Supplemental Online Content

Lun R, Dhaliwal S, Zitikyte G, Roy DC, Hutton B, Dowlatshahi D. Comparison of ticagrelor vs clopidogrel in addition to aspirin in patients with minor ischemic stroke and transient ischemic attack: a network meta-analysis. *JAMA Neurol*. Published online December 6, 2021. doi:10.1001/jamaneurol.2021.4514

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Search strategy used for all databases (Embase, Cochrane, and Medline)

1. exp stroke/

2. brain ischemia/ or ischemic attack, transient.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. (brain isch?em* or cerebral infarct*).tw.

4. ((brain or cerebral) adj isch?em*).tw.

5. stroke*.tw,kw.

6. ((brain or cerebral) adj infarct*).tw.

7. (brain infarct* or cerebral infarct*).kw.

8. transient isch?em* attack*.tw,kw.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. Ticagrelor/

11. (Ticagrelor or azd6140 or azd 6140 or brilinta).tw,kw.

12. 10 or 11

13. 9 and 12

14. Clopidogrel/

15. (Clopidogrel or pcr4099 or pcr 4099 or plavix).tw,kf.

16. aspirin/

17. (aspirin or acetylsalicylic acid).tw,kw.

18. (random* or placebo).mp. or trial.ti.

19. 14 or 15

20. 9 and 19

21. 13 or 20

22. 16 or 17

23. 18 and 21 and 22

24. limit 23 to "therapy (best balance of sensitivity and specificity)"

*Note that there is no limit like line 24 in Cochrane, so only the first 23 lines were used to pull articles from Cochrane.

eTable 2. Fixed-effects pairwise meta-analysis and homogeneity for outcomes

Comparison vs ASA	Treatment		Control				
	Number of participants	N events	Number of participants	N events	N trials	Pairwise meta-analysis	Heterogeneity: P-Value ; I^2 index (%)
90-day composite stroke + death (primary outcome)							
Clopidogrel	5229	505	5178	372	3	1.38 [1.20;1.59]	0.65 ; 0
Ticagrelor	5493	374	5523	322	1	-	-
90-day ischemic stroke							
Clopidogrel	5229	471	5178	328	3	1.47 [1.27;1.70]	0.75 ; 0
Ticagrelor	5493	345	5523	276	1	-	-
90-day hemorrhagic stroke							
Clopidogrel	5229	12	5178	16	3	0.74 [0.35;1.57]	0.65 ; 0
Ticagrelor	5493	2	5523	10	1	-	-
90-day mortality							
Clopidogrel	5035	22	4980	28	2	0.78 [0.44;1.36]	0.49 ; 0
Ticagrelor	5493	27	5523	36	1	-	-
90-day major hemorrhage							
Clopidogrel	5229	19	5178	37	3	0.51 [0.29;0.89]	0.14 ; 50
Ticagrelor	5493	11	5523	36	1	-	-
90-day adverse events							
Clopidogrel	5229	313	5178	339	3	0.91 [0.77;1.07]	0.58 ; 0
Ticagrelor	5493	325	5523	307	1	-	-
90-day functional disability							
Clopidogrel	5035	623	4980	589	2	1.05 [0.93;1.19]	0.08 ; 66
Ticagrelor	5493	1284	5523	1282	1	-	-
30-day composite stroke + death							
Clopidogrel	5035	426	4980	316	2	1.37 [1.17;1.59]	0.95 ; 0
Ticagrelor	5493	374	5523	322	1	-	-

eTable 3. Random-effects (RE) model measures for efficacy and safety for studies with available data*

Effect measures are reported as hazard ratios with 95% credible intervals. Probabilities of treatments being the "best" treatment based on surface under the cumulative rank curve (SUCRA) plots are presented for comparison. Statistically significant results are outlined in **bold.**

