Online Only Supplemental Material

Suppl table 1 Comparison of DEFUSE and EPITHET study characteristics

Trial Profile	DEFUSE	EPITHET
Funding	National Institutes of Health (NINDS), RO1 NS39325, Genentech	National Health and Medical Research Council, Australia; National Stroke Foundation, Australia; Heart Foundation of Australia
Number of sites	6	15
Location	United States, Canada, Belgium	Australia, New Zealand, Belgium, UK
Years of enrollment	April 2001 – April 2005	April 2001 – January 2007
Number of patients screened	1020	3908
Study Design		
Treatment allocation	Open-label single arm study of IV tPA	Double blind RCT of IV tPA
Treatment window	3 to 6 hours after symptom onset	3 to 6 hours after symptom onset
Primary outcome measure	*Favorable clinical response* defined as an improvement of 8 points or more on the NIHSS between baseline and 30 days or a score of 0-1 at day 30.	*Infarct growth* defined as the ratio of 90-day infarct volume over baseline DWI lesion volume
Primary analysis	The odds ratio of favorable clinical response associated with reperfusion in mismatch patients	The difference in mean infarct growth between tPA and placebo in mismatch patients
Inclusion criteria	1) 18 years or older 2) clinical diagnosis of ischemic stroke 3) NIHSS > 5 4) tPA start in 3 to 6 hour window	1) 18 years or older 2) acute hemispheric ischaemic stroke 3) NIHSS > 4 4) treatment in 3-6 hour time-window
Exclusion criteria	1) comatose or severely obtunded 2) rapidly improving symptoms 3) a history of stroke within the last 6 weeks 4) premorbid mRS score of 3 or higher 5) seizure at symptom onset 6) previous intracranial hemorrhage 7) evidence of acute hemorrhage 8) clearly identifiable hypodensity involving more than one third of the MCA territory on the baseline non-contrast brain CT	1) premorbid mRS score of 3 or higher 2) acute hemorrhage on non-contrast CT 3) major early ischemic change (defined as ischaemia of more than one third of the MCA territory) 4) inability to undergo MRI 5) standard contraindications to alteplase 6) confounding neurological diseases such as dementia or life-threatening illness
Imaging Protocol		
Baseline MRI	Before treatment: DWI, PWI, MRA, GRE	Before treatment: DWI, PWI, MRA, GRE
Early f/u MRI	3 to 6 hours after tPA: DWI, PWI, MRA-COW, GRE	3 to 5 days after treatment: DWI, PWI, MRA-COW, GRE
Final MRI	Day 30: FLAIR	Day 90: T2
PWI lesion segmentation	Tmax>2sec threshold	Tmax≥2sec threshold
DWI lesion segmentation	Semi-automated outline based on b1000 signal intensity that is >3 SDs higher than in contralateral control region	Manual outline of lesion on b1000 map

Suppl Table 2 **Comparison of MRI profiles between assessments with RAPID and with software used in the original study analyses**

		MR profile assessment according to RAPID			
		Target Mismatch	**Malignant**	**No Mismatch**	**Small**
MR profile assessment according to original study method	**Target Mismatch**	65	1	11	6
	Malignant	12	28	0	0
	No Mismatch	5	0	7	3
	Small	0	0	2	19

The interrater agreement between the original study method and RAPID was good (kappa=0.61). Reclassification in terms of MR profile between original and RAPID-derived assessment occurred in 40 patients. It was generally the result of smaller RAPID derived PWI lesion volumes compared to original PWI lesion volumes.

Supplemental textbox 1. Processing steps for DWI lesion segmentation in RAPID

Step 1. DWI segmentation based on an absolute threshold: An absolute threshold of ADC < $615x10^{-6}$ mm^2/s was applied, followed by a morphologic opening operation with structural element size of 2 mm to remove spike noise in the mask obtained by thresholding.

Step 2. DWI segmentation based on relative thresholds: Mean (M) and standard deviation (SD) of the signal intensity in normal brain tissue was obtained for b=1000 (a.k.a. isotropic diffusion) and exponential-attenuation (EA) images; normal tissue was defined as tissue with ADC values between 750 and 1900 x 10^{-6} mm^2/s. This yielded values of M_b1000, SD_b1000 and M_EA, SD_EA. Relative thresholds (t) were constructed: t_b1000 = (M_b1000 + k * SD_b1000), and t_EA = (M_EA + k * SD_EA). The value of k was empirically determined to be 2.7. These thresholds were then applied to b1000 and EA maps to outline the lesion. Stroke core outlined using relative threshold was detected in voxels where both b1000 and EA values were above the respective thresholds simultaneously.

Step 3. The final DWI lesion was obtained as a union of the relative and absolute thresholding (i.e. at least one of the ADC-based or b1000/EA-based methods delivered positive identification).

Supplemental textbox 2. Processing steps for PWI lesion segmentation in RAPID

Step 1. Patient motion in the raw PWI dynamic scans was corrected in-slice using 2D spatial corregistration of individual timepoints to a mean image obtained by averaging of all timepoints.

Step 2. Measured MRI signals were converted to values of relative shortening of the transverse relaxivity.

