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Supplementary Materials: Data extraction Tables

1.1 Objective 1

1.1.1 Baseline Details

Table 1 Baseline details of studies included in Objective 1

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Lan et al. (2019)[46] **Country** China **Study Design** Controlled trial **Funding** Non industry **Setting** China	**Condition:** Stroke **Inclusion Criteria:** 45–80 years Patients diagnosed with acute cerebral infarction within 24 h after symptom onset. National Institutes of Health Stroke Scale(NIHSS) score ≤ 5 Non-cardiogenic cerebral infarction confirmed by imaging examinations in all patients **Exclusion Criteria:** Patients with cerebral haemorrhage and massive infarction Heart, liver, kidney, or any other important organ failure Active bleeding Platelet count < 100x10^9 L Allergy to ticagrelor, aspirin or clopidogrel **Number of eligible patients (enrolled):** 180 **Omeprazole use:** NR **Age – Mean (SD):** Only reported by study arm: group A: 69 (3.4), group B: 68.9 (3.7) **Sex - % female:** 37.7% **Ethnicities included:** Not reported but likely Chinese	***CYP2C19* test:** Gene chip image analysis software (Affymetrix) **Poor metaboliser (PM) definition:** Two LOF alleles (*2/*2, *3/*3, *2/*3) **Intermediate metaboliser (IM) definition:** One LOF allele (*1/*2, *1/*3) **Extensive metabolisers (EM):** (*1/*1) **Ultra-fast (UF) metabolism: at least one LOF allele** (*1/*17, *17/*17)	**Genetic testing + individualized treatment** **Regimen:** Acute phase: Clopidogrel loading dose of 300 mg, and thereafter at 75 mg/day + aspirin 100 mg/day) for 21 days. Long term: EM and UF: clopidogrel 75 mg/day for 1 year IM and PM: aspirin 100 mg/day for 1 year	**Genetic testing but all given standard treatment** **Regimen:** Acute phase: Clopidogrel loading dose of 300 mg, and thereafter at 75 mg/day + aspirin 100 mg/day) for 21 days. Long term: Clopidogrel 75 mg/day for 1 year

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Xia et al. (2021)[45] **Country** China **Study Design** Non-randomised study of an intervention **Funding** NR **Setting** Hospital in China	**Condition:** Stroke **Inclusion Criteria:** **-** Patients with diagnosis of stroke by computed tompgraphy (CT) or magnetic resonance imaging (MRI) scan **Exclusion Criteria:** - Patients with cerebral haemorrhage and massive infarction - Heart, liver, kidney, or any other important organ failure - Active bleeding - Platelet count < 100x10^9 L - Allergy to ticagrelor, aspirin or clopidogrel **Number of eligible patients (enrolled):** 80 **Omeprazole use:** NR **Age – Mean (SD):** 69.6 (12.4) **Sex - % female:** 37.5% **Ethnicities included:** Not reported but likely Chinese	***CYP2C19* test:** NR **Poor metaboliser definition:** Two LOF alleles (*2/*2, *3/*3, *2/*3) **Intermediate metaboliser definition:** One LOF allele (*1/*2, *1/*3) **Fast metabolism:** (*1/*1) **Ultra-fast metabolism: at least one GOF allele** (*1/*17, *17/*17)	**Genetic testing + individualized treatment** **Regimen:** Slow metabolism: ticagrelor 90 mg twice daily or aspirin 100 mg daily Intermediate metabolism: clopidogrel 150 mg once a day Fast and ultra-fast metabolism: clopidogrel 75 mg daily	**Control group – no testing** **Regimen:** Clopidogrel 75 mg once daily

1.1.2 Risk of bias assessment

Table 2 Risk of bias assessment of studies included in Objective 1

Study Details	Lan (2019)[46]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	N
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	N
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**High**
Rationale for judgement: Allocation was based on genetic profile but unclear how equal numbers were allocated to each group	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	PY
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Y
Risk of bias judgement	**High**
Rationale for judgement: Participants and carers probably aware of intervention, no data on potential deviations from intended interventions, no information on type of statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Y
Risk of bias judgement	**High**
Rationale for judgement: 12/90 and 13/90 patients were lost to follow-up, which could be associated with the outcomes	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**Low**
Rationale for judgement: objective, clinical outcomes taken from clinical records and follow-up visits	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	NI
Risk of bias judgement	**Some concerns**
Rationale for judgement: protocol not available	

OVERALL RISK OF BIAS	**High**
Rationale for judgement: Participants and carers probably aware of intervention, no data on potential deviations from intended interventions, no information on type of statistical analysis High proportion loss to follow-up, which could be associated with presence of events	

PY: Probably yes; PN: Probably No; NI: No information

Study Details	Xia(2021)[45]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**High**
Rationale for judgement: There was no indication about randomisation of allocation	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	PY
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Y
Risk of bias judgement	**High**
Rationale for judgement: Participants and carers probably aware of intervention, no data on potential deviations from intended interventions, no information on type of statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**Low**
Rationale for judgement:	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**Low**
Rationale for judgement: objective, clinical outcomes taken from clinical records and follow-up visits	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions,	NI

time points) within the outcome domain?	
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	NI
Risk of bias judgement	**Some concerns**
Rationale for judgement: There is no indication about randomisation of allocation, No information on statistical analysis methodology, statistical analysis protocol not available	

OVERALL RISK OF BIAS	**High**
Rationale for judgement: There is no indication about randomisation of allocation, protocol not available	

1.1.3 Results

Table 3 Results details of studies included for objective 1

Study details				Standard treatment		Test + Personalised treatment		Effect Estimate*			
Study details	Type of outcome	Outcome	Follow-up Time (days)	No. patients	No. Events	No. patients	No. Events	HR	LCI	UCI	p-value
Lan (2019)[46]	Incidence of secondary vascular occlusive events	Ischaemic stroke	365	90	3	90	1	0.33	0.03	3.20	>0.05
	Incidence of secondary vascular occlusive events	Haemorrhagic stroke	365	90	1	90	0	0.33	0.01	8.17	>0.05
	Incidence of secondary vascular occlusive events	Myocardial infarction	365	90	0	90	1	3.00	0.12	73.74	>0.05
	Incidence of secondary vascular occlusive events	Composite outcome	365	90	4	90	2	0.50	0.09	2.74	NR
Xia (2021)[45]	Incidence of secondary vascular occlusive events	Composite outcome	90	40	17	40	9	0.53	0.24	1.18	0.033
	Incidence of secondary vascular occlusive events	Ischaemic stroke	90	40	12	40	5	0.42	0.15	1.18	NR
	Incidence of secondary vascular occlusive events	TIA	90	40	2	40	1	0.50	0.05	5.53	NR
	Incidence of secondary vascular occlusive events	Myocardial infarction	90	40	3	40	3	1.00	0.2	4.95	NR
	Incidence of secondary vascular occlusive events	Vascular death	90	40	3	40	3	1.00	0.2	4.95	NR

HR: hazard ratio; LCI: Low confidence interval; UCI: Upper confidence interval
*All HRs were calculated using a hazard rate analysis of event frequencies in relation to time at risk.

1.2 Objective 2

1.2.1 Baseline Details

Table 4 Baseline details of studies included in Objective 2

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Chen et al. (2019)[52, 180, 181] **Country** China **Study Design** Sub-analysis RCT **Funding** Non-industry **Setting** 26 hospitals in China	**Condition:** Stroke & TIA **Inclusion Criteria** • Age≥ 40 years and <80 years. • Acute non-disabling ischemic stroke (NIHSS≤ 3) or TIA (ABCD2 score ≥4) **Exclusion Criteria** • Other pathology on baseline head CT or MRI • Isolated or pure sensory symptoms (e.g., numbness), visual changes, or dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI. • Modified Rankin Scale Score > 2 at randomization. • Contraindication to ticagrelor, clopidogrel or aspirin • Severe renal or hepatic insufficiency, cardiac failure • Major surgery <30 days. • Low white blood cell, platelet count or hematocrit (Hct) • Clear indication for anticoagulation • Continuous use of ticagrelor or clopidogrel >5 days before randomization • Current treatment with heparin or anti coagulation therapy • Receipt of intravenous/ intra-arterial thrombolysis or mechanical thrombectomy < 24 hours prior to randomization. • Diagnosis or of acute coronary syndrome. • Anticipated requirement for long-term (>7 days) non-study anti-platelet drugs, or NSAIDs (nonsteroidal anti-inflammatory drugs) affecting platelet function. • Qualifying TIA or minor stroke induced by angiography or surgery. • Planned or likely revascularization < 3 months. • Scheduled for surgery or interventional treatment requiring study drug cessation. • Severe non-cardiovascular comorbidity with life expectancy < 3 months. **Eligible (total study):** 5644 **Enrolled (total study):** 675 **Enrolled (our cohort of interest):** 374 **Age – Mean (SD):** 60.8 (8.7); **Sex - % female:** 26.8%; **Ethnicities:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel + aspirin for first 21 days **Regimen:** 75 mg clopidogrel (loading dose of 300mg followed by **75 mg daily till day 90**) combined with aspirin (loading dose of 100-300mg followed by **100 mg once daily till day 21**)	**Antiplatelet drug:** Ticagrelor + aspirin for first 21 days **Regimen:** 90 mg ticagrelor (loading dose of 180 mg followed **by 90 mg twice daily till day 90**) combined with aspirin (loading dose of 100-300mg followed by **100 mg once daily till day 21**)

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Han et al. (2017)[47, 182-186] **Country** South Korea **Study Design** Sub-analysis of RCT **Funding** Industry **Setting** 18 tertiary-care hospitals in South Korea	**Condition:** Stroke **Inclusion Criteria** • non-cardiogenic ischemic stroke of TOAST classification < 30 days prior to screening • ≥ 20 years of age • Written informed consent **Exclusion Criteria** • History of bleeding tendency or recent major bleeding within 2 weeks • Chronic liver disease or renal dysfunction • Thrombocytopenia • Contraindication to antiplatelet agents • Severe congestive heart failure • Need to take anticoagulants ≥2 antiplatelet agents • Severe concomitant disease with expected survival < 2 years **Number of Participants** **Eligible (total study):** 795 **Enrolled (total study):** 784 **Enrolled (our cohort of interest):** 484 **Omeprazole use:** Proton pump inhibitor use prohibited **Age Mean (SD)** Reported by study arm: Triflusal: 61.6 (10.5); Clopidogrel: 61.2 (11.1) **Sex - % female:** Reported by study arm: Triflusal: 32%: Clopidogrel: 35% **Ethnicities included:** Not reported - likely most patients asian (South Korean)	***CYP2C19* test:** Seeplex *CYP2C19* ACE genotyping system and Real-Q *CYP2C19* genotyping kit **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel **Regimen:** 75 mg clopidogrel once daily	**Antiplatelet drug:** Triflusal **Regimen:** 300 mg triflusal twice per day (600 mg/day)

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2

Author (Year)
Meschia et al. (2020)[48]
 	
Country
NR
 	
Study name:
POINT
 	
Study Design
Sub-analysis of RCT
 	
Funding
Non-industry
 	
Setting
International
	Condition
	Stroke & TIA
	
	Inclusion Criteria
	• Neurologic deficit attributed to focal brain ischemia and EITHER:
	  • High risk TIA: resolution of deficit prior to randomization AND ABCD2 score >4; or
	  • Minor ischemic stroke: residual deficit with NIHSS <3
	• Ability to randomize <12 hours of symptom onset.
	• Head CT or MRI ruling out hemorrhage or other pathology
	
	Exclusion Criteria
	• Age <18 years
	• Symptoms of TIA limited to isolated numbness, visual changes, or dizziness/vertigo.
	• Candidate for thrombolysis or endovascular interventior or received <1 week prior to index event
	• Gastrointestinal bleed or major surgery <3 months
	• History of nontraumatic intracranial hemorrhage.
	• Known internal carotid artery stenosis >50%
	• Clear indication for anticoagulation anticipated during study period
	• Qualifying ischemic event induced by angiography or surgery.
	• Comorbidity with life expectancy <3 months.
	• Contraindication to clopidogrel or aspirin.
	• Anticipated requirement for long-term non-study antiplatelet drugs or NSAIDs affecting platelet function
	
	Number of Participants
	Eligible (total study): 4881
	Enrolled (total study): 4881
	Enrolled (our cohort of interest): 667
	
	Omeprazole use:
	PPI and other drugs that may affect clopidogrel metabolism will be avoided, with others substituted.
	