Outcome Measure	Estimates from NMA			
	Cl + ASA versus ASA	Tic + ASA versus ASA	Cl+ ASA versus Tic + ASA	SUCRA (values nearest 1 denote preferred treatment)
	HR (95% CrI)	HR (95% CrI)	HR (95% CrI)	
90-day outcomes				
Primary outcome: composite stroke + death	**0.74 (0.65, 0.85)**	**0.78 (0.67, 0.91)**	0.95 (0.78, 1.16)	Cl+ASA: 0.69 Tic+ASA: 0.31 ASA: 0.00
Ischemic stroke only	**0.71 (0.62, 0.83)**	**0.73 (0.61, 0.87)**	0.97 (0.78, 1.22)	Cl+ASA: 0.59 Tic+ASA: 0.41 ASA: 0.00
Hemorrhagic stroke only	0.97 (0.53, 1.85)	1.47 (0.60, 3.62)	0.67 (0.24, 1.74)	Cl+ASA: 0.47 ASA: 0.40 Tic+ASA: 0.13
Mortality	**0.64 (0.46, 0.91)**	**0.54 (0.36, 0.78)**	1.20 (0.78, 1.89)	Tic+ASA: 0.78 Cl+ASA: 0.22 ASA: 0.00
Major hemorrhage	**1.77 (1.07, 2.97)**	**2.63 (1.47, 4.85)**	0.68 (0.32, 1.37)	ASA: 0.99 Cl+ASA: 0.01 Tic+ASA: 0.00
Adverse events	1.02 (0.88, 1.19)	0.86 (0.73, 1.01)	1.18 (0.97, 1.46)	Tic+ASA: 0.93 Cl+ASA: 0.05 ASA: 0.02
Functional disability	0.82 (0.74, 0.92)	0.96 (0.89, 1.04)	**0.85 (0.74, 0.98)**	Cl+ASA: 0.99 Tic+ASA: 0.01 ASA: 0.00
30-day outcomes				
Composite stroke + death	**0.68 (0.59, 0.79)**	**0.82 (0.71, 0.96)**	0.83 (0.67, 1.02)	Cl+ASA: 0.96 Tic+ASA: 0.04 ASA: 0.00

*30-day outcomes and functional disability only include data from THALES, POINT, and CHANCE; mortality only included data from THALES, POINT, CHANCE, and PRINCE

eTable 4. Summary of fixed-effects and random-effects model fit statistics from network meta-analysis by outcome

All outcomes are measured up to 90 days, except the sensitivity analysis at 30 days.

Model	Number of data points	Posterior total residual deviance	DIC*
Composite stroke + death			
FE consistency	10	13.51	20.03
FE inconsistency	10	12.69	20.1
RE consistency	10	13.36	20.06
Ischemic stroke			
FE consistency	10	11.8	18.54
FE inconsistency	10	11.8	17.25
RE consistency	10	11.56	18.5
Hemorrhagic stroke			
FE consistency	10	12.99	18.2
FE inconsistency	10	13.34	19.23
RE consistency	10	13.22	18.53
Mortality			
FE consistency	8	79.25	82.43
FE inconsistency	8	79.37	82.92
RE consistency	8	79.25	82.41
Major hemorrhage			
FE consistency	10	11.85	18.3
FE inconsistency	10	12.72	20
RE consistency	10	11.6	18.1
Adverse events			
FE consistency	10	19.05	25.22
FE inconsistency	10	20.27	27.3
RE consistency	10	19.08	25.34
Functional disability			
FE consistency	6	22.91	27.66
FE inconsistency	6	22.92	27.65
RE consistency	6	22.77	27.55
Sensitivity Analysis: 30-day composite stroke + death			
FE consistency	6	7.94	12.73
FE inconsistency	6	7.94	12.79
RE consistency	6	8.03	12.87