Step 3. Arterial input function (AIF) was selected automatically by the software in location where signals with high amplitude, early arrival time, and below-average width were spatially clustered; the program ensured that only anatomically meaningful locations were considered. A typical result of the selection was AIF in the middle cerebral, internal carotid, or anterior cerebral arteries.

Step 4. After vascular signals were identified, a correction for nonlinear effect of gadolinium tracers in tissue and in bulk blood was applied.[10]

Step 5. Quantitative perfusion parameters (CBV, CBF, MTT, Tmax) were obtained by deconvolving tissue signals with the AIF. The deconvolution was applied in the frequency domain (equivalent to circular deconvolution), with a regularization filter that removed components with amplitude below 15% of the maximum component.

Step 6. The Tmax parameter was identified as the time of global maximum of the deconvolved tissue residue function.

Supplemental figure

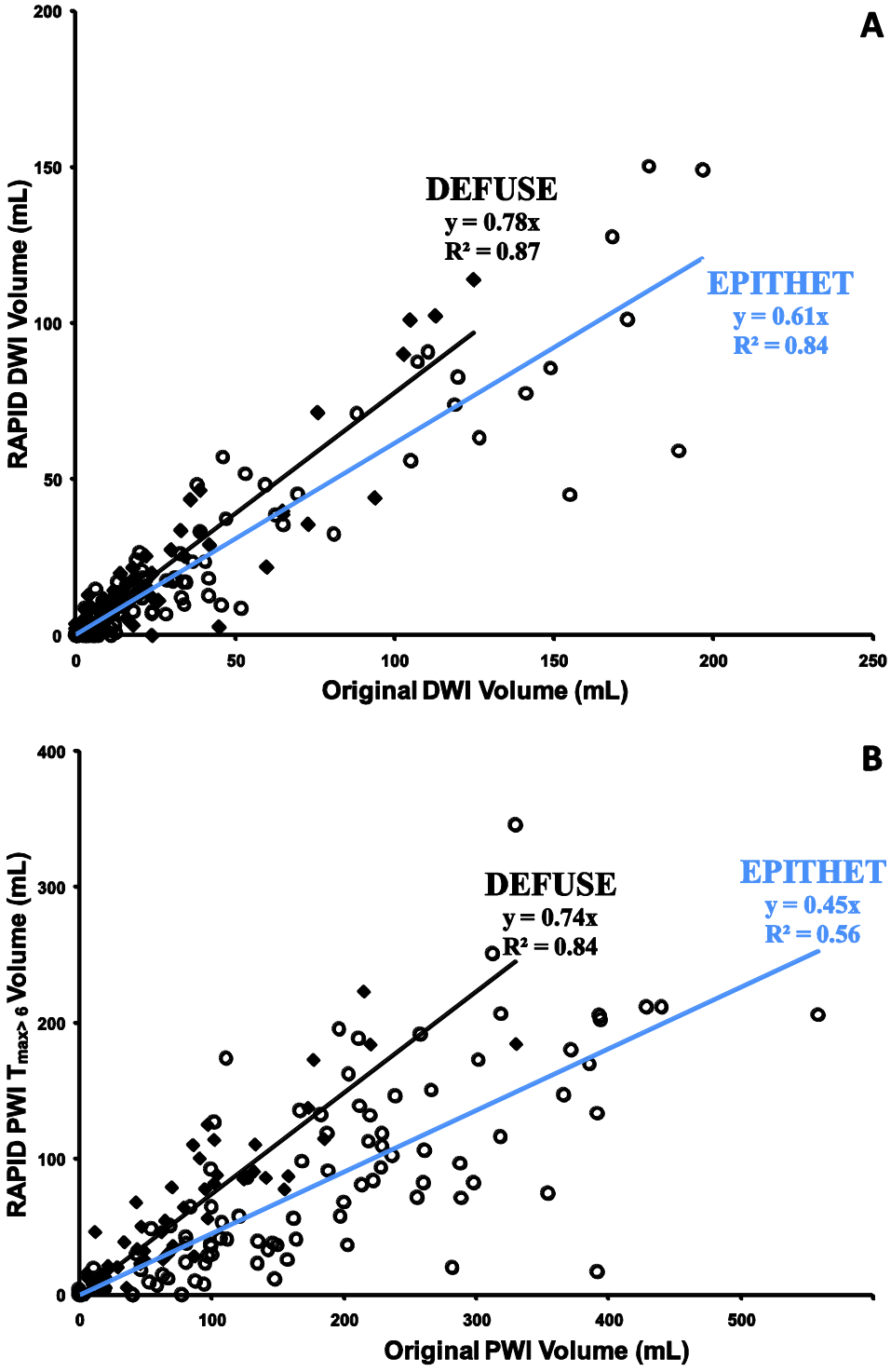

Figure Legend

Figure A shows the correlation between DWI lesion volumes, determined as part of the primary data analyses of the DEFUSE and EPITHET studies, and DWI lesion volumes determined using RAPID, an automated image processing system. Figure B shows the same correlation for PWI volumes. Data for DEFUSE are indicated by solid diamonds (♦); EPITHET data by open circles (o). The difference between original and RAPID-derived lesion volumes was significantly smaller for DEFUSE data compared with EPITHET data for both DWI (Fig A, p=0.001 for difference between regression coefficients) and PWI (Fig B, p=0.006 for difference between regression coefficients).