

The Dabigatran following Acute Transient ischemic Attack and minor Stroke trial: Final Results

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European Stroke Organization Conference, 2018



Faculty Disclosure (KSB and MS)

<i>Company Name</i>	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties/ Patent</i>	<i>Stock Options</i>	<i>Ownership/ Equity Position</i>	<i>Employee</i>	<i>Other (please specify)</i>
Boehringer-Ingelheim	x	x	x					
Bayer	x	x	x					
BMS-Pfizer Alliance	x	x	x					
Servier, Daiichi-Sankyo	x							



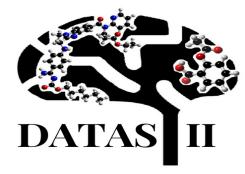
Disclosures

4th European Stroke
Organisation Conference

16-18 May 2018 | Gothenburg, Sweden

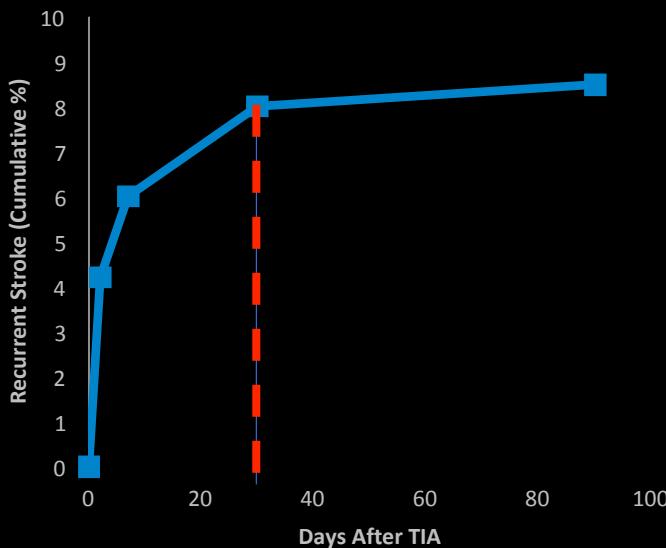
- The trial sponsor was the ‘The Governors of the University of Alberta’
- The trial was registered: NCT02295826
- Grant Support:
 - Canadian Institutes for Health Research
 - Alberta Innovates Collaborative Research and Innovation Opportunities
 - Population Health Research Institute
 - Canada Research Chairs Program
 - Heart and Stroke Foundation of Alberta, NWT and Nunavut
- Dabigatran is not indicated for use in stroke patients without atrial fibrillation.
- The manufacturer of dabigatran (Boehringer Ingelheim) had no role in the design or conduct of this trial and provided no monetary or in kind support



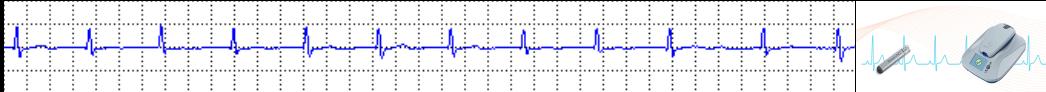


Rationale For Acute Oral Anticoagulation After TIA/Minor Ischemic Stroke

Recurrent Stroke

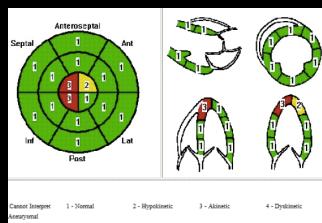


Occult paroxysmal AF (16%) (*Gladstone et al, NEJM, 2014*)

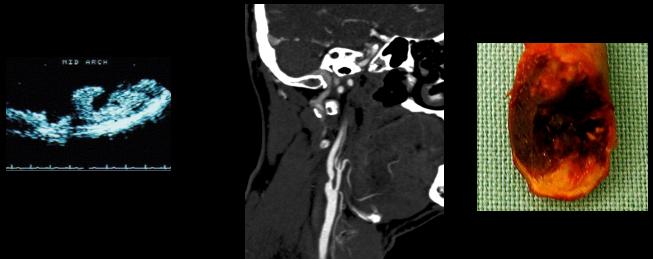


Other sources of recurrent thromboembolism:

Left Ventricular Thrombus



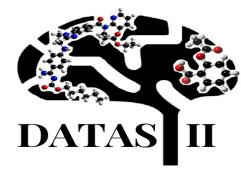
Intraluminal Thrombus



Hypothesis: Acute Anticoagulant therapy
reduces **early recurrent stroke rates**,
relative to antiplatelet therapy

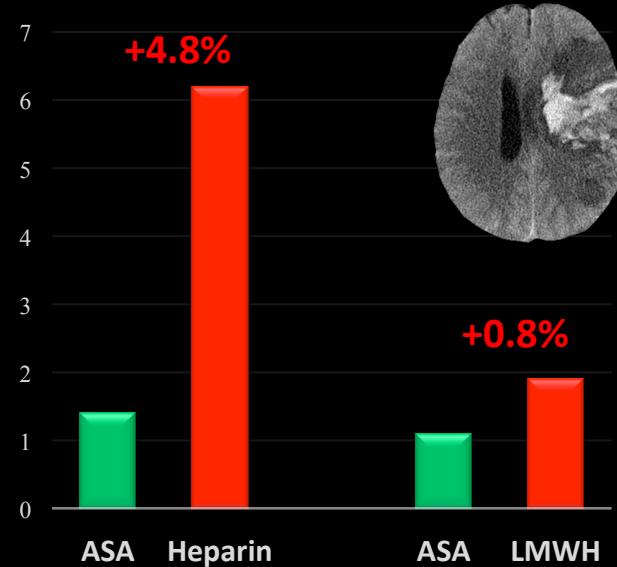
Gladstone, D. J. et al. CMAJ 2004;170:1099-1104