*DIC = Deviance information criteria

eTable 5. Definitions of stroke and bleeding events across all included trials

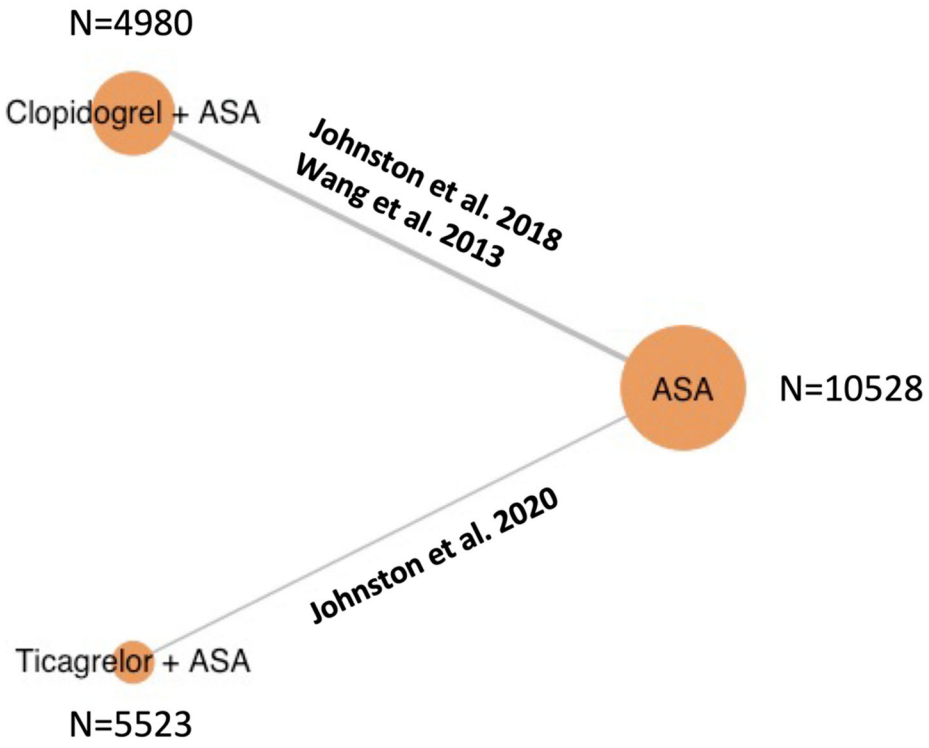
Definition of Stroke events	
CHANCE	Defined as an acute focal infarction of the brain or retina with one of the following: sudden onset of a new focal neurologic deficit, with clinical or imaging evidence of infarction lasting 24 hours or more and not attributable to a non-ischemic cause (i.e., not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurologic disease);a new focal neurologic deficit lasting for less than24 hours and not attributable to a non-ischemic cause but accompanied by neuroimaging evidence of new brain infarction; or rapid worsening of an existing focal neurologic deficit lasting more than 24 hours and not attributable to a non-ischemic cause, accompanied by new ischemic changes on MRI or CT of the brain and clearly distinct from the index ischemic event.
FASTER	WHO definitions of TIA and stroke
POINT	POINT uses the tissue-based definition of stroke and TIA. (Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke; a journal of cerebral circulation. 2009; 40(6):2276–2293.) If a subject has rapid resolution of symptoms, and no brain imaging suggesting tissue infarction, he/she is considered to have had a TIA. Any brain imaging evidence of infarction or clinical evidence (such as symptoms persisting beyond 24 hours) qualifies the event as a stroke. Any patient initially diagnosed with stroke that does not have further brain imaging with evidence of infarction, but who has complete resolution of symptoms within 24 hours is considered TIA.
PRINCE	Any stroke (ischaemic or haemorrhagic); and composite clinical vascular events (ischaemic/haemorrhagic stroke, transient ischaemic attack, myocardial infarction, or vascular death) at 90 days
THALES	STROKE: The definition for stroke is based on the standardized definitions for endpoints (Hicks et al2015). All strokes occurring post-enrolment will be recorded asSAEs. All strokes occurring post-randomization will be considered endpoints. Stroke is defined as an acute episode of focal or global neurological dysfunction caused by cerebral vascular injury as a result of infarction or hemorrhage not caused by trauma. Investigators will classify strokes into 1 of 3mutually exclusive categories: Ischemic, hemorrhagic, or undetermined. Whenever possible, stroke diagnoses should be confirmed using neuroimaging (CT or MRI) to minimizet he number of strokes classified as “undetermined”. Ischemic stroke: An acute episode of focal cerebral dysfunction caused by cerebral infarction. Either of the following is considered an ischemic stroke:1.Rapid onset (or existence on awakening) of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)2.Rapid worsening of an existing focal neurological deficit (e.g., the index stroke event) that is judged by the Investigator to be attributable to a new infarction or extension of a previous infarction in the same vascular bed, based on persisting symptoms or imaging evidence of infarction and no evidence of a non-ischemic etiology. In case imaging is inconclusive, persistent symptoms is defined as duration of ≥24 hours or until death