	Age – Mean (Interquartile Range (IQR)): 63 (53-72)
	
	Sex - % female: 44.5%
	
	Ethnicity: White: 175 (67%), black: 65 (24.5%), other: 25 (9.4%)
		***CYP2C19* test:**
		Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay
		
		Poor metaboliser definition:
		one or more *CYP2C19* *2 or *3 alleles
			Antiplatelet drug:
			Clopidogrel + Aspirin
			
			Regimen:
			Clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin at a dose of 50 to 325 mg per day
				Antiplatelet drug:
				Aspirin
				
				Regimen:
				Aspirin at a dose of 50 to 325 mg per day

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Wang et al. (2016a)[51, 73, 191-194] **Study name** CHANCE **Country** China **Study Design** Sub-analysis of RCT **Funding** Non-industry **Setting** 73 among 114 sites from CHANCE (China)	**Condition** Stroke & TIA **Inclusion Criteria** • Age ≥ 40 years • Acute non-disabling ischemic stroke (NIHSS≤3 at the time of randomization) or TIA with moderate/high risk of recurrence that can be treated with study drug <24 hours of symptoms onset. **Exclusion Criteria** • Diagnosis of haemorrhage or other pathology on baseline head CT or MRI. • Isolated or pure sensory symptoms without acute infarction on baseline head CT/MRI • Modified Rankin Scale Score > 2 at randomization • Clear indication for anticoagulation • Contraindication to clopidogrel or aspirin. • History of intracranial haemorrhage. • Anticipated requirement for long-term non-study antiplatelet drugs or NSAIDs affecting platelet function. • Current treatment with heparin therapy or oral anticoagulation. • Gastrointestinal bleed or major surgery <3 months. • Planned or likely revascularization <next 3 months • Scheduled for surgery or interventional treatment requiring study drug cessation. • Qualifying TIA or minor stroke induced by angiography or surgery. • Severe non-cardiovascular comorbidity with life expectancy < 3 months. **Eligible (total study):** 3010 **Enrolled (total study):** 2933 **Enrolled (our cohort of interest):** 1726 **Omeprazole use:** PPI will be avoided, with others substituted. PPI use: 10 patients within the carrier group and 10 within the non carrier group (20 out of 2933) **Age – Median (IQR):** 62.3 (54.5-71.2) **Sex - % female:** 32.6% **Ethnicities:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform (Sequenom). **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel + aspirin for first 21 days **Regimen:** • Day 1: four tablets of clopidogrel 75 mg and open label aspirin (75 mg - 300 mg) • D2 to D21±2 days: one tablet of clopidogrel 75mg and one tablet of aspirin 75 mg per day • D22±2 days visit to D90±7 days: one tablet of clopidogrel 75mg and one tablet of placebo aspirin 75 mg per day	**Antiplatelet drug:** Aspirin **Regimen:** • Day 1: four tablets of placebo clopidogrel 75 mg and open label aspirin (75 mg - 300 mg) • D2 to D21±2 days: one tablet of placebo clopidogrel 75mg and one tablet of aspirin 75 mg per day • D22±2 days visit to D90±7 days: one tablet placebo of clopidogrel 75mg and one tablet of ASA 75 mg per day

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Wang et al. (2021)[49, 187-190] **Country** China **Study Design** RCT **Funding** Mixed - Drugs and tests were supplied by industry at no cost and with no restrictions **Setting** 202 centers in China	**Condition:** Stroke and TIA **Inclusion Criteria** • Age ≥40 years • Acute non-disabling ischemic stroke (NIHSS≤), or TIA with moderate-to-high risk of stroke (ABCD2 score ≥4), treated with study drug within 24 hours of symptoms onset • *CYP2C19* loss-of-function allele carrier. **Exclusion Criteria** • Other major non-ischemic brain disease on baseline head CT or MRI. • Symptoms without evidence of acute infarction on baseline head CT or MRI. • Iatrogenic causes. • Modified Rankin scale [mRS] score 3-5 • Contraindication to clopidogrel, ticagrelor or aspirin • Increased risk of bleeding • History of severe renal or hepatic insufficiency or cardiac failure • Low white blood cell, platelet count or haematocrit • Clear indication for anticoagulation • Requirement for long-term (>7 days) non-steroidal anti-inflammatory drugs (NSAIDs) • Planned or likely revascularization <3 months • Severe non-cardiovascular comorbidity with life expectancy < 3 months • Dual antiplatelet treatment < 72 hours before randomization • Current treatment with heparin therapy or oral anticoagulation • Intravenous thrombolytic therapy or mechanical thrombectomy < 24 hours prior to randomization • Gastrointestinal bleed within 3 months or major surgery within 30 days **Number of Participants** **Eligible (total study):** 6412 **Enrolled (total study):** 6412 **Enrolled (our cohort of interest):** 6412 **Omeprazole use:** strong *CYP2C19* inhibitors prohibited, including some PPI. **Age - Mean (SD):** 64.8 (NR) **Sex - % female:** 33.8% **Ethnicity:** Han Chinese ethnic group 98%; others not reported	***CYP2C19* test:** GMEX point-of-care genotyping system **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	Clopidogrel + aspirin for first 21 days **Regimen:** Placebo ticagrelor plus a 300-mg loading dose of clopidogrel on day 1, followed by **75 mg daily on days 2 through 90**, plus aspirin at a loading dose of 75 to 300 mg, **followed by 75 mg daily for 21 days.**	Ticagrelor + aspirin for first 21 days **Regimen:** 90 mg twice daily Placebo clopidogrel plus a 180-mg loading dose of ticagrelor on day 1, followed **by 90 mg twice daily on days 2 through 90**, plus aspirin at a loading dose of 75 to 300 mg, **followed by 75 mg daily for 21 days.**

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Wu et al. (2020)[50] **Country** China **Study Design** RCT **Funding** Non-industry **Setting** Single centre - China	**Condition:** Stroke **Inclusion Criteria** Acute ischaemic stroke; continuously hospitalised Aged ≥40 years and ≤ 75 years Moderate to severe cerebral artery stenosis < 7 days of ischaemic stroke onset Access to the study drug within 24 h of admission National Institutes of Health Stroke Scale (NIHSS) score ≤ 5 **Exclusion Criteria** Attack confirmed as non cerebrovascular attack Significant signs of anticoagulation Bleeding from the gastrointestinal tract <1 year Positive faecal occult blood on admission to hospital History of intracranial haemorrhage Severe heart failure, asthma, liver, or kidney insufficiency History of coagulation abnormalities or systemic bleeding disorders History of hemocytopenia, leukopoenia, or thrombocytopenia; Given aspirin combined with clopidogrel therapy at randomisation **Eligible (total study):** 162 **Enrolled (total study):** 131 **Enrolled (our cohort of interest):** 131 **Omeprazole use:** All patients administered pantoprazole during dual antiplatelet therapy **Age - Median (IQR):** Reported by study arm: High dose group: 60± 10.4, Normal dose group: 63.2 ±9.3 **Sex - % female:** Reported by study arm: High dose group: 20.97%, Normal dose group: 27.54 **Ethnicities included:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** Not reported **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel + aspirin for 21 days followed by aspirin alone **Regimen:** Day 1: 300 mg clopidogrel Day 2-21: 75mg clopidogrel + 100 mg aspirin Day 21-90: 100 mg aspirin	**Antiplatelet drug:** High dose clopidogrel + aspirin for 21 days followed by aspirin alone **Regimen:** Day 1: 300 mg clopidogrel Day 1: 300 mg clopidogrel Day 2-21: 150mg clopidogrel + 100 mg aspirin Day 21-90: 100 mg aspirin

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Yi et al. (2018)[53] **Country** China **Study Design** Sub-analysis of RCT **Funding** Non-industry **Setting** Hospitals in China	**Condition** Stroke **Inclusion Criteria** • ≥ 18 years • Diagnosis of ischemic stroke by cranial computed tomography and magnetic resonance imaging scanning **Exclusion Criteria** • No previous carotid endarterectomy or carotid stent therapy, or during treatment. **Number of eligible patients (randomised):** **Eligible (total study):** 570 **Enrolled (total study):** 570 **Enrolled (our cohort of interest):** 257 **Omeprazole use:** NR **Age – Mean (SD)** NR (For our cohort) **Sex - % female** NR (For our cohort) **Ethnicities included:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** NR **Poor metaboliser definition:** One or more *CYP2C19**2 alelles	**Antiplatelet drug:** Clopidogrel + aspirin for first 30 days **Regimen:** Aspirin plus clopidogrel (200 mg aspirin and 75 mg clopidogrel) for 30 days, and 75 mg/d clopidogrel thereafter	**Antiplatelet drug:** Aspirin **Regimen:** 200 mg/d for 30 days and 100 mg/d thereafter

1.2.2 Risk of bias assessment

Table 5 Risk of bias assessment of studies included in Objective 2

Study Details	Chen (2019)[52]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No major issues observed regarding allocation and randomisation	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Participants and carers aware of intervention (ope-label trial) but no significant deviations and appropriate analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no significant missing data on outcome	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant issues on outcome assessment	

DOMAIN 5: Bias in selection of the reported result

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Pre-specified and registered protocol	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No significant concerns on any domain	

Study Details	Han (2017)[47]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Allocation sequence is random and assigned through a secure web-based registration system.	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: although there was no masking, there's no evidence suggesting deviations because of the trial context	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Y
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Potentially significant missing data, but per-protocol (PP) analysis was consistent with intention to treat (ITT) analysis	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: measuring methods appropriate	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data	Y

were available for analysis?	
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Data analysed in accordance with a pre-specified plan	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No significant concerns on any domain	

Study Details	Meschia (2020)[48]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Even though we are assessing a subanalysis, the intervention was randomised in the subgroup and baseline characteristics are adequately balanced	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No issues with blinding and intervention deviations	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PY
Risk of bias judgement	**HIGH**
Rationale for judgement: No clear data on loss to follow up, and it could potentially be related to the outcomes	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Outcomes definitions are clear and objective, assessed by blinded staff	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data	Y

were available for analysis?	
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Data analysis was defined and published before outcome data was available	

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: No clear data on loss to follow up, and it could potentially be related to the outcomes	

Study Details	Wang et al (2016a)[206]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No information on allocation concealment, but no baseline differences.	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	N

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No data on blinding, no information on statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement:	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant issues with outcome measurement	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Wang (2021)[49]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No issues with outcome measurement	

DOMAIN 5: Bias in selection of the reported result

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: NO major issues on any domain	

Study Details	Wu (2020)[50]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: No concerns	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No data on blinding, but no evidence of deviations	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No information on assessors awareness of intervention, but not likely to influence assessment.	

DOMAIN 5: Bias in selection of the reported result

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No evidence of pre-specified protocol, but outcomes similar to similar studies	

OVERALL RISK OF BIAS	
Rationale for judgement:	

Study Details	Yi (2018)[53]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: No information on allocation concealment, but no baseline differences.	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NI
Risk of bias judgement	**HIGH**
Rationale for judgement: No data on blinding, no information on statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement:	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant issues with outcome measurement	

DOMAIN 5: Bias in selection of the reported result

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: No information on allocation concealment, no data on blinding, no information on statistical analysis	

1.2.3 Results

Table 6 Results details of studies included in Objective 2

Study details					Clopidogrel group		Alternative group		Effect Estimates		
Study	**Ethnicity**	**Comparison**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
Chen (2019)[52]	Asian	Ticagrelor + Aspirin (short-term) vs. Clopidogrel + Aspirin (short-term)	90	Any bleeding	190	30	184	29	1.01	0.01	0.26
				Any stroke	190	22	184	15	0.69	-0.37	0.34
				Composite events	190	24	184	16	0.68	-0.39	0.32
				Haemorrhagic stroke	190	2	184	1	0.52	-0.65	1.21
				Ischaemic stroke	190	20	184	14	0.71	-0.34	0.35
				TIA	190	2	184	1	0.52	-0.65	1.21
				Myocardial infarction[1]	190	1	184	0	0.34	-1.07	1.63
				Vascular death[1]	190	2	184	0	0.21	-1.58	1.55
Han (2017)[47]	Asian	Triflusal vs. Clopidogrel	985	Any stroke	244	14	240	16	1.23	0.21	0.41
				Any bleeding	244	14	240	12	0.97	-0.03	0.39
				Haemorrhagic stroke	244	3	240	2	0.74	-0.30	0.92
				Ischaemic stroke	244	11	240	14	1.37	0.31	0.40
				Myocardial infarction	244	1	240	1	1.11	0.10	1.41
				Mortality	244	3	240	3	1.11	0.10	0.82
				Any stroke	244	14	240	16	1.23	0.21	0.41
Meschia (2020)[48]	Mixed	Aspirin vs. Clopidogrel + Aspirin	90	Mild bleeding[2]	131	2	134	2	1.00	0.00	1.00
				Any stroke[2]	131	3	134	9	3.03	1.11	0.66
				major ischaemic events[2]	131	3	134	9	3.03	1.11	0.66
				Ischaemic stroke[2]	131	3	134	9	3.03	1.11	0.66
Wang (2016a)[51]	Asian	Aspirin vs. Clopidogrel + Aspirin (short-term)	90	Any bleeding[2]	854	20	872	12	0.61	-0.50	0.37
				Mild bleeding[2]	854	8	872	2	0.25	-1.40	0.79
				Severe or Moderate bleeding[1]	854	3	872	0	0.14	-1.97	1.51
				Any stroke[2]	854	80	872	94	1.08	0.07	0.15
				Composite event[2]	854	80	872	95	1.09	0.08	0.15
				Ischaemic stroke[2]	854	78	872	93	1.18	0.16	0.15
Wang (2021)[49]	Asian	Ticagrelor + Aspirin (short-term) vs. Clopidogrel + Aspirin (short-term)	90	Any bleeding	3207	80	3205	170	2.18	0.78	0.14
				Severe or moderate bleeding	3207	11	3205	9	0.82	-0.20	0.45
				Any stroke	3207	243	3205	191	0.77	-0.26	0.10

Study details					Clopidogrel group		Alternative group		Effect Estimates		
Study	**Ethnicity**	**Comparison**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
				vascular event	3207	293	3205	229	0.77	-0.26	0.09
				Ischaemic stroke	3207	238	3205	189	0.78	-0.25	0.10
				Mortality	3207	18	3205	9	0.50	-0.69	0.41
Wu (2020) [50]	Asian	Clopidogrel HD + Aspirin vs. Clopidogrel + Aspirin	90	Any bleeding[1]	69	1	62	0	0.37	-0.99	1.63
				Composite outcome	69	6	62	1	0.18	-1.70	1.08
				Ischaemic stroke[1]	69	3	62	1	0.37	-0.99	1.15
				Vascular death[1]	69	1	62	0	0.37	-0.99	1.63
Yi (2018)[53]	Asian	Aspirin vs. Clopidogrel + Aspirin	1825	Composite outcome[1]	128	29	129	27	0.92	-0.08	0.27

[1] HR estimates calculated using a hazard rate analysis of event frequencies in relation to time at risk.