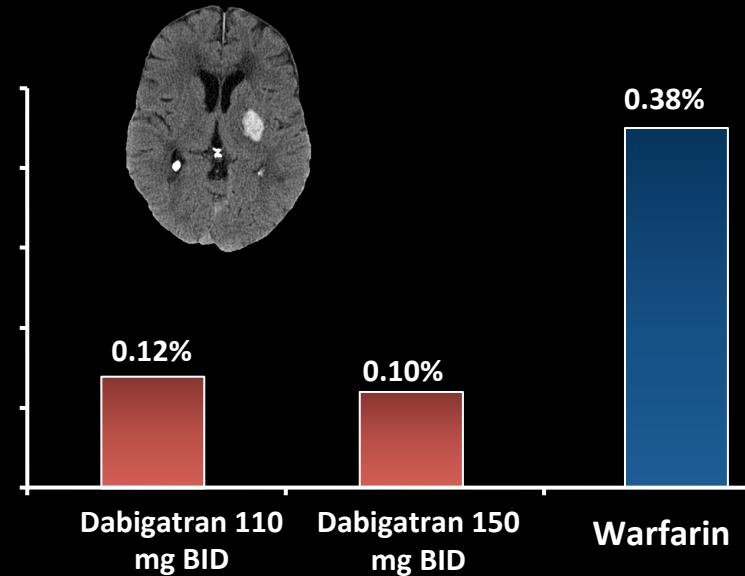
Risks of Anticoagulation In Acute Stroke

Symptomatic Hemorrhagic Transformation Rate Increases with Heparin (Acute)



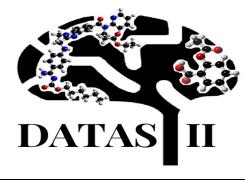
Camerlingo, M et al, *Stroke*, 2005;36:2415-20
Bath P , et al. *Stroke* 2000;31:1770-1778

Intracerebral Hemorrhage Rate Decreases with Dabigatran (Long-term)



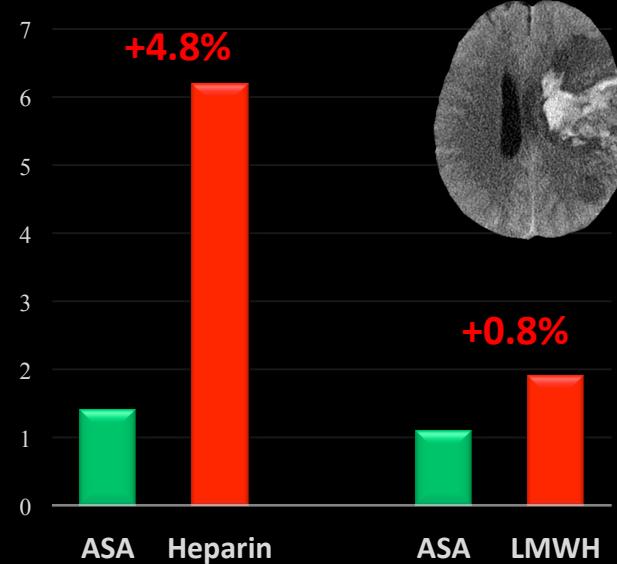
Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151





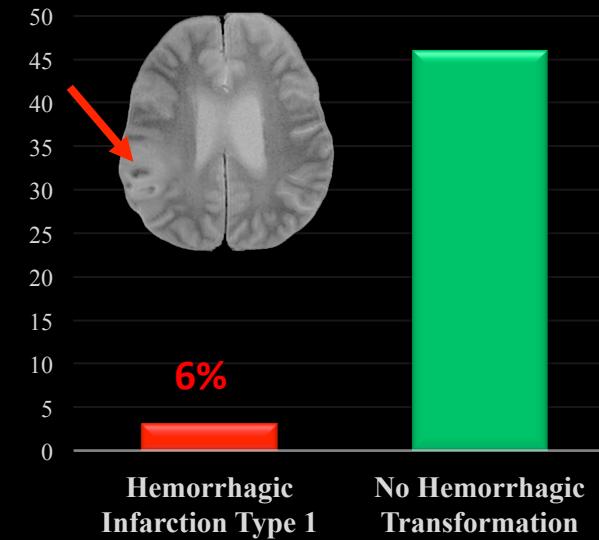
Risks of Anticoagulation In Acute Stroke

Symptomatic Hemorrhagic Transformation Rate Increases with Heparin (Acute)



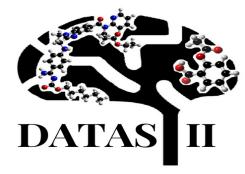
Camerlingo, M et al, *Stroke*, 2005;36:2415-20
Bath P , et al. *Stroke* 2000;31:1770-1778

No Symptomatic Hemorrhagic Transformation When Dabigatran Initiated within 24 hours of Onset



Kate, M et al, *Stroke*, 2015; 46:2685-2687





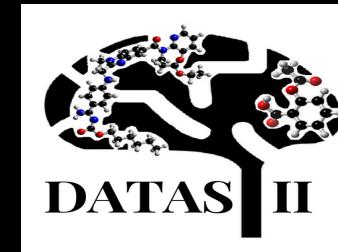
DATAS II Hypothesis

Hypothesis: Symptomatic Hemorrhagic Transformation rates in acute stroke/TIA treated with dabigatran and ASA patients are not significantly different.