	Definition of Hemorrhagic Stroke
CHANCE	Hemorrhagic Stroke: acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurologic symptoms
FASTER	Intracranial hemorrhage: intraparenchymal, subdural, epidural, and subarachnoid hemorrhage. Does not include hemorrhagic transformation.
POINT	Hemorrhagic stroke: includes hemorrhagic transformation, intracranial hemorrhage, and subarachnoid hemorrhage
PRINCE	Not stated
THALES	Hemorrhagic Stroke: an acute episode of focal or global cerebral dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage not caused by trauma. Subdural hematomas are ICH events but not strokes. Hemorrhagic transformations are not considered to be hemorrhagic strokes nor to be stroke endpoints. Hemorrhagic transformations may be either symptomatic or asymptomatic: symptomatic hemorrhagic transformation should be reported as SAEs and be GUSTO classified as an ICH.
Definition of Bleeding Events	
CHANCE	Moderate to severe bleeding event, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition
FASTER	Haemorrhagic events were reviewed and assigned into intracranial and extracranial groups (determined by the source of bleeding). The extracranial group was further divided as follows: severe—defined as life threatening, resulting in haemodynamic compromise or hypovolaemic shock, requiring inotropic support or other means to maintain cardiac output, requiring blood transfusion of more than 2 units of packed red blood cells, or associated with a fall in haemoglobin greater than or equal to5 g/L; moderate—defined as requiring a transfusion of2 units of packed red blood cells or less, not severe as defined above, or associated with a fall in haemoglobin of less than 5 g/L; mild—defined as bleeding not requiring transfusion, not causing haemodynamic compromise, usually including haematoma, subcutaneous bleeding, oozing from puncture sites, and may require modification of drug regimen; and asymptomatic—defined as bleeding that results in no symptoms
POINT	The definition of major bleeding is adapted from the protocol and the International Society on Thrombosis and Hemostasis and PRoFESS Trial definitions. Major hemorrhage is one that results in symptomatic intracranial hemorrhage, intraocular bleeding causing loss of vision, need for transfusion of 2 or more units of red cells or equivalent amount of whole blood, need for hospitalization or prolongation of an existing hospitalization or causing death. This may include bleeding events related to surgical procedures. (ISTH)
PRINCE	defined as that in the PLATO study classification of haemorrhagic events: fatal or life threatening bleed, major bleed, and other (supplementary appendix, PLATO bleeding classification
THALES	**Followed the GUSTO Bleeding Definitions:** **GUSTO Severe Bleeding:** Any one of the following: -Fatal -Intracranial -Bleeding that caused hemodynamic compromise requiring intervention (e.g., systolic blood pressure<90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention) **GUSTO Moderate Bleeding**: Bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise (as defined above) **GUSTO Mild Bleeding:** Bleeding without blood transfusion or hemodynamic compromise **No GUSTO Bleeding Event**: Asymptomatic hemorrhagic transformations and microhemorrhages