[2] HR estimates were extracted from the paper and inverted (1/original estimate)

1.3 Objective 3

1.3.1 Baseline Details

Table 7 Baseline details of studies included in Objective 3

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Chen et al. (2019)[52, 180, 181] **Study Name** PRINCE **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** 26 hospitals in China	**Condition** Stroke & TIA **Inclusion Criteria** • ≥ 40 years and <80 years • Acute non-disabling ischemic stroke (NIHSS≤ 3) or TIA with ABCD2 score ≥ 4 treated with study drug within 24 hours of onset **Exclusion Criteria** • Diagnosis of intracranial haemorrhage or other pathology • Symptoms without evidence of acute infarction on head CT or MRI • Modified Rankin Scale Score > 2 • Contraindication to ticagrelor, clopidogrel or aspirin • Indication for anticoagulation • Intravenous/ intra-arterial thrombolysis or mechanical thrombectomy < 24 hours prior to randomization, or likely within 3 months • History of intracranial haemorrhage, cerebral artery amyloidosis or aneurysm • Indication for non-study anti-platelet drugs, or NSAIDs • Previous significant bleeding • Primary event induced by angiography or surgery • Life expectancy < 3 months • Haematocrit (Hct) < 30% **Number of Participants** **Eligible (total study):** 675 **Enrolled (total study):** 675 **Enrolled (our cohort of interest):** 329 **Omeprazole use:** 22.7% **Age** 61.7 (8.5) **Sex - % female** 28.8% **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Dose** 75 mg **Regimen** clopidogrel (loading dose of 300mg followed by 75 mg daily until day 90) combined with aspirin (loading dose of 100-300mg followed by 100 mg once daily until day 21)	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Unknown metabolisers

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Diaz-Villamarin et al. (2018)[54, 196] **Country** Spain **Study Design** Retrospective Cohort **Funding** Not stated **Setting** San Cecilio University Hospital	**Condition** Stroke & TIA **Inclusion Criteria** • >18 years old • Stroke/TIA • Treatment with clopidogrel 75 mg from diagnosis to hospital discharge and at least for a month. **Exclusion Criteria** • Contraindication to clopidogrel. • Indication for anticoagulants • Impossibility to access clinical records during the treatment period **Number of Participants** **Eligible (total study):** 114 **Enrolled (total study):** 67 **Enrolled (our cohort of interest):** 67 **Omeprazole use:** PPI: total: 30/67 (44.78%), *CYP2C19* LOF 10/18 (55.56%), CPY2C19 no LOF: 20 (40.82%) **Age - Mean (SD):** 68.2 (9.8) **Sex - % female** 35.8% **Ethnicities included:** White 100% (Caucasian)	**Antiplatelet** Clopidogrel **Regimen** 75 mg daily	***CYP2C19* test:** TaqMan genotyping assays technology. **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Poor metaboliser if accompanied by a LOF allele, extensive metaboliser if not.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Fu et al. (2020)[55] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • Patients diagnosed with acute ischemic stroke and treated with clopidogrel • ≥18 years • Computed tomography (CT) or magnetic resonance imaging (MRI) evidence of stroke • Baseline (NIHSS) score ≤22. **Exclusion Criteria** • Recent cerebral or gastrointestinal haemorrhage, any bleeding disorder or significant coagulopathy • History of tumours or other terminal medical comorbidities • Allergic or intolerant to clopidogrel • Platelet count <100 x10^12/L or >450x10^12/L. **Number of Participants** **Eligible (total study):** 175 **Enrolled (total study):** 131 **Enrolled (our cohort of interest):** 131 **Omeprazole use:** NR **Age** **Mean (SD):** 61.4 (10.9) **Sex - % female** 21% **Ethnicities included:** Asian: All the patients are Chinese-Han origins	**Antiplatelet** Clopidogrel **Dose** 75 mg **Regimen** Clopidogrel 75mg/d without loading dose	***CYP2C19* test:** (PCR-RFLP) **Alleles tested for:** *1, *2, and *3 **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Fukuma et al. (2022)[56, 197] **Study Name** PRAISE **Country** Japan **Study Design** Prospective Cohort **Funding** Non-industry **Setting** Japan	**Condition** Stroke & TIA **Inclusion Criteria** • Acute ischaemic stroke (IS)/TIA with symptomatic atherosclerotic stenosis (≥ 50%) or occlusion of ipsilateral intracranial or extracranial arteries • < 7 days after onset and treated with clopidogrel • ≥20 years • NIHSS score of 0 to 20 before treatment **Exclusion Criteria** • Modified Rankin Scale score >3 • Cardio-embolic source • Contraindication to MRI scanning • Treatment with ozagrel • Intracranial or severe systemic haemorrhage. **Number of Participants** **Eligible (total study): 230** **Enrolled (total study): 230** **Enrolled (our cohort of interest): 194** **Omeprazole use:** 21.33% (For 230 patients enrolled) **Age Mean (SD)** 72.1 **Sex - % female** 28 **Ethnicities included:** Not reported - likely most patients Asian (Japanese)	**Antiplatelet** Clopidogrel **Dose** Clopidogrel 75 mg **Regimen** • Clopidogrel (i) continued at 75 mg/day standard dose used before admission, (ii) newly administered at 75 mg/day standard dose, or (iii) newly administered at 300 mg loading and followed by 75 mg/day standard dose • With or without other antiplatelet agents (including aspirin at 200 mg/day and cilostazol at 200 mg/day), anticoagulant agents (including argatroban injection)	***CYP2C19* test:** TaqMan **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Excluded from analysis

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Han et al (2017)[47, 182-186] **Study Name** MAESTRO **Country** South Korea **Study Design** Prospective Cohort **Funding** Industry - test manufacturer **Setting** 18 tertiary-care hospitals in South Korea	**Condition** Stroke **Inclusion Criteria** • Non-cardiogenic ischemic stroke of TOAST classification <30 days prior to screening • ≥ 20 years of age • Written informed consent **Exclusion Criteria** • History of bleeding tendency or recent major bleeding within 2 weeks • Chronic liver disease or renal dysfunction • Thrombocytopenia • Contraindication of antiplatelet agent • Severe congestive heart failure • Need to take anticoagulants or >= antiplatelet agents • Severe concomitant disease with expected survival < 2 years **Number of Participants** **Eligible (total study): 795** **Enrolled (total study): 795** **Enrolled (our cohort of interest): 393** **Omeprazole use:** Proton pump inhibitor use was prohibited **Age - Mean (SD):** 61 **Sex - % female:** 32 **Ethnicities included:** Not reported - likely most patients Asian (South Korean)	**Antiplatelet** Clopidogrel **Regimen** 75 mg clopidogrel once daily	***CYP2C19* test:** Seeplex *CYP2C19* ACE genotyping system and Real-Q *CYP2C19* genotyping kit **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele (including *17) **How were 17* alleles handled?** Intermediate metaboliser if accompanied by a LOF allele, extensive metaboliser if not.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Hoh et al. (2016)[57] **Country** US **Study Design** Retrospective Cohort **Funding** Non-industry **Setting** 3 US centres	**Condition** Stroke & TIA **Inclusion Criteria** • ≥18 years • Stroke or transient ischemic attack (TIA) attributable to 50% or greater stenosis of a major intracranial artery • Treatment with aspirin and clopidogrel for ≥3 months. **Exclusion Criteria** • Patients with moyamoya disease **Number of Participants** **Eligible (total study): NR** **Enrolled (total study): 188** **Enrolled (our cohort of interest): 188** **Omeprazole use:** 58% **Age** Mean (SD): 67 (NR) **Sex - % female** 36.7 **Ethnicities included:** Mixed: White: 84.6%, Black: 12.8%, Other: 2.7%	**Antiplatelet** Clopidogrel + aspirin **Regimen** NR	***CYP2C19* test:** Sequenom (Qiagen) and TaqMan Assay **Alleles tested for:** *1, *2, *3, *8 and *17 **Poor metaboliser definition:** 2 copies of LOF alleles **Intermediate metaboliser definition:** One copy of LOF allele **How were 17* alleles handled?** NR

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Lin et al. (2021)[58] **Country** China **Study Design** Retrospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • Clinical diagnosis of IS confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) • ≥18 years • Clopidogrel for 5 days or longer **Exclusion Criteria** • Recurrence or sequelae of stroke • Clopidogrel contraindicated • Platelet count >450×109/L or <150×109/L • Other anticoagulation drugs Recent history of active bleeding • Severe kidney or liver diseases • Major surgery within 1 month of the study. **Number of Participants** **Eligible (total study): 122** **Enrolled (total study): 122** **Enrolled (our cohort of interest): 89** **Omeprazole use:** 20.22 **Age - Mean (SD)** Only reported by study arm: non-carriers of LOF 65.1 (14.1), carriers of LoF 65.1 (12.3) **Sex - % female** Only reported by study arm: non-carriers 39.5%, carriers 53.3% **Ethnicities included:** Asian: Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** NR **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Liu et al. (2020)[59] **Country** China **Study Design** Prospective Cohort **Funding** Not stated **Setting** First Affiliated Hospital of Shantou University Medical College, China	**Condition** Stroke **Inclusion Criteria** • Acute IS confirmed by computed tomography or magnetic resonance imaging within 1 week of onset. • Patient suitable for clopidogrel treatment. **Exclusion Criteria** • Clotting or other blood disorders. • Serious heart, liver, and kidney diseases • Patients received proton pump inhibitors. • IS caused by cardio embolism. **Number of Participants** **Eligible (total study):** 289 **Enrolled (total study):** 289 **Enrolled (our cohort of interest):** 289 **Omeprazole use:** Patients receiving PPI excluded **Age - Mean (SD)** 66.6 (10.90) **Sex - % female** 41.9 **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Regimen** 75mg clopidogrel after the onset of symptoms daily.	***CYP2C19* test:** *CYP2C19* genotyping kit **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Lv et al. (2022)[60, 198] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • ≥35 years • Acute ischemic stroke within 14 days, diagnosed by computer tomography (CT) or magnetic resonance imaging (MRI) • Informed consent **Exclusion Criteria** • cardiogenic cerebral embolism. • Ischemic stroke caused by other causes. • Under dual antiplatelet therapy • Allergy or contraindication to clopidogrel or aspirin • Active bleeding or bleeding tendency. • Severe liver or renal failure • Usage of *CYP2C19* inhibitors, NSAIDS, anticoagulants, and other antiplatelet drugs **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 485 **Enrolled (our cohort of interest):** 314 **Omeprazole use:** patients taking PPI excluded **Age Mean (SD)** NR **Sex - % female:** NR **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Regimen** 75 mg daily	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled:** those with two GoF alleles (*17) or one functional allele (*1) and one GoF allele (*17) were classified as ultrarapid metabolizers

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) McDonough et al. (2015)[61, 199] **Study Name** SPS3 study **Country** International **Study Design** Prospective Cohort **Funding** Non-industry	**Condition** Stroke & TIA **Inclusion Criteria** • ≥30 years-old • Small subcortical ischemic stroke or subcortical TIA. • Lacunar stroke clinical syndrome lasting > 24 hrs within the past 6 months • Absence of signs or symptoms of cortical dysfunction. • No ipsilateral cervical carotid stenosis (≥50%) • No major-risk cardioembolic sources requiring anticoagulation or other specific therapy. **Exclusion Criteria** • Modified Rankin Scale ≤4 • Previous intracranial haemorrhage (excluding traumatic) or haemorrhagic stroke • High risk of bleeding • Prior cortical stroke or prior cortical or retinal TIA • Prior ipsilateral carotid endarterectomy • eGFR <40 • Intolerance or contraindications to aspirin or clopidogrel. • Folstein Mini Mental Status Examination < 24 **Number of Participants** **Eligible (total study): NR** **Enrolled (total study): 3020** **Enrolled (our cohort of interest): 522** **Omeprazole use:** No data **Age – Mean (SD) :** 62.5 (10.5) **Sex - % female:** 28% **Ethnicities included:** Mixed: Hispanic (244/46.7%), white (176/33.71%), and black (73/13.98%), NR: 29/5.6%	**Antiplatelet** Clopidogrel + aspirin **Regimen** 325 mg aspirin plus 75 mg clopidogrel daily	***CYP2C19* test:** TaqMan assays **Alleles tested for:** *1 and *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Meschia et al (2020)[48] **Study Name** POINT Trial **Country** US **Study Design** Prospective Cohort **Funding** Non-industry **Setting** International	**Condition** Stroke & TIA **Inclusion Criteria** • Neurologic deficit attributed to focal brain ischemia and EITHER: - High-risk TIA: Complete resolution of the deficit prior to randomization AND ABCD2 score >4, OR - Minor ischemic stroke: residual deficit with NIHSS <3 • Ability to randomize within 12 hours of symptom onset. • Head CT or MRI ruling out haemorrhage or other pathology **Exclusion Criteria** • Age <18 years • Candidate for intravenous or intra-arterial thrombolysis, or done within 1 week prior to index event. • Gastrointestinal bleed or major surgery < 3 months • History of nontraumatic intracranial haemorrhage. • Internal carotid artery stenosis >50%. • Indication for anticoagulation. • Primary event induced by angiography or surgery. • Life expectancy <3 months. • Contraindication to clopidogrel or aspirin. • Indication for non-study antiplatelet drugs or NSAIDs affecting platelet function. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** NR **Enrolled (our cohort of interest):** 457 **Omeprazole use:** Proton pump inhibitors will be switched when possible and new prescriptions will be avoided. **Age - Mean (SD):** only reported by study arm and as median (IQR): LOF carriers: 61 (51-71), Non-carriers: 64 (54-72) **Sex - % female:** Reported by study arm: LOF carriers: 34.3, non-carriers: 42.9 **Ethnicities included:** White: 175 (66.7%), black: 65 (24.5%), other: 25 (9.4%)	**Antiplatelet** Clopidogrel **Dose** 75 mg **Regimen** Clopidogrel at a loading dose of 600 mg on day 1, followed by **75 mg per day**, plus aspirin at a dose of 50 to 325 mg per day	***CYP2C19* test:** Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Unknown