Long-term Novel Oral Anticoagulant Therapy in Selected Patients

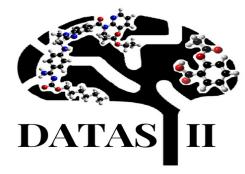


Short-term Novel Oral Anticoagulant Therapy in High Risk Patients

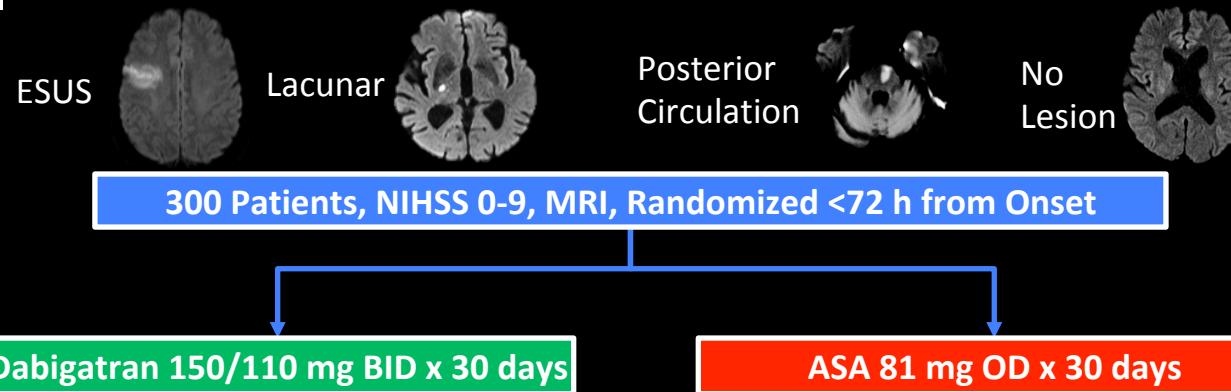


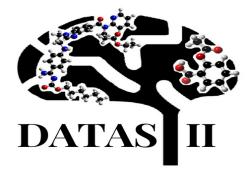
Short-term Aggressive Antiplatelet Therapy in High Risk Patients