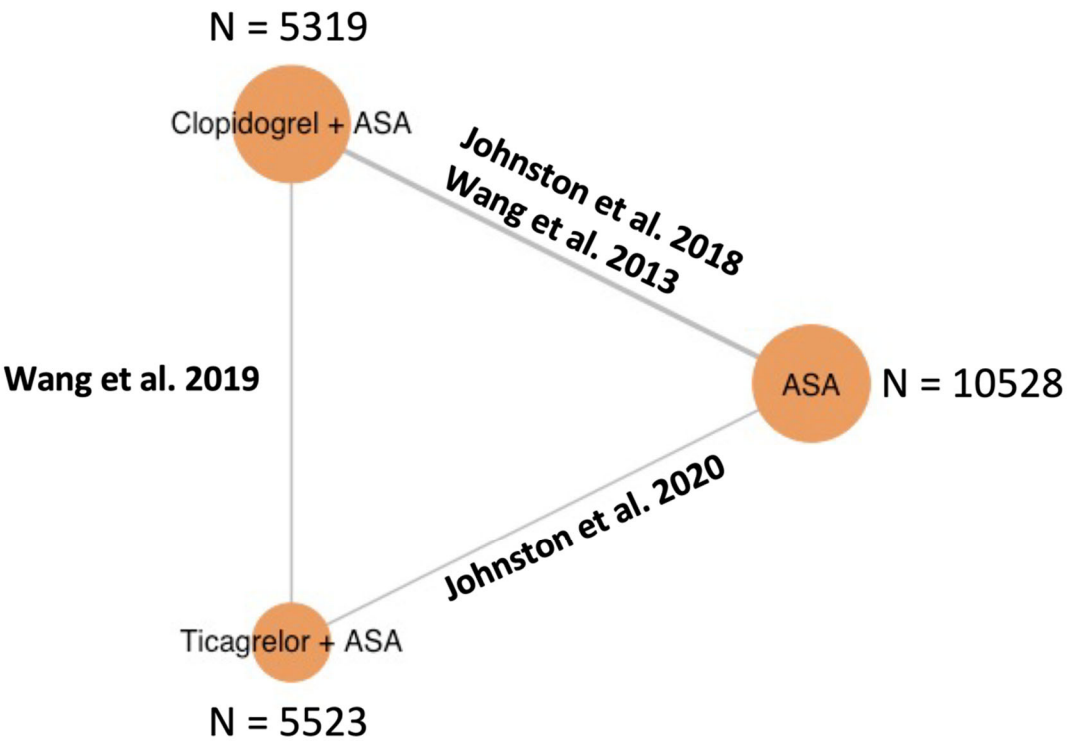
Definition of Serious Adverse Events (SAE)	
CHANCE	Adverse event and Serious adverse events by MedDRA body system. SAEs included death, hemorrhagic stroke, and others (not otherwise defined).
FASTER	"Adverse event" includes outcome (I.e. Ischemic or hemorrhagic stroke) and safety events (I.e. bleeding)
POINT	Serious adverse events by MedDRA body system, excluding components of the primary efficacy outcome measure.
PRINCE	No specific definition given
THALES	"Adverse events that met the criteria for serious adverse events or that led to discontinuation of the trial treatment were recorded in case report forms by the investigators, who were unaware of the treatment assignments." Serious adverse events were reported by system organ class, and excluded strokes. Note that Asymptomatic hemorrhagic transformations of ischemic strokes were not considered to be SAEs. If the investigator chooses to discontinue IP permanently/prematurely due to such an event, it should be classified as a DAE.

eFigure 1. Risk of bias assessment for all included randomized clinical trials using the Cochrane Risk of Bias tool for randomized trials

eFigure 2. Network diagram of total number of patients analyzed in each treatment arm for 30-day sensitivity analysis and functional disability up to 90 days