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Ni et al.(2017)[62] **Study Name** Nanjing Stroke Registry Program **Country** China **Study Design** Prospective Cohort **Funding** Not stated **Setting** Nanjing Stroke Registry Program (NSRP) Feb 2012 to Feb 2014	**Condition** Stroke **Inclusion Criteria** • Clinical diagnosis of acute cerebral infarction within 7 days after stroke onset - ≥ 35 years or older • Head magnetic resonance imaging or computerized tomography scan • Chinese Han ethnicity • Treated with clopidogrel at enrolment. **Exclusion Criteria** • Thienopyridine or glycoprotein IIb/IIIa inhibitor within one week • Allergy to clopidogrel • Atrial fibrillation • Oral anticoagulation therapy • NIHSS) score was > 15 • Serious kidney or liver disorders - Increased risk of bleeding • Major bleeding or intracranial haemorrhage within 3 months • Autoimmune disease • Platelet count < 100×109/L or > 500×109/L • Haemorrhage transformation after cerebral infarction. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 191 **Enrolled (our cohort of interest):** 191 **Omeprazole use:** 5.2% using PPI **Age mean (SD)** 61.5 (10.5) **Sex - % female:** 33% **Ethnicities included:** Asian: Chinese Han ethnicity	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** improved Multiple Ligase Detection Reaction (iMIDR) **Alleles tested for:** NR **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Unknown

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Patel et al. (2021)[63] **Country** US **Study Design** Retrospective Cohort **Funding** Mixed **Setting** US	**Condition** TIA **Inclusion Criteria** • ICAD diagnostic code • *CYP2C19* genotyping data available. • Clopidogrel exposure (two separate mentions of clopidogrel as identified by MedEx natural language processing software) • Established prior patient care (at least one visit between 1 year and 1 month prior to study start). **Exclusion Criteria** • Acute ischemic stroke up to 2 weeks following study start • Previous diagnosis of intracranial aneurysm or arteriovenous malformation. • Last mention of clopidogrel occurring < 1 month after study start. **Number of Participants** **Eligible (total study):** 337 **Enrolled (total study):** 337 **Enrolled (our cohort of interest):** 161 **Omeprazole use:** NR **Age - Mean (IQR)** 70 (61.0,77.0) **Sex - % female** 29.1 **Ethnicities included:** Mixed: White: 89.4%, African American 10.6%	**Antiplatelet** Clopidogrel **Regimen** Patients undergoing dual antiplatelet therapy were not excluded. Dosing of medications was performed by the treating physician and was not standardized or mandated.	***CYP2C19* test:** TaqMan and Illumina BeadExpress microarrays, or the Infinium Expanded Multi-Ethnic Genotyping Array. **Alleles tested for:** *1, *2, *3, *4, *5, *6, *7, *8. and *17 **Poor metaboliser definition:** At least one LoF allele (*2, *3, *4, *5, *6, *7, or *8). **Intermediate metaboliser definition:** No intermediate **How were 17* alleles handled?** GoF were *1/*17 or *17/*17. Lof allele/*17 not defined.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Qiu et al. (2015)[64] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** Second Hospital of Tianjin Medical University	**Condition** Stroke **Inclusion Criteria** • Patients admitted to hospital within a week after symptoms onset, diagnosed as acute ischemic stroke by a neurologist **Exclusion Criteria** • Treatment with anticoagulants, thrombolytic agents and other antiplatelet drugs within 2 weeks. • Cranial bleeding or active haemorrhage. • Trauma, surgery, deep vein or arterial thrombosis within the preceding 3 months • Severe hepatic or renal dysfunction • Malignant diseases • Chronic inflammatory diseases • Infectious conditions at study entry. **Number of Participants** **Eligible (total study):** 211 **Enrolled (total study):** 211 **Enrolled (our cohort of interest):** 211 **Omeprazole use:** Usage of PPI: Noncarriers 29/82 (35.4%), carriers 56/129 (44.1%) **Age Mean (SD)** Reported only by study arm: non-carriers 67.4 (13.6), carriers: 66.7 (11.5) **Sex - % female** Reported only by study arm: non-carriers 41.5 carriers: 47.3 **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Regimen** patients enrolled were given clopidogrel (75 mg once daily)	***CYP2C19* test:** Cwbiotech **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Sen et al. (2014)[65] **Country** Turkey **Study Design** Prospective Cohort **Funding** Not stated **Setting** Neurology Outpatient Clinic at Çanakkale Onsekiz Mart Üniversity Research Hospital, Çanakkale, Turkey.	**Condition** Stroke **Inclusion Criteria** • Patients who started clopidogrel 75 mg/day as a result of acute ICVD in the previous 2 years, and who were monitored for at least 1 year. **Exclusion Criteria** • Patients who stopped attending the clinic, or who did not take their medication regularly. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 51 **Enrolled (our cohort of interest):** 51 **Omeprazole use:** NR **Age Mean (SD)** 66.4 (9.6) **Sex - % female** 58.83 **Ethnicities included:** NR	**Antiplatelet** Clopidogrel **Regimen** Clopidogrel 75 mg daily	***CYP2C19* test:** Lightmix **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Spokoyny et al. (2014)[66, 200] **Country** US **Study Design** Retrospective Cohort **Funding** Not stated **Setting** US	**Condition** TIA & Stroke **Inclusion Criteria** Patients tested for the clopidogrel *CYP2C19* genotype between April 2010 and February 2012, and had suffered at least 1 stroke or TIA. **Exclusion Criteria** NR **Number of Participants** **Eligible (total study):** 53 **Enrolled (total study):** 53 **Enrolled (our cohort of interest):** 43 **Omeprazole use:** There were 9 patients concurrently taking a PPI and Clopidogrel. **Age Mean (SD)** 69.6 (NR) **Sex - % female** 46.6 **Ethnicities included:** Mixed: White: 70%, Middle eastern: 2%, Asian 11%, Hispanic 7%, African American 4%, Filipino 4%, Indian: 2% [this is for full population of 53 people]	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** NR **Alleles tested for:** NR **Poor metaboliser definition:** NR **How were 17* alleles handled?** NR

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Sun et al. (2015)[67] **Study Name** Nanjing Stroke Registry Program (NSRP) - May 2008 to April 2010 **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • First-ever ischemic stroke evaluated by a neurologist < 7 days from stroke onset. • Computerized tomography (CT) or magnetic resonance imaging (MRI) scan. • Chinese Han ethnicity. • ≥18 years. • Treated with clopidogrel at time of enrolment. **Exclusion Criteria** • Hemodynamic instability • Oral anticoagulation therapy • Antiplatelets other than clopidogrel • Contraindications to clopidogrel treatment • Atrial fibrillation, malignancies, severe kidney, liver, or heart diseases. • Platelet count < 80x10^9 l^-1; • Active bleeding or bleeding diathesis • Intracranial haemorrhage < 3 months. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 625 **Enrolled (our cohort of interest):** 625 **Omeprazole use:** PPIs avoided when possible. If a PPI was warranted, pantoprazole was prescribed. **Age Mean (SD):** 61.6 (12.2) **Sex - % female:** 25.6 **Ethnicities included:** Asian: Cohort of Chinese patients	**Antiplatelet** Clopidogrel The patients were given a standard clopidogrel dose of 75 mg daily.	***CYP2C19* test:** Improved Multiple Ligase Detection Reaction (iMLDR) **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Unknown

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Tanaka et al. (2019)[68, 201] **Country** Japan **Study Design** Prospective Cohort **Funding** NR **Setting** Stroke institutions, Japan	**Condition** Stroke & TIA **Inclusion Criteria** • ≥20 years or older. • Ischemic stroke or transient ischemic attack (TIA) (excluding cardiogenic embolism) in the 3 years prior but not in the past month. • Long-term clopidogrel therapy (75 mg once a day) for secondary prevention of stroke (for at least 1 month). **Exclusion Criteria** • Malignancies • Congenital bleeding tendency • Atrial fibrillation • Use of anticoagulant agent • Platelet count <100×10^9/L or >450×10^9/L within 3 months of enrolment • Modified Rankin Score >4. **Number of Participants** **Eligible (total study):** 518 **Enrolled (total study):** 518 **Enrolled (our cohort of interest):** 501 **Omeprazole use:** 99 (19.8%) **Age Mean (SD):** 68 (61-74) **Sex - % female** 27.3% **Ethnicities included:** Asian: 100% Japanese	**Antiplatelet** Clopidogrel **Regimen** 75 mg once a day	***CYP2C19* test:** TaqMan **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Excluded

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Tomak et al (2018)[69] **Country** Czech Republic **Study Design** Retrospective Cohort **Funding** Not stated **Setting** Stroke center, Czech Republic	**Condition** Stroke **Inclusion Criteria** • Clopidogrel monotherapy after recent non-cardioembolic ischemic stroke. • Availability of complete clinical and laboratory dataset. • ≥18 years • Czech origin **Exclusion Criteria** • Homozygotes *CYP2C19**2/*2 were excluded. **Number of Participants** **Eligible (total study):** 130 **Enrolled (total study):** 130 **Enrolled (our cohort of interest):** 130 **Omeprazole use:** Used by 20.8% of patients **Age Mean (SD):** 64.5 (13.81) **Sex - % female** 40% **Ethnicities included:** White: (100% Czech)	**Antiplatelet** Clopidogrel **Regimen** 75 mg daily	***CYP2C19* test:** LightScanner system **Alleles tested for:** *1, *2, and *17 **Poor metaboliser definition:** *1/*2 **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** *2/*17 analysed on the LOF carrier group