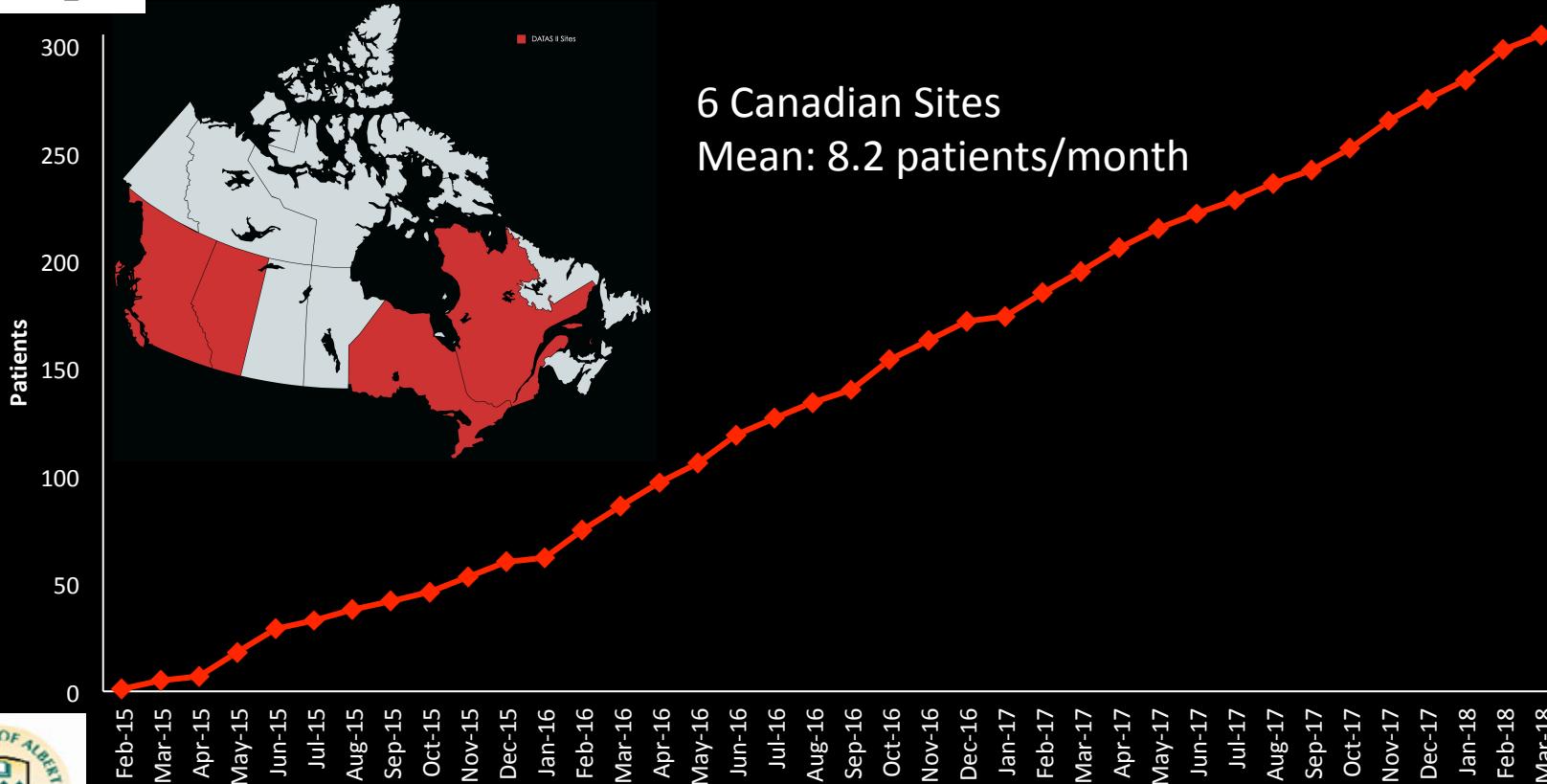


DATAS II Protocol



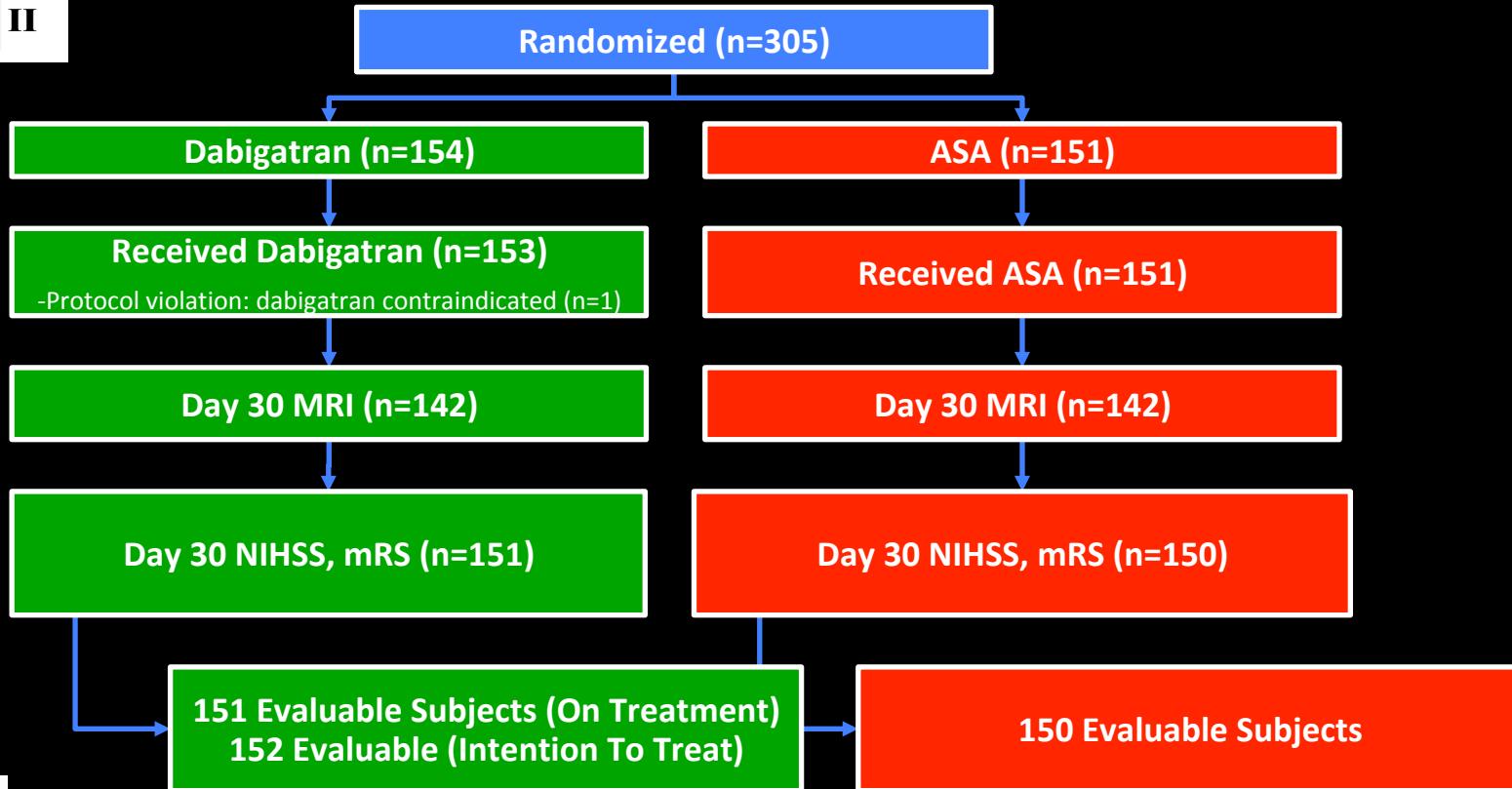
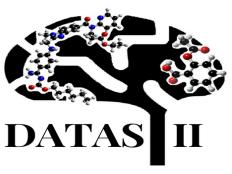


Patient Recruitment



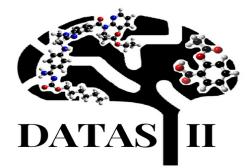
6 Canadian Sites
Mean: 8.2 patients/month





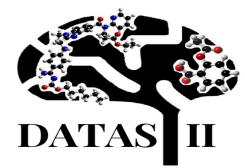
Database lock as of 05/09/2018





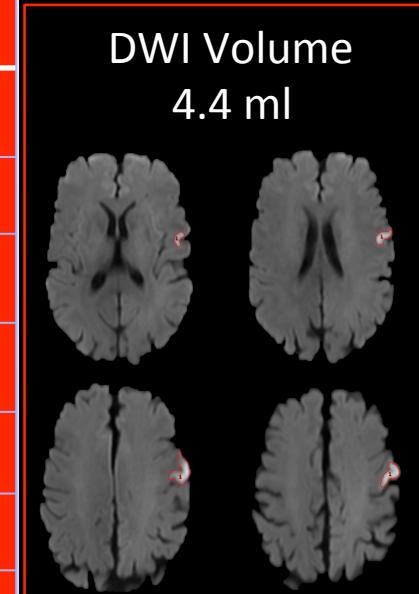
Baseline Characteristics

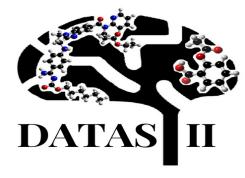
	Dabigatran (n=154)	ASA (n=151)
Mean Age	65.0 ± 13.3	68.2 ± 12.9
Female	62 (40.3%)	55 (36.4%)
Prior Stroke/TIA	36 (23.38%)	35 (23.18%)
Coronary Artery Disease	11 (7.14%)	9 (5.96%)
Hypertension	88 (57.1%)	85 (56.3%)
Diabetes	37 (24.0%)	35 (23.2%)
Baseline Systolic BP (mmHg)	150.7 ± 27.3	149.5 ± 21.8
Median NIHSS Score (IQR)	1 (0-2)	1 (0-2)
Mean Time To Randomization (days)	1.62 ± 0.86	1.74 ± 0.79