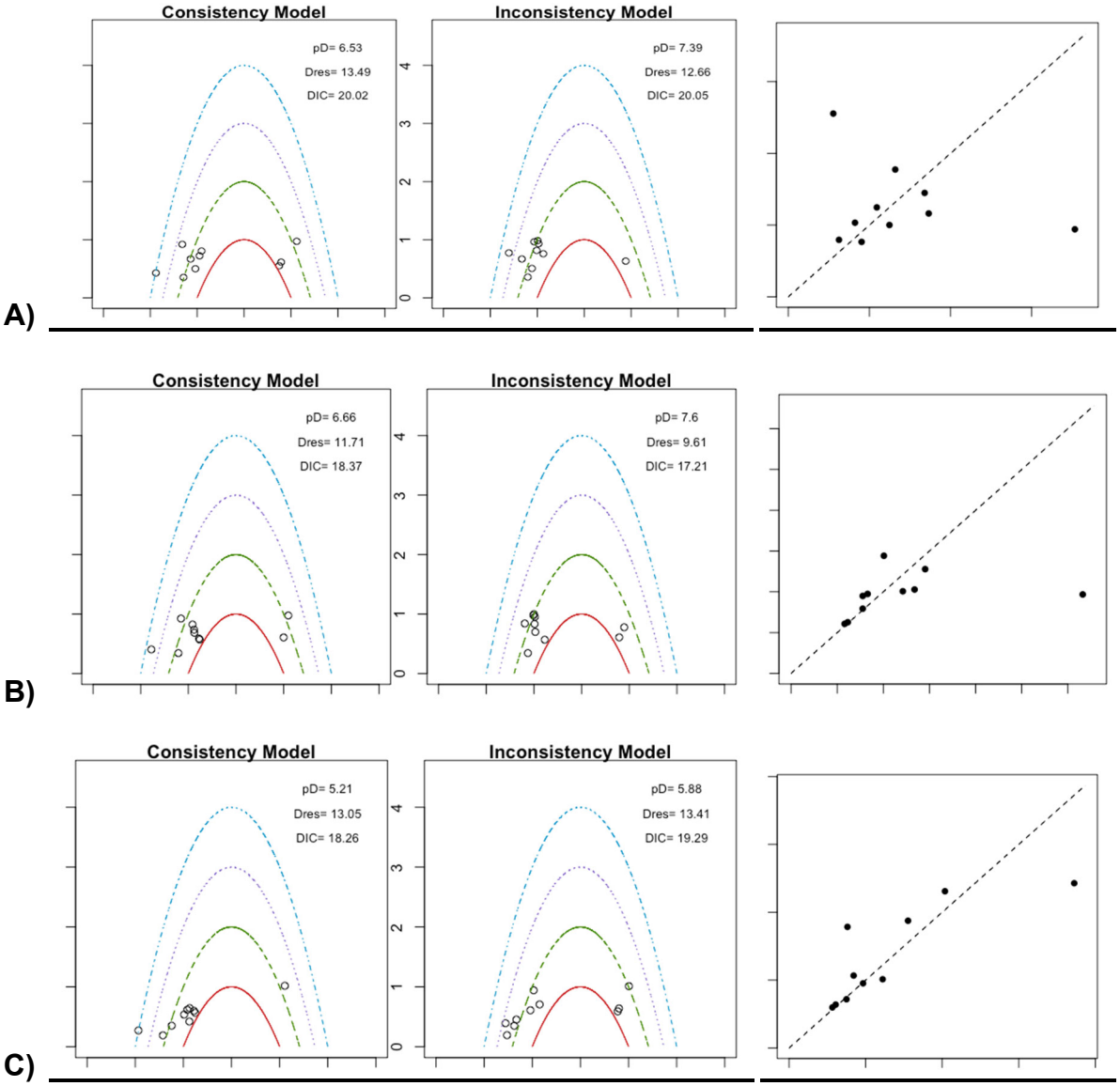


eFigure 3. Network diagram of total number of patients analyzed in each treatment arm for mortality

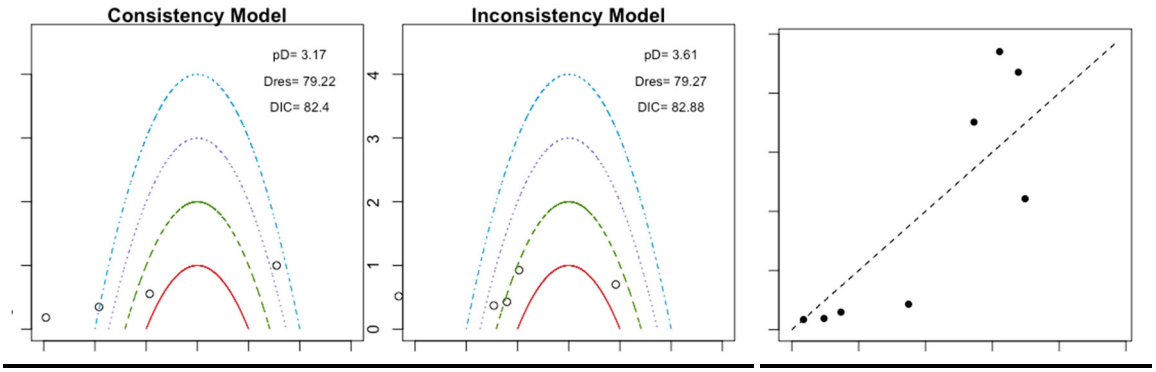


eFigure 4. Leverage plots of fixed-effects consistency and inconsistency models for network meta-analysis by outcome