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Tornio et al. (2018)[70, 202, 207] **Study Name** GoDARTS **Country** Scotland **Study Design** Retrospective Cohort **Funding** Non-industry **Setting** GoDARTS bioresource	**Condition** Stroke **Inclusion Criteria** Individuals in GoDARTS, genotyped for *CYP2C19**2 polymorphism and who had also redeemed at least one prescription for clopidogrel up to 21 days following hospitalization for arterial thrombo-occlusive events **Exclusion Criteria** NR **Number of Participants** **Eligible (total study):** 651 **Enrolled (total study):** 651 **Enrolled (our cohort of interest):** 94 **Omeprazole use:** NR **Age Mean (SD)** 74 **Sex - % female** 38% **Ethnicities included:** White: Ethnicity not reported but implies mostly Caucasian	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** NR **Alleles tested for:** *1 and *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Wang et al. (2016a)[51, 73, 191-194] **Study Name** CHANCE **Country** China **Study Design** Prospective cohort **Funding** Non-industry **Setting** 73 among 114 sites from CHANCE (China)	**Condition** Stroke & TIA **Inclusion Criteria** • ≥ 40 years • Acute non-disabling ischemic stroke (NIHSS≤3) or TIA with ABCD2 score ≥ 4, treated with study drug < 24 hours after onset. **Exclusion Criteria** • Diagnosis of haemorrhage or other pathology. • Symptoms without evidence of acute infarction on baseline head CT or MRI. • Modified Rankin Scale Score > 2 • Indication for anticoagulation • Contraindication to clopidogrel or ASA • History of intracranial haemorrhage • Indication for long-term non-study antiplatelet drugs, or NSAIDs affecting platelet function • Gastrointestinal bleed or major surgery <3 months • Planned or likely revascularization within the next 3 month • Primary event induced by angiography or surgery • Life expectancy < 3 months. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 3010 **Enrolled (our cohort of interest):** 1463 **Omeprazole use:** Proton pump inhibitors will be switched when possible and new prescriptions will be avoided. (10 patients within the carrier group and 10 within the non carrier group (20 out of 2933)) **Age Mean (SD):** Carrier 62.2 (54.4-71.2), non-carrier: 63.1 (55.5-71.5) **Sex - % female:** Reported by study arm: Carrier 31.4, non-carrier: 34.8 **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Regimen** *Day 1*: four tablets of clopidogrel 75 mg and open label ASA (75 mg -300 mg) *From D2 to D21±2 days*: one tablet of clopidogrel 75mg and one tablet of ASA 75 mg per day *From D22±2 days visit to D90±7 days*: one tablet of clopidogrel 75mg and one tablet of placebo ASA 75 mg per day	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform (Sequenom). **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** At least 1 LOF allele **How were 17* alleles handled?** (*2/*17 or *3/*17) were classified as unknown metabolizers.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Wang et al. (2016b)[71] **Study Name** Nanjing Stroke Registry Program (NSRP) – April 2009 – March 2011 **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • Patients with ischemic stroke registered in Nanjing Stroke Registry Program (NSRP) between April 2009 and March 2011, confirmed by computer tomography or magnetic resonance imaging • ≥18 years • Treated with clopidogrel ≥3 months **Exclusion Criteria** • Other oral anticoagulation drugs. • Moyamoya diseases • Severe kidney or liver diseases. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 321 **Enrolled (our cohort of interest): 321** **Omeprazole use:** PPI: 10 (5.2%) **Age categories included** Only reported by study arm: non-carriers of LOF 62 (53-69), carriers of LOF: 62 (53-70) **Sex - % female** Only reported by study arm: non-carriers of LOF: 20.3%, carriers of LOF: 28.8% **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** improved Multiple Ligase Detection Reaction (iMIDR) **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Yi et al.(2018)[53] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • ≥18 years • Diagnosis of ischemic stroke by cranial computed tomography and magnetic resonance imaging scanning. • Cause of stroke: large-artery atherosclerosis • No carotid endarterectomy or carotid stent therapy at enrolment and during the 30 days of treatment **Exclusion Criteria** • Coma or NIHSS score ≥ 13 • Clinically relevant arrhythmia on admission • Major concurrent illness including renal failure and malignancies - Any relevant hemodynamic compromise on admission • Use of ticlopidine, dipyridamole, other nonsteroidal anti-inflammatory drugs, or other aspirin-containing drugs previously or at the time of the index stroke • Administration of heparin or low-molecular-weight heparin within 24 hours before their enrolment in the study • Major surgical procedure within 1 week before enrolment • Increased risk of bleeding **Number of Participants** **Eligible (total study):** 570 **Enrolled (total study):** 570 **Enrolled (our cohort of interest):** 284 **Omeprazole use:** NR **Age Mean (SD):** 69.2 (10.1) **Sex - % female:** 45.1% **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel + aspirin **Regimen** aspirin plus clopidogrel (200 mg aspirin and 75 mg clopidogrel for 30 days, and 75 mg/d clopidogrel thereafter.	***CYP2C19* test:** NR **Alleles tested for:** *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Yi et al. (2017)[72] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • ≥ 40 years of age • IS-related atherothrombotic or small artery disease. • Not taking clopidogrel for at least 7 days before admission • NIHSS score <15. **Exclusion Criteria** • Allergy to clopidogrel • Cardiac cerebral embolism or any other determined or undetermined aetiology • Thrombolytic or anticoagulation therapy with warfarin or heparin within 7 days • Patients who received a proton pump inhibitor before or during hospital admission • Haemorrhagic stroke • Haematological, autoimmune, or other severe concomitant diseases • Platelet count < 1 x 10^11/L or > 4.5 x 10^11/L. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 375 **Enrolled (our cohort of interest):** 375 **Omeprazole use:** Proton pump inhibitors usage is exclusion criteria **Age Mean (SD)** Reported by study arm: clopidogrel resistant: 69.97 (11.23), clopidogrel sensitive: 67.04 (12.16) **Sex - % female** Reported by study arm: clopidogrel resistant: 35.14, clopidogrel sensitive: 35.58 **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel + aspirin **Dose** 75 mg **Regimen** 75 mg clopidogrel once daily or clopidogrel (75 mg, once daily) plus aspirin (200 mg, once daily), for the initial 2 weeks, followed by treatment with clopidogrel alone (75 mg, once daily) for at least 6 months.	***CYP2C19* test:** Mass ARRAY RT software **Alleles tested for:** *1 and *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not measured

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Zhang et al. (2017)[73] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke % TIA **Inclusion Criteria** • High risk acute TIA or acute minor stroke (ABCD2 score ≥ 4 or NIHSS score ≤ 3) • Diagnosis confirmed by CT and MRI. • ≥ 40 years • Able to receive treatment ≤ 24 hours after the onset of event. **Exclusion Criteria** • Haemorrhage or other major non-ischemic brain disease • Fever, hypoxia, unconsciousness, or hemodynamic disorder at admission • Modified Rankin scale >2 • Drugs within 1 week of the stroke that would affect platelet aggregation function • Platelet count > 450 × 10^9/L or < 100 × 10^9/L • Severe liver or renal insufficiency, tumours, or disease of the immune or respiratory systems • Gastrointestinal bleeding, severe trauma, or surgery within three months of the stroke. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 417 **Enrolled (our cohort of interest):** 417 **Omeprazole use:** 0.6% **Age Mean (SD)** Reported by study arm: LOF carriers: 64.31 (8.87), non-carriers: 63.18 (9.63). **Sex - % female** Reported by study arm: LOF carriers: 40.9, non-carriers: 35.5 **Ethnicities included:** Not reported - likely most patients Asian (Chinese)	**Antiplatelet** Clopidogrel **Regimen** Loading dose of 300 mg of clopidogrel on day 1, followed by 75 mg of clopidogrel per day for 6 months, plus 100 mg of aspirin per day for the first 21 days).	***CYP2C19* test:** Perkin Elmer Gene Amp PCR Systems 9600, **Alleles tested for:** *1, *2, *3 and *17 **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** included

*Number of participants randomised to our cohort of interest = everyone genotyped and receiving clopidogrel alone or in combination with another antiplatelet
Age/sex/ ethnicity is extracted for our cohort of interest (as above)

1.3.2 Risk of bias assessment

Table 8 Risk of bias assessment of studies included in Objective 3

Review Level considerations	
List potential confounders	Ethnicity

Study Details	Chen et al. (2019)[52]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions	N

about whether the exposure has an important effect on the outcome?	

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	PN
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Objective and well-defined outcomes, no information on outcome assessors' awareness of study participants' *CYP2C19* status, they do mention platelet data blinded, so likely included there	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA

7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Results come from a RCT with a pre-specified analysis plan	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure, so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Diaz-Villamarin et al. (2018)[54]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N

4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Objective and well-defined outcomes, no information on outcome assessors' awareness of study participants' *CYP2C19* status, they do mention platelet data blinded, so likely included there	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	N
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N

7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No information on pre-specified protocol but definitions of exposures and outcomes similar to similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure, so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Fu et al. (2020)[55]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: outcomes assessed by phone call or clinical visits, which could be open to bias, however the outcome definitions are objective	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**

Rationale for judgement: No information on pre-specified protocol but this is a secondary outcome that was not "statistically significant", so not likely to have been selected based on desirability	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Fukuma et al. (2022)[56]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)

2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	N
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA

5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Objective outcome - exposure blinded to outcome assessors	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	PY
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: The paper mentions an approved protocol, but it's not available. Primary outcome is secondary stroke, and it's the only reported one considering different exposures.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Han et al (2017)[47]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	N
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Y

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**

Rationale for judgement: registered trial with pre-published protocol	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Hoh et al. (2016)[57]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	PY
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Estimates adjusted for race, which is likely to be measured accurately	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (stroke, death, MI, TIA) are likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	*N*

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN

Risk of bias judgement	**LOW**
Rationale for judgement: Paper mentions study approval by institutional reviews, so likely it had a pre-specified protocol, but it's not available. Results against the study hypothesis, and primary outcome clearly defined, so it's likely it wasn't selected	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Lin et al. (2021)[58]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**Some concerns**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**

Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: NO information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (stroke, death, MI, TIA) are likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on specified protocol, but results not likely to be selected	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Liu et al. (2020)[59]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N

4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (stroke, death, MI, TIA) are likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN

Risk of bias judgement	**LOW**
Rationale for judgement: No information on specified protocol, but results not likely to be selected	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Lv et al. (2022)[60]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions

4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	N
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	SY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**VERY HIGH**
Rationale for judgement: from 345 eligible patients, 314 were genotyped and included in the analysis. From the 345, authors report follow-up up for 54 months for a total of 270 patients (no data on how many genotyped patients).	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN

7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No mention or a pre-specified protocol and analysis plan, but selected result it's very typical primary outcome for similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**VERY HIGH**
Rationale for judgement: Outcome data not available for a significant proportion of the population, missing data likely related with the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	McDonough et al. (2015)[61]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	PY
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors controlled for ethnicity on overall result and stratified by ethnicity too	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	PN
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	NI
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	WY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: No data on loss to follow-up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: "All primary events, the primary safety outcome, and most secondary outcomes were adjudicated by a blinded events-adjudication committee"	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	PY
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: This is a sub analysis of a pre-registered clinical trial, protocol not available. Exposure definitions and primary and secondary outcomes as in similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: NO data on loss to follow-up, potential missing data likely related to outcome. Lifetime exposure so follow-up does not begin at the start of the exposure window	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Meschia et al (2020)[48]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with an homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	N
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**

Rationale for judgement: registered trial with pre-published protocol	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Ni et al.(2017)[62]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Chinese Han patients only.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	NI
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	WY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: No data on loss to follow up. Potential missing data likely to be related with the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Assessors were blinded to genotype	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: a study protocol is mentioned but not available -Exposure definitions and primary and secondary outcomes as in similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: No data on loss to follow up. Potential missing data likely to be related with the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Patel et al. (2021)[63]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a mostly Caucasian population	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	PN
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: outcome assessment by clinical records, based on diagnostic codes	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: No mention of pre-specified protocol. Exposure definitions and primary and secondary outcomes as in similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Qiu et al. (2015)[64]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Chinese Han patients only	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no reported loss of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	Y
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Data collection and follow-up were completed by another independent group and were unaware of the genotypic and platelet function information.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: No info on predetermined analysis plan, but this was not reported as primary outcome, exposure and outcomes similar to other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Sen et al. (2014)[65]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	NI
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NI
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NI
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: population likely not ethnically homogeneous, no info on ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	PN
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (are likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN

Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes similar to other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: population likely not ethnically homogeneous, no info on ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Spokoyny et al. (2014)[66]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	SN
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: ethnicity is a common cause of CYP219 variations and recurrent events - mixed population, results probably not adjusted by ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	PY
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN

Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: ethnicity is a common cause of CYP219 variations and recurrent events - mixed population, results probably not adjusted by ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Sun et al. (2015)[67]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	PY
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Chinese Han patients only	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no reported loss of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: NO information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN

Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Tanaka et al. (2019)[68]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Japanese patients only	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions

4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no reported loss of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	PN
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: outcome assessors not aware of exposure	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN

7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Registered and pre specified protocol. Primary outcome definitions like other studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Tomak et al (2018)[69]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Outcomes assessed separately.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: NO info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Tornio et al. (2018)[70]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PY
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PY
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	PN
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	SN
Risk of bias judgement	**HIGH**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is dependent on hospitalization for arterial thrombo-occlusive events and redemption of at least one prescription for clopidogrel up to 21 days following hospitalization.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**

Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Study done on patients on GoDarts cohort by medical record linkage - potential for missing data, but ATO events likely to be accurately reflected on clinical records	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is dependent on hospitalization for arterial thrombo-occlusive events and redemption of at least one prescription for clopidogrel up to 21 days following hospitalization.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Wang et al.(2016a)[51]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	N
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA

7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: registered trial with pre-published protocol	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Wang et al. (2016b)[71]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	N
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	SY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NI
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	PN
Risk of bias judgement	**HIGH**
Rationale for judgement: loss of follow: 14/321 patients, likely associated with outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: The adjudication of these events was blinded to genotype data.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: Significant loss to follow-up, likely associated with outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Yi et al.(2018)[53]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Among the 284 patients, 7 patients in the clopidogrel group were lost to follow-up, 12 patients (2.1%) discontinued the study medication before the end of the study, 5 patients underwent carotid stent therapy during the follow-up period.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype was blinded to outcome assessors.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	PY
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN

Risk of bias judgement	**LOW**
Rationale for judgement: The paper mentions a preapproved study protocol but it's not available, however exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Yi et al. (2017)[72]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	N
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: out of 375 patients, 363 (96.8%) completed 6 months of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN

Risk of bias judgement	**LOW**
Rationale for judgement: The paper mentions a pre-approved protocol, but it's not available. However, outcomes similar to similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: *Rationale for judgement:* Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Zhang et al. (2017)[73]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no mention of loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: No mention of pre-specified protocol, outcomes like similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