Baseline Imaging Characteristics

	Dabigatran (n=154)	ASA (n=151)
Baseline DWI Lesion	119 (77.3%)	120 (79.5%)
Baseline Infarct Volume (ml)	3.7 ± 5.2	4.6 ± 8.6
Cortical	57 (37.4%)	62 (41%)
Sub-cortical/brainstem/cerebellum	62 (39.9%)	58 (38.5%)
Chronic Infarcts	43 (27.9%)	44 (29.1%)
Median Fazekas Score (IQR)	2 (1)	2 (1)
Extracranial Atherosclerotic Disease	16 (10.4%)	27 (17.9%)
Intracranial Atherosclerotic Disease	23 (14.9%)	18 (11.9%)





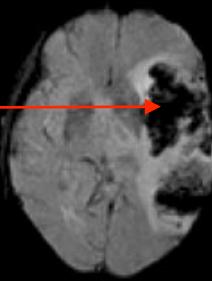
Primary Outcome (Safety)

Symptomatic HT:

1. >30% of the infarcted area on DWI (PH2)
2. ≥4 point increase NIHSS
3. <5 weeks of treatment initiation

PH2

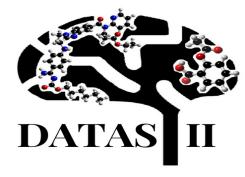
(SWI MRI)



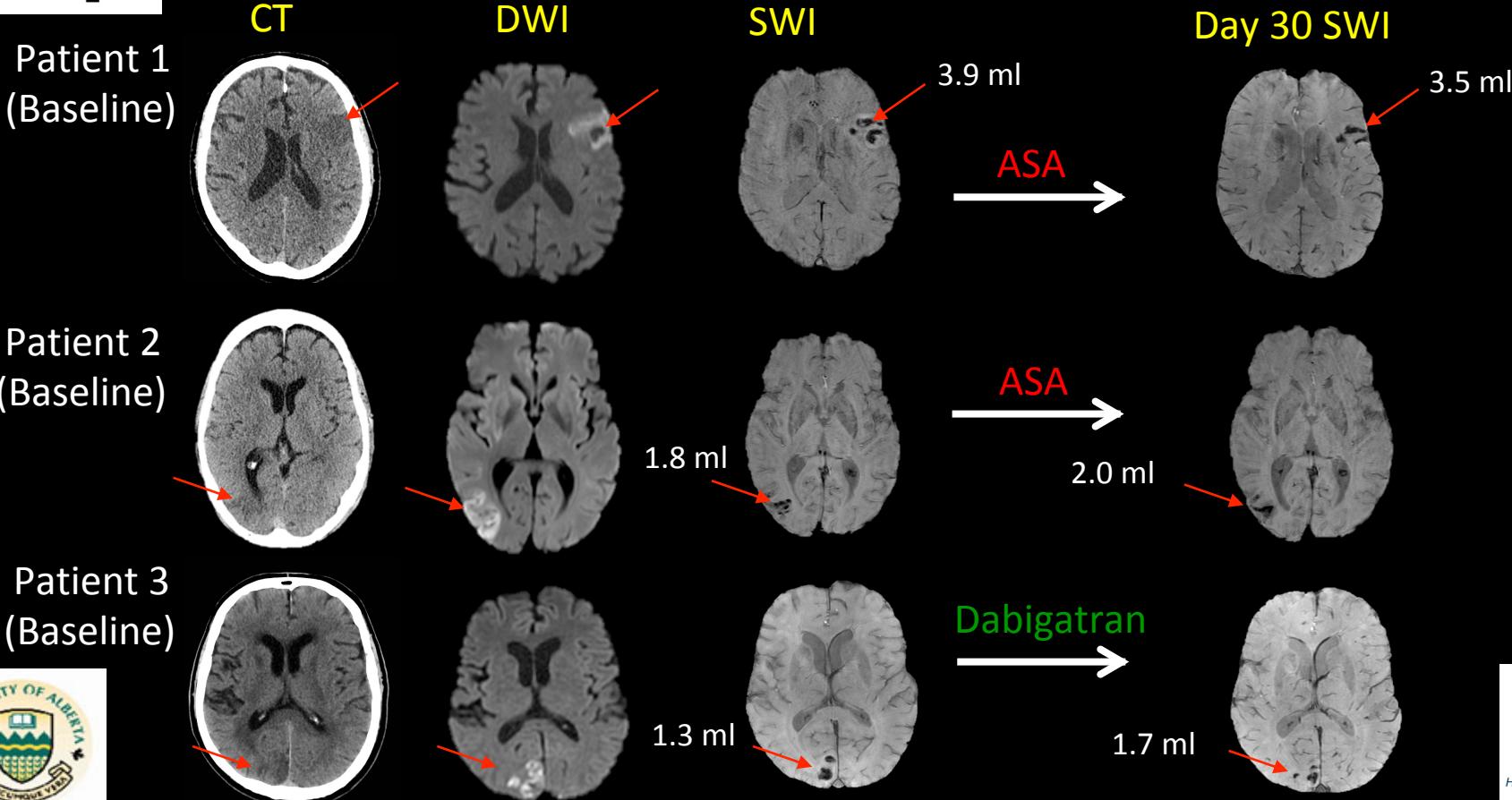
On Treatment	Dabigatran (151)	ASA (153)	Relative Risk (95% CI)
Symptomatic Hemorrhagic Transformation	0	0	N/A

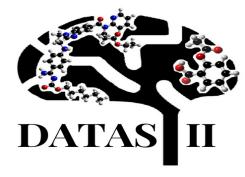
Dabigatran did not increase the rate of symptomatic Hemorrhagic Transformation relative to ASA.