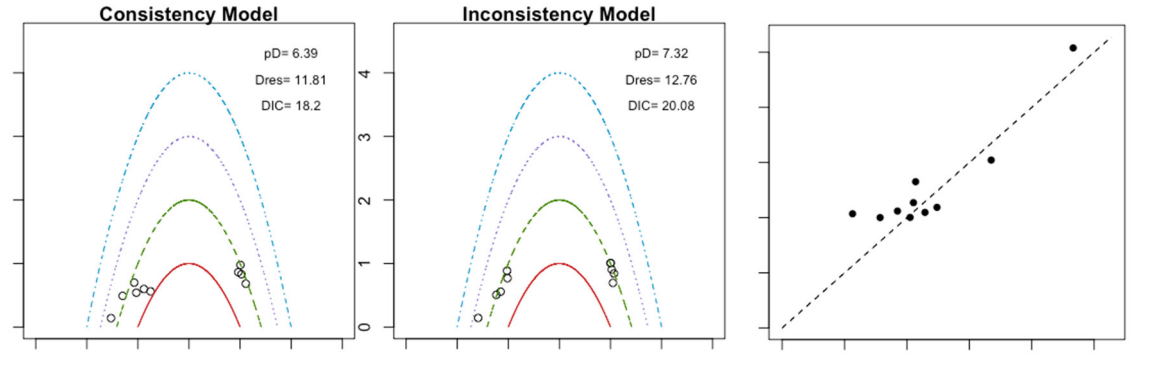
A) composite stroke + death up to 90 days, B) ischemic stroke up to 90 days, C) hemorrhagic stroke up to 90 days, D) mortality up to 90 days, E) major hemorrhage up to 90 days, F) adverse events up to 90 days, G) functional disability up to 90 days, and H) composite stroke + death up to 30 days



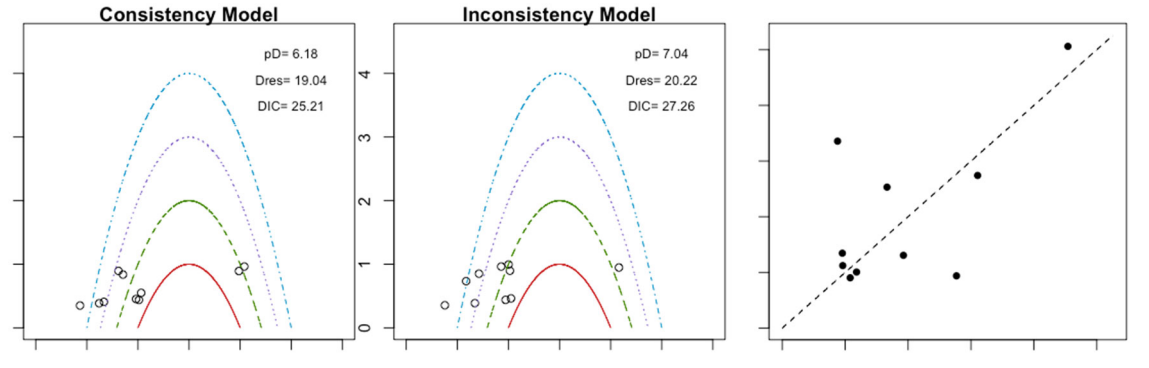
D)



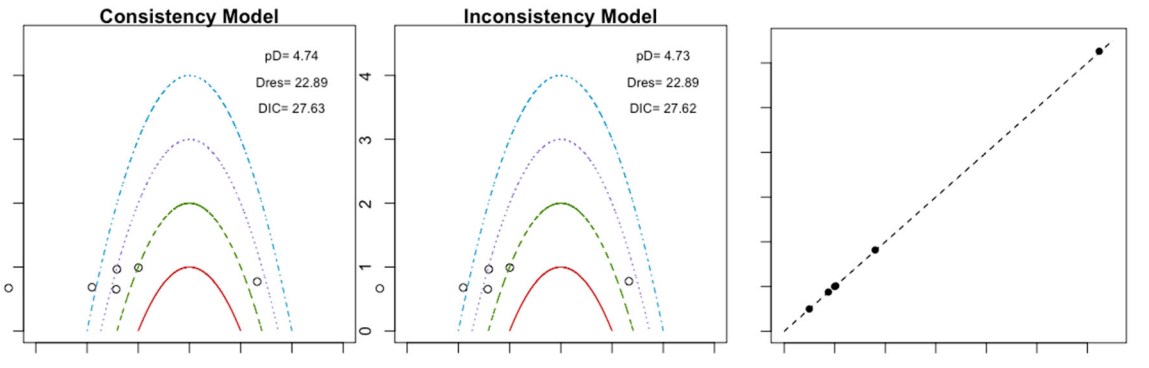
E)



F)



G)



H)