1.3.3 Results

Table 9 Results details of studies included in Objective 3

Study details							Loss of function carriers		Loss of function non-carriers		Effect measure		
Study	**Drug regimen**	**Alleles**	**Event**	**Ethnicity**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
Chen (2019)[52]	Clopidogrel + Aspirin (short-term)	*2, *3	Stroke - TIA	Asian	90	Any bleeding[1]	190	30	139	18	1.22	0.20	0.29
						Any stroke[1]	190	22	139	8	2.01	0.70	0.41
						Composite outcome[1]	190	24	139	8	2.19	0.79	0.41
						Haemorrhagic stroke[1]	190	2	140	1	3.66	1.30	1.55
						Ischaemic stroke[1]	190	20	139	8	1.82	0.60	0.42
						Mortality[1]	190	2	140	1	3.66	1.30	1.55
						Myocardial infarction[1]	190	1	140	1	2.20	0.79	1.63
						Severe bleeding[1]	190	3	139	1	2.19	0.79	1.15
						Vascular death[1]	190	2	140	1	3.66	1.30	1.55
Diaz-Villamarin (2018)[54]	Clopidogrel	*2, *3	Stroke - TIA	White	90	Composite outcome	18	7	49	7	3.01	1.10	0.56
Fu (2020)[55]	Clopidogrel	*2, *3	Stroke	Asian	180	Composite outcome	53	8	78	9	1.24	0.22	0.50
Fukuma (2017)[56]	Clopidogrel +/-other antiplatelet agents	*2, *3	Stroke - TIA	Asian	90	Ischaemic stroke[1]	139	25	55	6	1.65	0.50	0.45
Han (2017)[47]	Clopidogrel	*2, *3	Stroke	Asian	985.5	Any bleeding[2]	244	14	149	13	0.60	-0.51	0.39
						Any stroke[1]	244	14	149	6	1.42	0.35	0.49
						Composite outcome[2]	244	15	149	6	1.56	0.45	0.48
						Haemorrhagic stroke[2]	244	3	149	2	0.94	-0.06	0.91
						Ischaemic stroke[2]	244	11	149	4	1.69	0.53	0.58
						Myocardial infarction[1]	244	1	150	1	1.83	0.61	1.63
Hoh (2016)[57]	Clopidogrel + Aspirin	*2, *3, plus others	Stroke - TIA	Mixed	365	Composite outcome	51	0	138	1	0.27	-1.31	0.63
Lin (2021)[58]	Clopidogrel	*2, *3	Stroke	Asian	365	Any bleeding[1]	51	1	39	1	2.24	0.81	1.63
						Ischaemic stroke[1]	51	13	38	2	4.84	1.58	0.76
Liu (2020)[59]	Clopidogrel	*2, *3	Stroke	Asian	180	Ischaemic stroke[1]	159	31	130	10	2.53	0.932	0.36
Lv (2022)[60]	Clopidogrel	*2, *3	Stroke	Asian	1620	Composite outcome	187	79	127	16	2.05	0.72	0.23
McDonough	Clopidogrel +	*2	Stroke	Mixed	1241	Any stroke[1]	107	9	386	17	1.91	0.65	0.41

Study details							Loss of function carriers		Loss of function non-carriers		Effect measure		
Study	**Drug regimen**	**Alleles**	**Event**	**Ethnicity**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
(2015)[61]	Aspirin	*2	- TIA			Severe bleeding[1]	107	4	386	19	0.76	-0.27	0.55
Meschia (2020)[48]	Clopidogrel + Aspirin	*2, *3	Stroke - TIA	Mixed	90	Any stroke[1]	131	3	326	12	0.62	-0.47	0.64
						Composite outcome[1]	131	3	326	12	0.62	-0.47	0.64
						Ischaemic stroke[1]	131	3	326	11	0.68	-0.39	0.65
						Mild bleeding[1]	131	2	326	6	0.83	-0.19	0.82
						Severe bleeding[1]	131	0	327	5	0.28	-1.29	1.49
Ni (2017)[62]	Clopidogrel	*2, *3	Stroke	Asian	NR	Composite outcome	114	21	77	5	2.90	1.06	0.50
Patel (2021)[63]	Clopidogrel	*2, *3, plus others	TIA	White	NR	Ischaemic stroke	NR	NR	NR	NR	NR	3.40	1.22
Qiu (2015)[64]	Clopidogrel	*2, *3	Stroke	Asian	180	Composite outcome[1]	129	12	82	3	2.54	0.93	0.64
Sen (2014)[65]	Clopidogrel	*2, *3	Stroke	Mixed	NR	Ischaemic stroke[3]	15	3	37	1	18.55	2.92	1.51
Spokoyny (2014)[66]	Clopidogrel		Stroke - TIA	Mixed	NR	Ischaemic stroke[3]	15	6	27	3	4.34	1.47	0.71
Sun (2015)[67]	Clopidogrel	*2, *3	Stroke	Asian	381	Any bleeding	377	8	248	5	1.26	0.23	0.59
						Composite outcome	377	65	248	20	2.31	0.84	0.26
						Myocardial infarction	377	3	248	4	0.57	-0.56	0.84
						Vascular death	377	11	248	2	5.53	1.71	0.80
Tanaka (2019)[68]	Clopidogrel	*2, *3	Stroke - TIA	Asian	720	Composite outcome[1]	319	18	182	10	1.03	0.03	0.39
						Ischaemic stroke[1]	319	12	182	5	1.37	0.31	0.53
						Myocardial infarction[1]	319	1	182	1	0.57	-0.56	1.41
						Severe bleeding[1]	319	3	182	1	1.71	0.54	1.15
						TIA[1]	319	3	182	2	0.86	-0.16	0.91
Tomak (2018)[69]	Clopidogrel	*2	Stroke	White	447	Composite outcome	44	10	86	9	2.92	1.07	0.50
						Ischaemic stroke	NR	NR	NR	NR	3.17	1.15	0.46
Tornio (2017)[70]	Clopidogrel	*2	Stroke	White	720	Composite outcome	27	11	67	17	2.23	0.80	0.33
Wang (2016a)[51]	Clopidogrel + Aspirin (short-term)	*2, *3	Stroke - TIA	Asian	90	Any bleeding [1]	854	20	609		0.95	-0.05	0.34
						Any stroke[1]	854	80	609	41	1.39	0.33	0.19
						Composite outcome[1]	854	80	609	41	1.39	0.33	0.19
						Ischaemic stroke[1]	854	78	609	39	1.43	0.35	0.20

Study details							Loss of function carriers		Loss of function non-carriers		Effect measure		
Study	**Drug regimen**	**Alleles**	**Event**	**Ethnicity**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
						Mild bleeding[1]	854	8	609	9	0.63	-0.46	0.49
						Moderate bleeding[1]	854	2	610	1	3.57	1.27	1.55
						Severe bleeding[1]	854	1	610	1	2.14	0.76	1.63
Wang (2016b)[71]	Clopidogrel	*2, *3	Stroke	Asian	NR	Composite outcome	198	NR	123	NR	1.97	0.68	0.29
Yi (2017)[72]	Clopidogrel + Aspirin (short-term)	*2	Stroke	Asian	180	Composite outcome	128	29	156	18	3.02	1.10	0.50
Yi (2018)[53]	Clopidogrel + Aspirin (short-term)	*2	Stroke	Asian	1825	Composite outcome	247	42	169	14	1.03	0.03	0.31
Zhang (2017)[73]	Clopidogrel + Aspirin (short term)	*2, *3	Stroke - TIA	Asian	180	Any bleeding	854	20	609	15	0.95	-0.05	0.34

[1] HR estimates calculated using a hazard rate analysis of event frequencies in relation to time at risk.

[2] HR estimates were extracted from the paper and inverted (1/original estimate)

[3] HR estimates were calculated from 2x2 tables of event numbers using complementary log-log (cloglog) transformations.

1.4 Objective 4

1.4.1 Baseline Details

Note: All studies below are also included for objective 5

Table 10 Baseline details of studies included in Objective 4

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Badhuin et al (2022)[74, 93] **Publication type:** Journal article **Funding:** Non-industry **Country:** US, Canada, South Korea, Mexico **Start date:** NR **Study name:** TAILOR-PCI **Study design:** Diagnostic test accuracy cohort within an RCT	**Population:** Healthy people – pre-trial validation of test performance **Inclusion/exclusion criteria:** NR **Number of participants:** 373 **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 373 **Alleles tested for:** *2, *3, *17 **Who administered test:** Onsite testing staff	Test accuracy Ease of use of test Number of people with variant forms of *CYP2C19* (%)
	Population: Acute coronary syndrome or stable coronary artery disease and undergoing PCI – main trial **Inclusion criteria:** 18+ years, target condition, planned 12 months of dual antiplatelet therapy (DAPT) **Number of participants:** 2641 **Mean age in years, SD, range:** NR, NR, 26-95 **Male %:** 75 **Ethnicity:** 68% white, 23% east Asian, 4% south Asian, 2% African American, 2% other, 3% Hispanic or Latinx ethnicity	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 2587 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Test failure rate Number of people with variant forms of *CYP2C19* (%)

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Choi et al. (2016)[78] **Publication type:** Journal article **Funding:** Non-industry **Country:** South Korea **Start date:** May 2013 **Study design:** Diagnostic test accuracy	**Population:** Acute coronary syndrome (ACS) undergoing PCI with drug-eluting stents **Inclusion criteria:** Aged 18+, symptomatic ACS including unstable angina/ non-STEMI 12hr from onset, stenosis >70% on angiography **Exclusion criteria:** Hemodynamic instability, malignancies, active bleeding, recent operation/ trauma, febrile disease, acute/ chronic inflammatory diseases, thrombocytopenia or anemia **Number of participants:** 119 **Baseline data only reported by metaboliser status:** **Mean age in years, SD:** Poor: 62.5, 12.1; Intermediate: 61.9, 10.9; Extensive: 64.3, 13.6; Ultra-rapid: 64.8, 12. **Male %:** Poor: 59.1%; Intermediate: 85.2%; Extensive: 79.5%; Ultra-rapid: 75%. **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 119 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Number of people with variant forms of *CYP2C19* (%) Time to results
Author, year: NCT01718535[82] **Publication type:** Trial registration **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** September 2012 **Study design:** Diagnostic test accuracy	**Population:** NR **Inclusion criteria:** Aged 16+ **Exclusion criteria:** None **Number of participants:** 327 **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan FRX (Genomadix Cube) **Number of participants tested:** 325 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: NCT04473586[76] **Publication type:** Online trial registry entry; additional information provided by Genomadix. **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** February 2020 **Study design:** Diagnostic test accuracy	**Population:** NR **Inclusion criteria:** No food/ drink and no smoking within 30min of sample retrieval **Number of participants:** 416 patients (621 tests) **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan Cube (Genomadix Cube) **Number of participants tested:** 621 tests **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Test failure rate
Author, year: NCT04473573[77] **Publication type:** Online trial registry entry; additional information provided by Genomadix. **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** October 2019 **Study design:** Diagnostic test accuracy	**Population:** NR **Inclusion criteria:** Availability to travel to 3 sites on 5 non-consecutive days **Number of participants:** 8 patients (960 tests) **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan Cube (Genomadix Cube) **Number of participants tested:** 960 samples **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Test failure rate

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Petrek et al. 2016 [79, 83] **Publication type:** Journal Article **Funding:** Unclear **Country:** Czech Republic **Start date:** March 2013 **Study design:** Diagnostic test accuracy	**Population:** PCI **Inclusion criteria:** Random subset of patients **Exclusion criteria:** NR **Number of participants:** 53 **Mean age in years, range:** 57, 13-77 **Male %:** 74% **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 53 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Test failure rate Time to results Ease of use of test
Author, year: Roberts et al. (2012)[75] **Publication type:** Journal article **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** 26 Aug 2010	**Population:** Healthy volunteers - pre-trial validation of test performance **Number of participants:** 37(267 tests) **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 37 (tested 267 times total) **Alleles tested for:** *1, *2 **Who administered test:** NR	Test accuracy Number of people with variant forms of *CYP2C19* (%) Test failure rate

Study details	Participants*	POCT Test Details	Outcomes reported
Study name: RAPID GENE **Study design:** RCT (diagnostic test accuracy cohort within an RCT)	**Population:** Undergoing PCI for treatment of non-ST-elevation ACS/ stable coronary artery disease – main trial. **Inclusion criteria:** 18-75 years, followed-up >1 week **Exclusion criteria:** Antiplatelet other than aspirin/ clopidogrel, or anticoagulation with warfarin/ dabigatran; history of stroke/ TIA; pregnancy; weight <60 kg; platelet <100 000 per µL; bleeding diathesis; haematocrit <30% or >52%, severe liver/renal disease **Number of participants:** 200 (102 rapid genotyping arm; 98 standard arm genotyped later) **Mean age in years, SD, range:** 60, 9, NR. **Male %:** 80 **Ethnicity:** 95% white	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 200 **Alleles tested for:** *1, *2 **Who administered test:** Trial nurses	Test accuracy Number of people with variant forms of *CYP2C19* (%) Time to results Ease of use of test
Author, year: So et al. (2016)[80] **Publication type:** Journal article **Funding:** Mixed (Industry – test manufacturer and non-industry) **Country:** Canada **Start date:** NR **Study name:** RAPID-STEMI **Study design:** Prospective randomized study (diagnostic test accuracy cohort within an RCT)	**Population:** PCI for STEMI. **Inclusion criteria:** Aged 18-75; PCI for STEMI. **Exclusion criteria:** Pre-treatment with prasugrel/ ticagrelor, need oral anti-coagulant, history of stroke/ TIA, body weight <60kg, platelet count <100,000 ul-1, bleeding diathesis, haemtocrit <30% or >52%, severe liver dysfunction, renal insufficiency, or <24hr treatment with glycoprotein IIb/IIIa inhibitors **Number of participants:** 102 **Mean age in years, SD, range:** 58, 10, NR **Male %:** 77 **Ethnicity:** 91% Caucasian	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 102 **Alleles tested for:** *2, *17 **Who administered test:** NR	Test accuracy Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Wirth et al. (2016)[81, 97] **Publication type:** Journal article **Funding:** Industry – other **Country:** Malta **Start date:** October 2014 **Study design:** Diagnostic test accuracy	**Population:** PCI with stent for ACS/ stable angina; eligible for DAPT post-PCI **Inclusion criteria:** As above **Exclusion criteria:** Aged <18 or >75, weight <60 kg, history of stroke/ TIA, active bleeding, coagulation disorders, platelet disorders and/or chronic liver disease **Number of participants:** 35 **Mean age in years, SD, range:** 65.8, 2.4, 49-75 **Male %:** 74 **Ethnicity:** 100% Caucasian	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 35 **Alleles tested for:** *2, *1 **Who administered test:** Clinical pharmacist researcher	Test accuracy Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results Ease of use of test Cost of testing

* When we are focusing on a cohort within an RCT, the 'number of participants' is the number of participants in the genotyping arm of a study (our cohort of interest), whilst the 'total number of participants tested' in the POCT column refers to the number tested with the POCT (not always the same number).