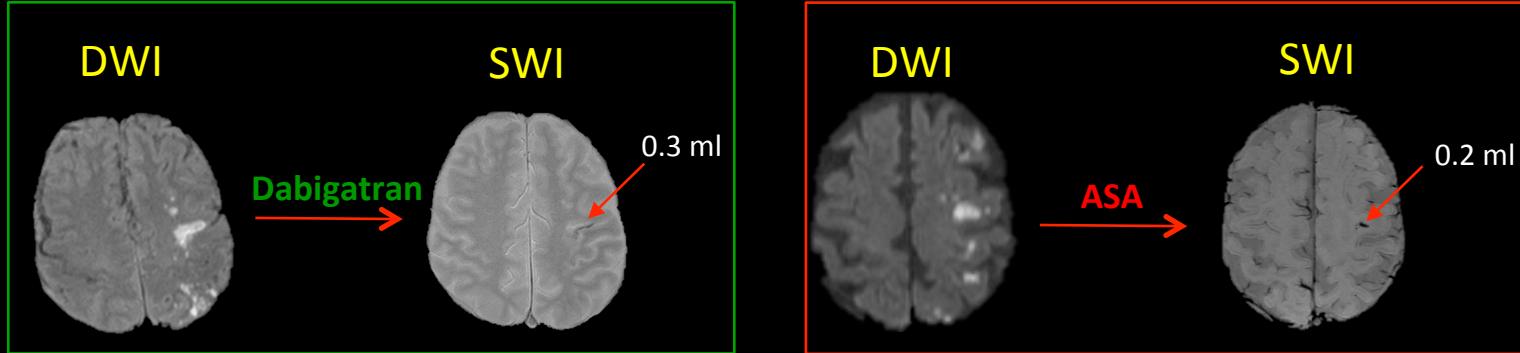


MRI Hemorrhagic Infarction Type 2



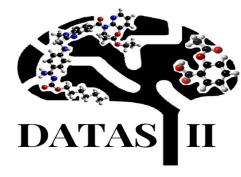


MRI Hemorrhagic Infarction Type 1 (Incident)



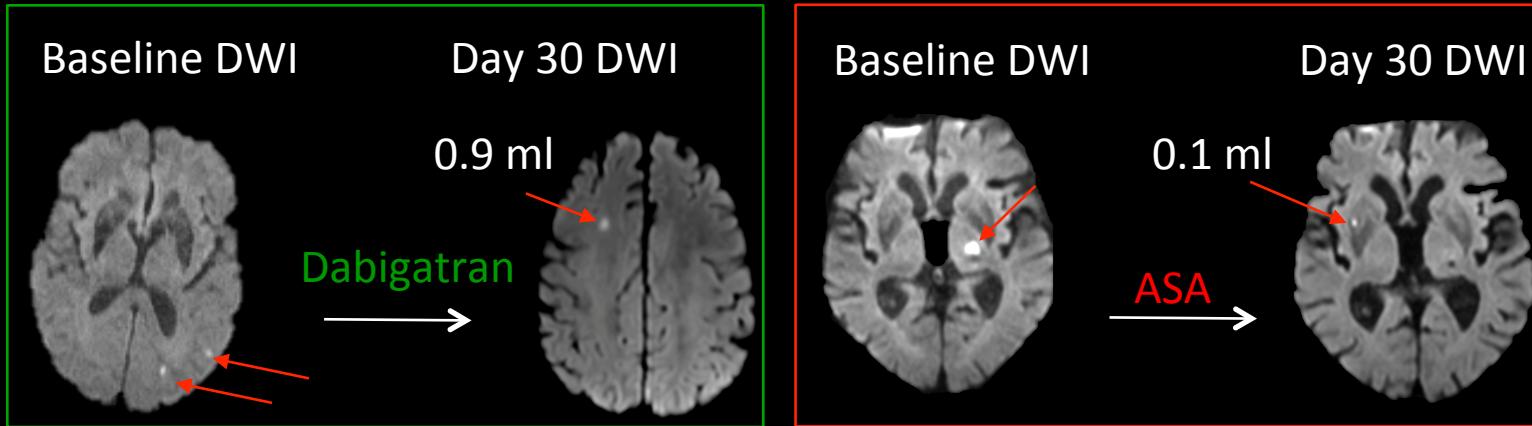
On Treatment	Dabigatran (141)	ASA (142)	Relative Risk (95% CI)
Hemorrhagic Infarction (%)	11 (7.8%)	5 (3.5%)	2.22 (0.79, 6.21)
Hemorrhage Volume (ml \pm SD)	0.22 \pm 0.11	0.34 \pm 0.28	0.12 (-0.08, 0.32)

