate	4.51 (0.85,	0.077
Good	24.0 (5.4, 107.8)	3×10^{-5}

Peak Sensitivity: 87.7%

Specificity: 70.7%

Likelihood Ratio: 3

Potential for less futile or harmful therapy

Multivariate prediction models – **Poor 90 day outcome** (mRS ≥ 5)

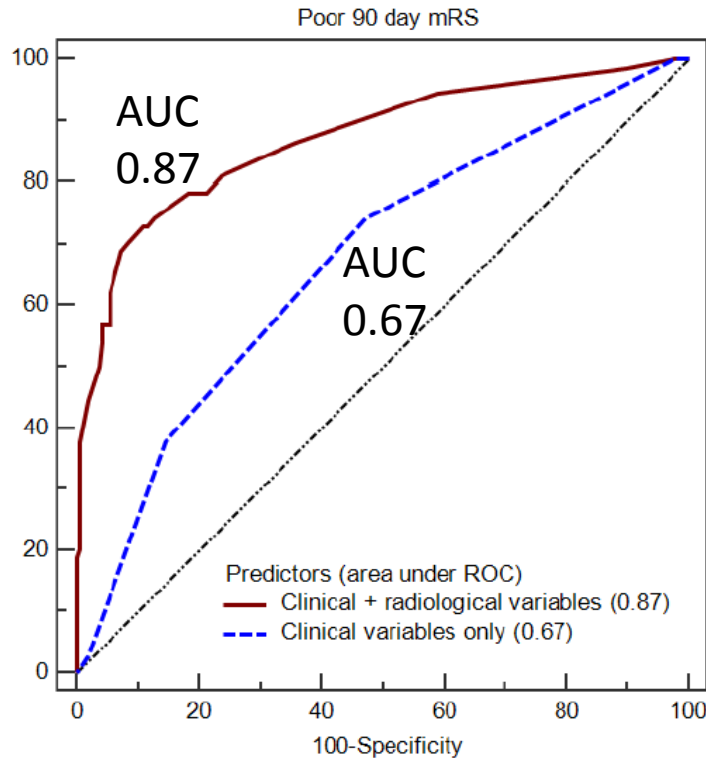


Table 3. Odds Ratios and P-values

Predictor	OR (95% CI)	P-val
DRAGON	1.55 (1.06, 2.26)	0.024
Large core	10.5 (4.5, 24.7)	6×10^{-8}
Collateral circ. (ref Good)		
Moderate	2.7 (1.04, 7.00)	0.041
Poor	6.4 (2.6, 15.7)	5×10^{-5}

Peak Sensitivity: 78.4%

Specificity: 81.8%

Likelihood Ratio: 4.3

Figure 3. ROC curves for **poor outcome**

?Potential avoidance of HT

Multivariate prediction models – Haemorrhagic transformation

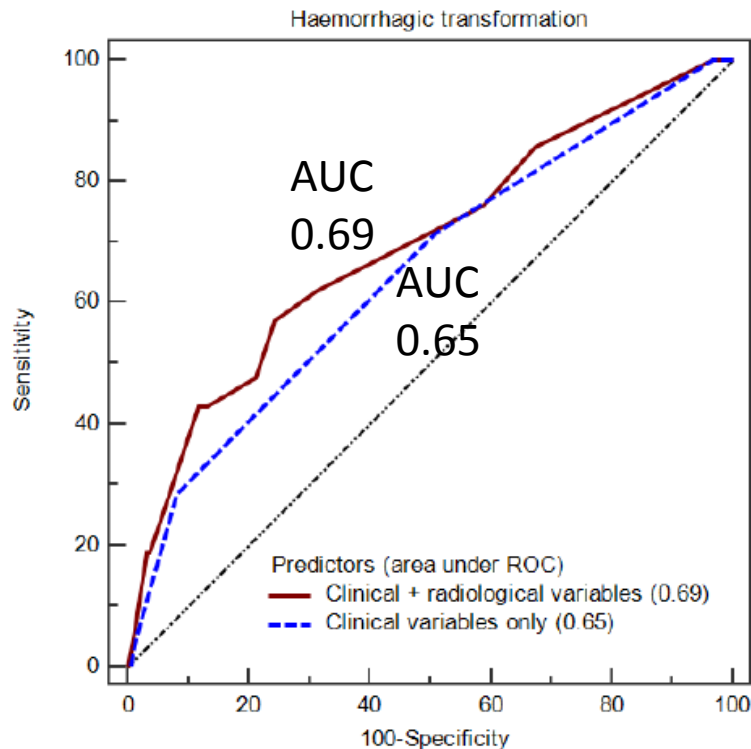


Figure 2. ROC curves for HT

Table 1. Odds Ratios and P-values

Predictor	OR (95% CI)	P-val
SEDAN	1.78 (1.03, 3.06)	0.037
Collateral circ. (ref Good)		
Moderate	1.43 (0.36, 5.72)	0.61
Poor	3.33 (1.20, 9.24)	0.021

Peak Sensitivity: 57.1%

Specificity: 75.6%

Likelihood Ratio: 2.3

Responsiveness and bleeding candidate biomarkers and genes

- Bleeding –
 - MMPs
 - Cellular fibronectin
 - Plasminogen Activator Inhibitor 1
 - Thrombin Activated Fibrinolysis Inhibitor
 - Vascular adhesion protein 1
 - S100B
- Responsiveness –
 - IFIT
 - Angiopoietin-1
 - Thrombin Antithrombin complex
 - PAI 1

C Nafria, Israel Fernandez-Cadenas, et al.....Vale De Hebron, Barcelona;
Stroke Research & Treatment 2011

Future plans

- Collections
 - Derivation cohort - n=1,000
 - Retrospective cohort – for DNA (approx 400 cases)
 - Prospective cohort – acute collections for DNS and serum
 - 2 active Australian sites – 5 additional Australian sites yet to commence collections
 - Validation cohort – n=1,000
 - ISGC – work to do on “international data harmonisation” and development of a central data repository
- Collaborative activity within the ISGC Outcomes and Endophenotypes groups