Abbreviations: PCI: percutaneous coronary intervention, NR: not reported, NA: not applicable, SD: standard deviation, STEMI: ST-segment elevation myocardial infarction, RCT: randomised controlled trial, DAPT: dual antiplatelet therapy, ACS: acute coronary syndrome

1.4.2 Risk of bias assessment

Table 11 Risk of bias assessment of studies included in objective 4

Study Details	Badhuin(2022)[208] *Pre-trial*

Domain 1: Patient selection	
373 volunteer samples analysed- no information about condition etc.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Volunteer samples, no case control design and likely avoided innappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Genomadix cube test - conducted on samples. Test conducted on-site by onsite testing staff. Suggests Genomadix test was conducted first, then the report was sent off to the lab along with a saliva sample for Sanger sequencing.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Test order means Genomadix cube results would be available before lab test	

DOMAIN 3: REFERENCE STANDARD	
Sanger sequencing by centralised laboratory - conducted after spartan test completed.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
373 samples tested and analysed	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**

Rationale for judgement: Patient flow was unlikely to have introduced bias - all patients received the same reference standard and were included in the analysis.

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Badhuin(2022)[74] *Main trial*

Domain 1: Patient selection	
Seems no inappropriate exclusions took place.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Unlikely that patient selection introduced bias as this is a subset of a randomised controlled trial, no case-control design and likely avoided inappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Spartan Rx test. Test conducted on-site by onsite testing staff. Spartan test was conducted on patients, then Taqman conducted 12 months later.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Taqman assay conducted in the research laboratory. Spartan test was conducted on patients, then Taqman conducted 12 months later.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
2385 patients received both tests - this is our sample of interest.; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias - all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Choi(2016)[78]

Domain 1: Patient selection	
Sampling procedure unclear. Not a case-control design. It seems the study avoided innapropriate exclusions.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: There is not much information given about patient selection however it seems unlikely this will have introduced bias in the accuracy of the genetic test. A case-control design was avoided and it seems likely that the study avoided innapropriate exclusions.	

DOMAIN 2: INDEX TEST	
The index test is the Spartan RX *CYP2C19* and was conducted and interpreted by researchers. It aimed to identify the *2, *3 and *17 allele. Results determined by Spartan and confirmed by ref standard.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
The reference standard was the Taqman SNP genotyping assay. It is unclear who conducted and interpreted it. Results determined by Spartan and confirmed by ref standard.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received both tests.; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: It seems unlikely that patient flow introduced bias- no missing data and all received same tests.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	NCT01718535(NR)[82]

Domain 1: Patient selection	
"Recruitment of study participants was performed without knowledge of participant genotypes by enrolling associates of operators and associates of Spartan Bioscience and Mount Sinai Services", suggesting it was not consecutive or random.	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient selection was not random or consecutive, however the study wasn't limited to a specific condition, but it seems unlikely this would bias genetic test accuracy. A case-control design was avoided, and unlikely there were innappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Spartan index test. No information about how tests were conducted and interpreted. Study states it is looking to identify *2, *3 and *17 allele.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Bidirectional sequencing is the lab test. No information about how it was conducted or interpreted.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard, bidirectional sequencing, is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
327 patients enrolled but data analysed for 325. Two patients did not receive the reference standard (it says bidirectional sequencing not possible for 2 patients) - no reasoning provided for why this was.; NA	
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Missing data is low and all patients who received the reference standard received the same one.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	NCT04473573(NR)[77]

Domain 1: Patient selection	
Limited information about patients - all ages, sexes and healthy volunteers eligible for inclusion if available to travel to 3 sites.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Limited information on sampling technique but it seems unlikely this would bias the accuracy of the genetic test.	

DOMAIN 2: INDEX TEST	
Spartan test conducted at 3 different test sites. Testing "performed by a total of six operators… … including individuals who are technologists, technicians and/or nurses". No info about interpretation.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Bidirectional sequencing - no info about conduct and interpretation other than to say "Bi-directional sequencing results will not be shared with the participants, operators or Principal investigators."	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
From the data provided by the company, it seems there were no exclusions;	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias- all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	NCT04473586(NR)[76]

Domain 1: Patient selection	
Non-randomised - no info about patient selection or patient condition other than the inclusion criteria being "Participants who will provide buccal samples and a saliva sample who have not eaten drank or smoked in the past 30 minutes".	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Limited information on sampling technique but it seems unlikely this would bias the accuracy of the genetic test.	

DOMAIN 2: INDEX TEST	
Spartan test conducted immediately after sample taken and 21hr after sample taken. No information on who conducted it. "The investigator will not see the bidirectional sequencing results"	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Bidirectional sequencing "generated by a third part from a saliva sample collected from the same patient"	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	
Rationale for judgement: The reference standard is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
From the data provided by the company, it seems there were no exclusions;	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias- all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Petrkova(2014)[83]

Domain 1: Patient selection	
Methods of patient selection are not reported. All patients were undergoing acute coronary angioplasty with stent implantation for ACS.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: There is not much information given about patient selection however it is unlikely this will have introduced bias in the accuracy of the genetic test. A case-control design was avoided. There is no information on exclusions but seems unlikely.	

DOMAIN 2: INDEX TEST	
"Obtained samples were tested by Spartan RX AnalyserTM according to the operator's manual". No information on how it was interpreted or order of tests.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
The reference standard was MassArray technology. No information on how it was conducted and interpreted, other than to say "patients' blood was sampled for DNA isolation and subsequent genotyping of *CYP2C19* polymorphisms"	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard.The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received the index test and reference standard and were included in the results.; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: It seems unlikely that patient flow would have introduced bias - the tests were conducted simultaneously, all patients did receive the same reference standard and were included in the results.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	Roberts(2012)[75] *Pre-trial*

Domain 1: Patient selection	
37 healthy volunteer samples.	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Healthy volunteer samples, no case control design and likely avoided innappropriate exclusions.	

DOMAIN 2: INDEX TEST	
No information on conduct or interpretation but seems Genomadix cube conducted before ref standard.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Order of tests means that reference standard results unlikley to have been available to person conducting the index test.	

DOMAIN 3: REFERENCE STANDARD	
DNA sequencing - limited information given on conduct and interpretation but seems Spartan conducted before ref standard.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received the index test and reference standard and were included in 2x2 table; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias- all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	Roberts(2012)[75] *Main trial*

Domain 1: Patient selection	
Patients who met the inclusion criteria were consecutively enrolled, then randomised. A case control design was avoided - all patients had the same condition. It seems the study avoided innappropriate exclusions.	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Low risk of bias because patients who met the inclusion criteria were consecutively enrolled, then randomised.	

DOMAIN 2: INDEX TEST	
The index test was Spartan RX *CYP2C19* point of care test. It was conducted by clinical trial nurses who had received a 30min training session but had no previous laboratory training. Seems Spartan test was conducted first and then the reference standard, but there is no information about interpretation of results.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: The conduct of the index test is outlined in the paper but the interpretation of the test is not. Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
The reference standard was DNA sequencing. DNA was extracted with the Arrow extaction robot and the Blood DNA 200 cartridge. Seems Spartan test was conducted first and then the reference standard, but there is no information about interpretation of results.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
Test results reported for 91/102 randomised and tested in the genotyping arm, and 96/98 randomised and tested in the standard treatment arm. Missing patients were due to not undergoing PCI, being withdrawn by physician, undergoing different surgery, refusing to return for day 7 blood test and being lost to follow-up.	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the selection of patients have introduced bias?	**Low**

Rationale for judgement: It seems unlikely that patient flow introduced bias. Not all patients are included in the analysis due to some being lost to follow-up but this doesn't seem like it is related to the true value.

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	So(2016)[80]

Domain 1: Patient selection	
Prospectively enrolled patients meeting inclusion criteria from University of Ottawa Heart Institute - no further detail on sampling method. All patients had to have undergone PCI for STEMI. It seems there were no innappropriate exclusions.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Limited information on sampling technique but it seems unlikely this would bias the accuracy of the genetic test. A case control design was avoided. It seems the study avoided inappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Spartan point of care test. Conducted appropriately, but no information on who did the test. Seems index test conducted/ interpreted first but limited explicit information on this. Threshold of looking for *2 allele specified.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Taqman assay. Conduct appropriate - extracting genomic DNA and underwent genetic analysis in the core laboratory. Seems index test conducted/ interpreted first but limited explicit information on this.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received the tests and no exclusions.; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias. all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	Wirth(2016)[81]

Domain 1: Patient selection	
The study used non-probability sampling. A case control design was avoided.	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: The study used non-probability sampling but it seems unlikely this would bias the accuracy of the genetic test.	

DOMAIN 2: INDEX TEST	
Genomadix cube conducted and interpreted by a clinical pharmacist researcher before lab test - not clear on order of interpretation but likely before ref standard.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Both the taqman assay and the GenID assay were conducted by a clinical pharmacist researcher in liaison with a medical laboratory scientist at the Molecular Diagnostics Unit at Mater Dei Hospital MDH. They were classified by the clinical pharmacist researcher and classified in the same manner as with the Spartan RX assay. Seems ref standard interpreted and conducted after POCT.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received all of the tests. One patient was excluded from the analysis as their Spartan index test was inconclusive and they could not be repeated as the patient had been discharged home.; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: It seems unlikely that patient flow introduced bias. One patient was not included in results due to inconclusive result.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

1.4.3 Results

Table 12 Results details of studies included in Objective 4

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
Badhuin et al (2022)[74, 93]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2 or *3	**Test name**: CLIA-based *CYP2C19* Sanger sequencing **Number participants tested:** 373 **Threshold for positive result:** NR	PRE-TRIAL	151	0	224	0	100	100	2 discordant due to pre-analytical sample mix-up at testing centre. Samples re-collected and re-tested, then concordant.
		Test name: Taqman **Number participants tested:** 2385 **Threshold for positive result:** *2 or *3	MAIN TRIAL	863	9	1502	11	99.0	99.3	21 discordant: 9 non-carrier by Spartan, but had *2 or *3 by TaqMan; 11 heterozygous *2 or *3 by Spartan, but non-carrier by TaqMan; 1 sample was heterozygous *2 by Spartan, but homozygous *2 by TaqMan.
Choi et al. (2016)[78]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2, *3	**Test name**: Taqman **Number participants tested:** 119 **Threshold for positive result:** *2, *3	NA	76	0	43	0	100	100	2 discordant:- *3/*17 on Spartan and *1/*3 on SNP; *1/*17 on Spartan and *1/*1 on SNP

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
NCT01718535.[82]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2 or *3	**Test name**: Bidirectional sequencing **Number participants tested:** 325 **Threshold for positive result:** *2 or *3	NA	181	0	144	0	100	100	None
NCT04473586.[76]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2 or *3	**Test name**: Bidirectional sequencing **Number participants tested:** 411 **Threshold for positive result:** *2 or *3	First pass (samples <1hr old)	178	0	217	0	100	100	2 discordant on 1hr samples - did not affect classification as carrier/non-carrier - two samples were mixed up due to a sample swap of two adjacent samples, a *1/*2 was called *2/*2 & a *2/*2 was called *1/*2
			Combined second pass (final call – 1hr)	186	0	223	0	100	100	
			First pass (samples 21 hr old)	94	0	116	0	100	100	
			Combined first pass (21hr + 1 hr)	272	0	333	0	100	100	
			Combined Final call (21hr + 1hr)	280	0	339	0	100	100	
NCT04473573 [77]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2 or *3	**Test name**: Bidirectional sequencing **Number participants tested:** 960 **Threshold for positive result:** *2 or *3	First pass	592	0	359	0	100	100	None
			Combined first and second pass	597	0	360	0	100	100	None

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
Petrek et al. 2016 [79, 83]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2, *3	**Test name**: MassArray technology **Number participants tested:** 53 **Threshold for positive result:** *2, *3	NA	NR	NR	NR	NR	100	100	None
Roberts et al. (2012)[75]	**Test name:** Genomadix Cube/ Spartan **Threshold for defining positive result:** *2	**Test name**: DNA sequencing **Number of participants tested:** 37 (total of 267 tests done in 37 people- 1 inconclusive) **Threshold for defining positive result:** *2	PRE-TRIAL	155	0	111	0	100	100	None Test level data; patient level data not reported
Roberts et al. (2012)[75]		**Number of participants tested:** 200 (data reported for 187 followed up)	MAIN TRIAL	45	0	141	1	100% (95% CI 92.3-100)	99.3% (95% CI 96.3-100)	One incorrectly classified as *2 carrier on Spartan
So et al. (2016)[80]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2	**Test name**: Taqman **Number participants tested:** 102 **Threshold for positive result:** *2		NR	NR	NR	NR	100% (95% CI 88.0-100)	97% (88.5-99.5)	There were some FP but it was not clear how many or how these were discordant.