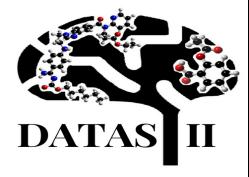




Secondary Outcome: Recurrent Infarcts

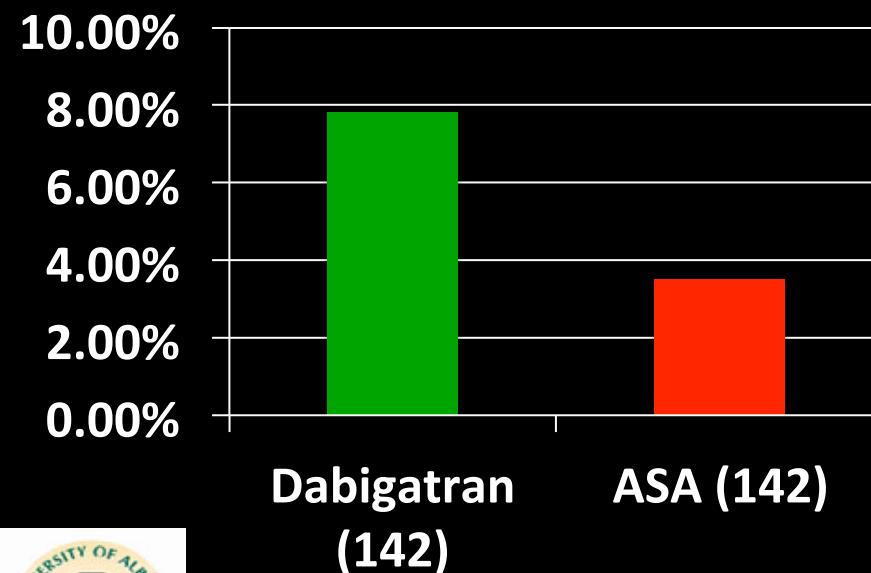
Intention To Treat	Dabigatran (142)	ASA (142)	Relative Risk (95% CI)
Recurrent Infarct on Day 30 MRI n (Proportion)	9 (6.3%)	14 (9.9%)	0.64 (0.29, 1.44)



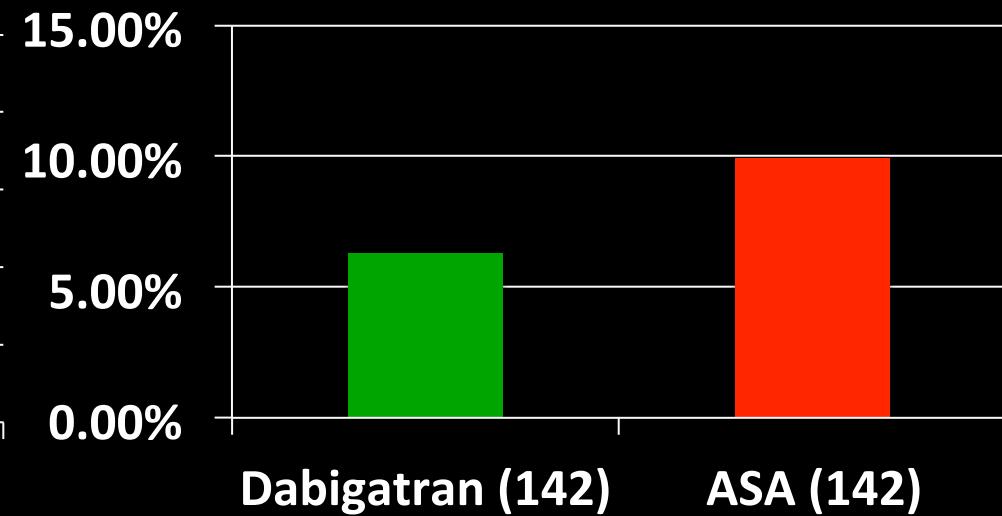


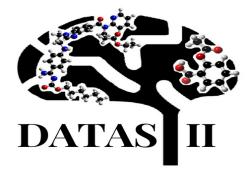
Relative Risk/Benefit

Hemorrhagic Transformation



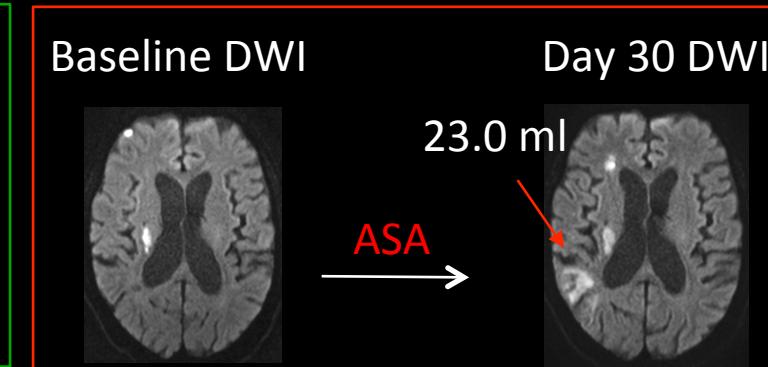
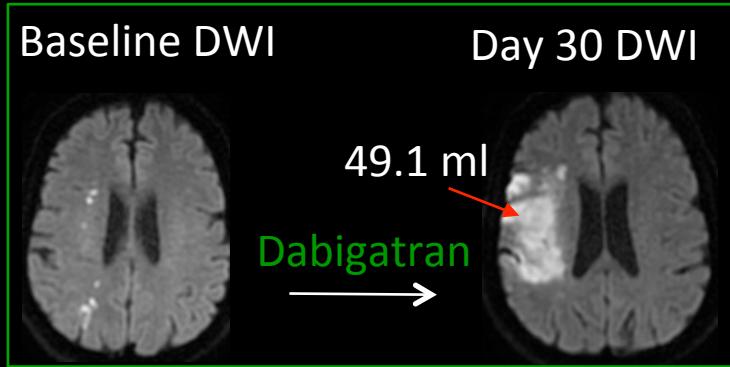
Recurrent Infarcts