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
Wirth et al. (2016)[81, 97]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2	**Test name**: Taqman assay **Number participants tested:** 35 (data for 34 due to inconclusive result) **Threshold for positive result:** *2		13	0	21	0	100	100	One incorrectly classified as *2/*2 on Spartan vs one 2* on Taqman and on GenID
		Test name: GenID assay **Number participants tested:** 34 **Threshold for positive result:** *2		13	0	21	0	100	100	None

* Number of people with LOF alleles deduced from Table 2[74]; it was not possible for numbers for both Taqman & Genomadix Cube to be correct in this table with the other information needed to calculate data for the 2x2 table; we therefore assumed that the numbers for Taqman were correct to allow us to construct our 2x2 table

Abbreviations: TP: true positive, FN: false negative, TN: true negative, FP: false positive, AUC ROC: area under the receiver operating characteristics curve, NR: not reported, NA: not applicable. Threshold for defining positive result: positive result meaning having loss of function.

1.5 Objective 5

All but one[82] of the studies included for objective 4 also provided data on test performance and so were also included for objective 5.

1.5.1 Baseline Details

Table 13 Baseline details of studies included in Objective 5

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Al-Rubaish et al. (2021)[84] **Funding:** Non-industry **Country:** Saudi Arabia **Start date:** 2018 **Study design:** Technical performance study	**Population:** Ischaemic stroke **Inclusion criteria:** Consecutive patients with ischaemic stroke **Exclusion criteria:** NR **Number of participants:** 256 **Mean age in years, SD, range:** 61, 12.5, 18-89 **Male %:** 65 **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 256 **Alleles tested for:** *1, *2 **Who administered test:** NR	Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Bergmeijer et al. (2014)[85, 94] **Publication type:** Journal article **Funding:** Non-industry (Spartan provided the tests) **Country:** Netherlands, Italy, Belgium **Study name:** The Popular Genetics Study **Start date:** June 2011 **Study design:** Technical performance study	**Population:** ST-segment elevation myocardial infarction (STEMI) **Inclusion criteria:** Aged ≥21; symptoms of acute myocardial infarction; primary PCI with stent implantation for STEMI **Number of participants:** 1238 **Baseline data only provided for 1038/1238 participants as data not yet available for others** **Mean age in years, SD, range:** 61.9, 11.2, NR **Male %:** 74 **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 411 **Alleles tested for:** *2, *3 **Who administered test:** Laboratory staff (1 site), local investigator or nurse (6 sites)	Test failure rate Ease of use of test Time to results
Author, year: Cavallari et al. (2018)[86] **Funding:** Non-industry (Spartan provided genotyping platforms and kits) **Country:** USA **Start date:** April 28, 2016 **Study design:** Technical performance study	**Population:** Percutaneous coronary intervention (PCI) **Inclusion criteria:** Patients undergoing emergent/ planned left heart catheterization with intent to undergo PCI **Number of participants:** 931 patients genotyped (392 underwent PCI) **Baseline data available only for those who underwent PCI:** **Mean age in years, SD, range:** 63, 11, NR **Male %:** 69 **Ethnicity:** White 74.5%, black 23.7%, asian 0.8%, other or not reported 1%.	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 931 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results Ease of use of test

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Davis et al. (2020)[87] **Funding:** Non-industry. **Country:** USA **Start date:** NR **Study design:** Diagnostic test accuracy study (but no relevant accuracy data for this review)	**Population:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR **Number of participants:** 23 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 23 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Ease of use of test
Author, year: Franchi et al. (2020)[88] **Publication type:** Journal article **Funding:** Non-industry (Spartan provided the Spartan RX system and reagents used free of charge) **Country:** USA **Start date:** NR **Study design:** Technical performance study	**Population:** Diagnostic coronary angiography **Inclusion criteria:** Consecutive patients aged 18-75 years scheduled to undergo diagnostic coronary angiography with intent to undergo ad hoc PCI **Number of participants:** 781 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 781 **Alleles tested for:** *1, *2, *3, *17 **Who administered test:** NR	Number of people with variant forms of *CYP2C19* (%) Time to results
Author, year: Gurbel et al. (2018)[89] **Conference abstract** **Funding:** NR **Country:** USA **Start date:** February 2017 **Study design:** Technical performance study	**Population:** Patients undergoing catheterisation **Inclusion criteria:** NR **Exclusion criteria:** NR **Number of participants:** 578 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 578 **Alleles tested for:** *1, *2, *3, *17 **Who administered test:** NR	Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: McDermott et al. (2020)[92] **Conference poster/ abstract** **Funding:** NR **Country:** United Kingdom **Start date:** NR **Study design:** Technical performance study	**Population:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR **Number of participants:** NR **Age, sex, ethnicity:** NR	**Test name:** Genedrive (early version) **Number of participants tested:** NR **Alleles tested for:** *1,*2,*3,*4,*4b,*10, *17 **Who administered test:** NR	Time to results Ease of use of test Cost of testing
Author, year: Tomaniak et al. (2017)[90, 95, 96] **Funding:** Non-industry **Country:** Poland **Start date:** NR **Study name:** ONSIDE TEST study **Study design:** Technical performance study	**Population:** Stable coronary artery disease **Inclusion criteria:** Patients aged 18-75 with stable coronary artery disease **Number of participants:** 34 **Mean age in years, SD, range:** 61.8, 10.6, NR **Male %:** 77.8 **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 34 **Alleles tested for:** *1, *2 **Who administered test:** NR	Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Zhou et al. (2017)[91, 98] **Publication type:** Journal article **Funding:** Non-industry **Country:** USA **Start date:** NR **Study design:** Diagnostic test accuracy (but no accuracy data relevant for this review)	**Population:** Volunteers and control samples – condition NR - for validation of the test **Number of participants:** 12 samples (9 volunteers, 3 Coriell samples, 4 CAP survey samples) **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 12 samples **Alleles tested for:** *2, *3, *17 **Who administered test:** Four laboratory technologists	Number of people with variant forms of *CYP2C19* (%) Time to results
	Population: Post-PCI patients **Number of participants:** 342 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 342 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results

1.5.2 Results

Table 14 Results details for studies included in Objective 5

Study details	Test name	Alleles tested for	Outcomes	Results
Al-Rubaish et al. (2021)[84]	Spartan RX (Genomadix Cube)	*1, *2	Number of people with variant forms of *CYP2C19* (%)	54 (21.1%)
			Time to results	First 50 patients: 90-120min to complete the results
Badhuin et al (2022)[74, 93] **Pre-trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Ease of use of test	Non laboratory trained personnel can successfully perform rapid genotyping in a POC setting
			Number of people with variant forms of *CYP2C19* (%)	151/373 (40%)
Badhuin et al (2022)[74, 93] **Main trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	172 (6%) patients with unavailable test result. 54/2642 (2%) had no Spartan result available (no definition of what this means); 118 (4%) had inconclusive results.
			Number of people with variant forms of *CYP2C19* (%)	837/2587 (32%)
Bergmeijer et al. (2014)[85, 94]	Spartan RX (Genomadix Cube)	*2, *3	Test failure rate	39 (8%) patients with unavailable test result - inconclusive results.
			Ease of use of test	**Description of feature of the test:** Buccal swab more patient friendly than venapuncture for blood sample, but test is limited to testing *2, *3, *17 for one patient at a time per genotyping device.
			Time to results	Result available within 1hr after collection of buccal swab.
Cavallari et al. (2018)[86]	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	129 (14%) with unavailable test result - 56 inconclusive results and 73 device errors.
			Number of people with variant forms of *CYP2C19* (%)	113/392 (29%)
			Time to results	For all patients genotyped: Median genotype test turnaround time was 96min (interquartile range of 78-144)

Study details	Test name	Alleles tested for	Outcomes	Results
			Ease of use of test	Could not be used as POCT due to absence of licensed molecular medical technologist so must be sent to central laboratory (the case for all of USA), and only a single sample genotyped at a time limiting number of patients that can be offered genotyping.
Choi et al. (2016)[78]	Spartan RX (Genomadix Cube)	*2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	76 (63.9%)
			Time to results	**Description of feature of the test:** time from sample to result ~60min
Davis et al. (2020)[87]	Spartan RX (Genomadix Cube)	*2, *3, *17	Ease of use of test	**Description of features of the test**: Barriers to implementation: time constraints, personnel requirements and coordination, storage and sample stability, samples unable to be collected by bedside nurses, patients unable to provide samples, sample recollection due to interference or improper techniques
Franchi et al. (2020)[88]	Spartan RX (Genomadix Cube)	*1, *2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	242/781 (28.5%)
			Time to results	Allele status within 1hr - readily available when the decision on choice of oral P2Y12-inhibiting therapy most commonly occurs.
Gurbel et al. (2018)[89]	Spartan RX (Genomadix Cube)	*1, *2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	168/578 (29%)
			Time to results	Results available in all patients within 90min
NCT04473586[76]	Spartan Cube (Genomadix Cube)	*2, *3, *17	Test failure rate	16 (2.6%) patients with unavailable test result on first pass. 2 (0.3%) with unavailable test result on final pass.
			Number of people with variant forms of *CYP2C19* (%)	281/621 (45.2%)
NCT04473573[77]	Spartan Cube (Genomadix	*2, *3, *17	Test failure rate	9 (0.9%) patients with unavailable test result on first pass. 3 (0.3%) with unavailable test result on final pass.

Study details	Test name	Alleles tested for	Outcomes	Results
	Cube)		Number of people with variant forms of *CYP2C19* (%)	600/960 (62.5%)
Petrek et al. 2016 [79, 83]	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	10 (18.9%) with unavailable test result due to failure during amplification process (n=4), inconclusive result (n=3), only two of three alleles tested for gave results (n=3)
			Time to results	Turnaround time (from buccal swab sampling to result print-out) was 60 min
			Ease of use of test	Simple and non-invasive
Roberts et al. (2012)[75] **Pre-trial**	Spartan RX (Genomadix Cube)	*1, *2	Number of people with variant forms of *CYP2C19* (%)	155 (59%)
			Test failure rate	1 (0.4%) test with unavailable test result – did not identify genotype.
Roberts et al. (2012)[75] **Main trial**	Spartan RX (Genomadix Cube)	*1, *2	Number of people with variant forms of *CYP2C19* (%)	46/187 (25%)
			Time to results	Main trial: Within 60min from test activation
			Ease of use of test	Main trial: Nurses with no previous laboratory training implemented test after 30min training session.
So et al. (2016)[80]	Spartan RX (Genomadix Cube)	*2, *17	Number of people with variant forms of *CYP2C19* (%)	37 (36%)
			Time to results	Within 55min of test carrier status for all alleles was available
Genomadix (test manufacturer) response to request for information	Spartan RX (Genomadix Cube)	NA	Cost of testing	**Description of feature of the test:** a) Platform cost: 3,500 GBP per testing platform, b) Testing assay cost: 175 GBP per test kit, c) external control kits: 50 GBP per external control kit
			Time to results	**Description of feature of the test:** Time to result is 64 minutes.
Tomaniak et al. (2017)[90, 95, 96]	Spartan RX (Genomadix	*1, *2	Test failure rate	4 (11.8%) patients with unavailable test result – inconclusive results.
			Number of people	14 (14.83%)

Study details	Test name	Alleles tested for	Outcomes	Results
	Cube)		with variant forms of *CYP2C19* (%)	
			Time to results	Mean (SD): 56min (11), from material collection to the testing results
Wirth et al. (2016)[81, 97]	Spartan RX (Genomadix Cube)	*2, *1	Test failure rate	5/35 (14.3%) patients with unavailable test result – 4 tests resulted in error (11.4% - no further details); 1 test inconclusive.
			Number of people with variant forms of *CYP2C19* (%)	13/34 (38%)
			Time to results	Collection of sample to genotyping result within 1 hour
			Ease of use of test	Simple procedure, portable, convenient, no laborious preparation, minimal training required to conduct test. User-friendly interpretation with no training required. Storage conditions limit ease of use.
			Cost of testing	Estimated cost per patient test: 225 euros (Taqman estimated at 13 euros and GenID at 23 euros). No indication of how this was calculated.
Zhou et al. (2017)[91, 98] **Pre trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	7/12 (58%)
			Time to results	**Description of feature of the test (pre trial and main trial):** results are returned in one hour turnaround time
Zhou et al. (2017)[91, 98] **Main trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	25 (7.3%) with unavailable test results - 14 inconclusive results (4%), 10 failed controls (3%), 1 instrument failure (0.3%) (no further information given).
			Number of people with variant forms of *CYP2C19* (%)	99 (37%)
			Time to results	**Description of feature of the test (pre trial and main trial):** results are returned in one hour turnaround time
McDermott et al. (2020)[92]	Genedrive (early version)	*1,*2,*3,*4,*4b,*10, *17	Time to results	**Description of feature of the test:** ~40min
			Ease of use of test	**Description of features of the test**: Portable, rapid (~40mins), no cold

Study details	Test name	Alleles tested for	Outcomes	Results
				chain, simple read out for non-specialist users.
			Cost of testing	Decision analytic model, comprising decision tree linked with a state transition Markov model, suggested POCT would generate net benefit of 0.130 QALYs and monetary benefit of £2595 per patient (uncertain evidence).