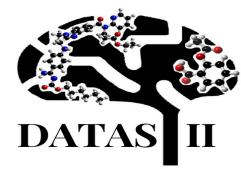




Recurrent Stroke

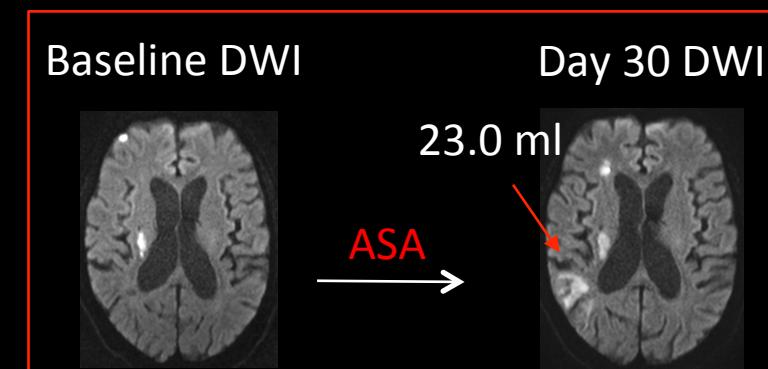
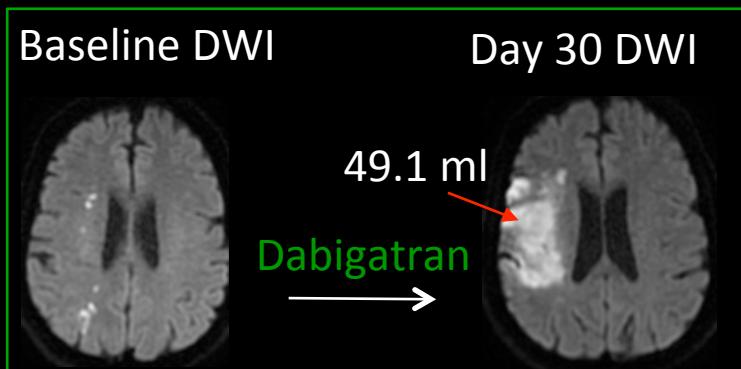
Intention To Treat	Dabigatran (152)	ASA (150)	Relative Risk (95% CI)
Recurrent Clinical Stroke	6 (4.2%)	4 (2.8%)	1.47 (0.42, 5.11)
Recurrent Stroke (Clinical + Day 30 MRI)	9 (6.34%)	16 (11.27%)	0.57 (0.26, 1.24)

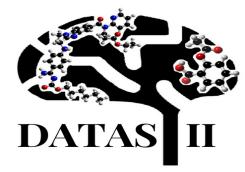




Volume of Recurrent Infarcts

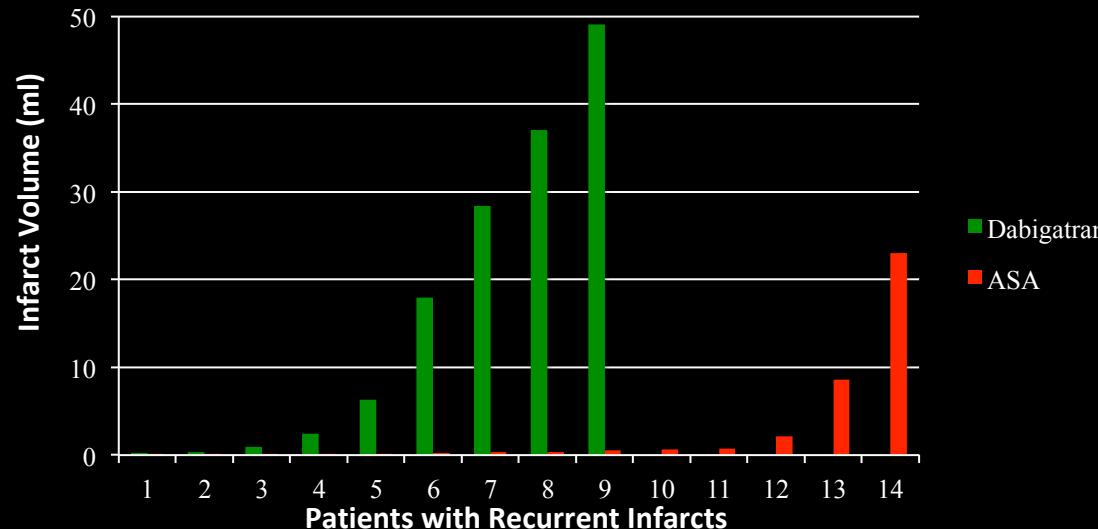
	Dabigatran (142)	ASA (142)	Relative Risk (95% CI)
Recurrent Infarct Volume (ml)	4.50 ± 8.24	0.38 ± 5.41	$-2.46 (-4.11, -0.81)$, $P=0.005$

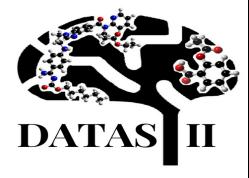




Volume of Recurrent Infarcts

	Dabigatran (145)	ASA (143)	Relative Risk (95% CI)
Recurrent Infarct Volume (ml)	4.50 ± 8.24	0.38 ± 5.41	$-2.46 (-4.11, -0.81)$, $P=0.005$





Conclusions

1. Dabigatran and ASA have similar safety profiles when administered to acute minor ischemic stroke patients
2. The hypothesis that dabigatran can reduce early recurrent ischemic stroke needs to be tested in a larger efficacy trial

