

MATCH: Clopidogrel ^{PLAVIX} + ASA ^{ASPIRIN} versus Clopidogrel ^{PLAVIX} in high-risk Patients with recent stroke or recent transient ischaemic attack (TIA)¹

Management of Atherothrombosis with Clopidogrel in High-risk patients

BOTTOM LINE

In **MATCH**, for high-risk patients with recent stroke or TIA:

- Dual antiplatelet therapy with clopidogrel + ASA, compared to clopidogrel alone, initiated within 3 months of index event (mean 26.5 days), for 18 months, did **NOT** reduce ischemic stroke, MI, vascular death or rehospitalization for acute ischemic event.
- Clopidogrel + ASA ↑ life-threatening bleeds (ARI 1.26%), major bleeds (ARI 1.36%), and minor bleeds (ARI 2.16%).
- Clopidogrel + ASA should **NOT** be combined long-term for secondary prevention of high-risk ischemic stroke (unless there is another indication). This is consistent with the Canadian Stroke Best Practices Recommendations 2014, & American 2014 guidelines, which recommend monotherapy (ASA or clopidogrel) or dipyridamole + ASA.^{2 (CSBPR'14 [A]),3 (AHA/ASA'14 IA/IB)}

BACKGROUND

- ASA is beneficial for secondary prevention of ischemic stroke.⁴ Clopidogrel is better than ASA in patients with recent ischemic stroke/MI/symptomatic PAD for ↓ischemic stroke/MI/vascular death in some high-risk subgroups.⁵ Clopidogrel + ASA was better than ASA alone in *coronary* atherothrombosis for prevention of vascular endpoints.^{6,7}
- Prior to **MATCH** (2004), the combination of clopidogrel + ASA had not been studied in *cerebrovascular* disease. **MATCH** was designed to determine if this combination was better than clopidogrel alone in the prevention of vascular events.
- Since **MATCH** (2004), other studies using dual antiplatelet therapy (DAPT) for ischemic strokes have been published. The **SPS3** antiplatelet arm (2012) did not find a benefit of clopidogrel + ASA vs. ASA alone in lacunar strokes, but **CHANCE** (2013) found clopidogrel + ASA x21 days followed by clopidogrel monotherapy for 90 days was beneficial in carefully chosen patients.^{8,9} Despite **CHANCE**, the Canadian Stroke Best Practices Recommendations 2014 are cautious on recommending clopidogrel + ASA routinely, and they await the results of the **POINT** trial.²

TRIAL BACKGROUND

DESIGN: randomized, double-blind, multi-centre 28 countries, intention-to-treat. Enrollment: Dec 2000 to April 2001.

Funding: Sanofi-Synthelabo, Bristol Myers Squibb

INTERVENTION: clopidogrel 75mg daily + ASA 75mg daily x 18 months vs. clopidogrel 75mg daily x18 months

INCLUSION: ischemic stroke or TIA in the previous 3 months AND ≥1 risk factor within the past 3 years (previous ischemic stroke, previous MI, angina pectoris, diabetes, symptomatic PAD)

EXCLUSION: <40 years old, severe comorbid conditions, increased risk of bleeding, scheduled for major or vascular surgery, contraindications for aspirin or clopidogrel

POPULATION at baseline: n=7599, mean time to randomization 26.5 days (SD 25), index event: TIA 21%, ischemic stroke 79%.

- For those who qualified with ischemic stroke: modified Rankin scale (0-2) 73%, small vessel occlusion (TOAST classification) 53%, large artery atherosclerosis (TOAST classification) 34%. 1 additional risk factor 79%, ≥2 additional risk factors 20%
- Non-modifiable risk factors: 63% ♂, mean age ~66 years old, previous MI 5%, previous ischemic stroke 26%, previous TIA 19%
- Modifiable risk factors for stroke or TIA: hypertension 78%, diabetes 68%, hyperlipidemia 56%, smoking (past or current) 47%, angina 12%, symptomatic PAD 10%
- 80% on ASA at randomization; proton-pump inhibitor use was not reported
- No imbalance in baseline characteristics were noted between the two groups

RESULTS follow-up: 18 months

TABLE 1: EFFICACY

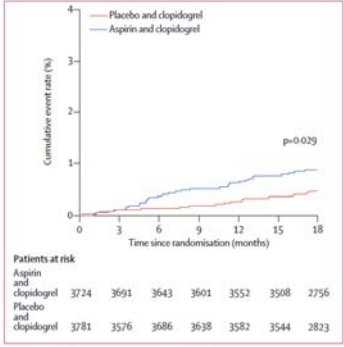
CLINICAL ENDPOINTS	CLOPIDOGREL 75MG + ASA 75MG DAILY n=3797	CLOPIDOGREL 75MG + PLACEBO DAILY n=3802	RRR 95% CI	ARR /ARI	COMMENTS																
PRIMARY ENDPOINT																					
First instance of ischemic stroke, MI, vascular death, or rehospitalisation for acute ischemic event	15.7% {n=596}	16.7% {n=636} (12.7%/yr)	6.4% (-4.6 to 16.3)	NS	<div style="text-align: center;">Kaplan-Meier for primary endpoint</div> <p style="text-align: right; font-size: small;">p=0.244</p> <table border="1" style="font-size: x-small; margin-top: 5px;"> <caption>Patients at risk</caption> <tr> <td>Aspirin and clopidogrel</td> <td>3797</td> <td>3576</td> <td>3440</td> <td>3321</td> <td>3229</td> <td>3130</td> <td>2441</td> </tr> <tr> <td>Placebo and clopidogrel</td> <td>3802</td> <td>3576</td> <td>3439</td> <td>3326</td> <td>3200</td> <td>3119</td> <td>2446</td> </tr> </table>	Aspirin and clopidogrel	3797	3576	3440	3321	3229	3130	2441	Placebo and clopidogrel	3802	3576	3439	3326	3200	3119	2446
Aspirin and clopidogrel	3797	3576	3440	3321		3229	3130	2441													
Placebo and clopidogrel	3802	3576	3439	3326		3200	3119	2446													
SECONDARY ENDPOINTS																					
Ischemic stroke (fatal or not)	7.9% (n=299)	8.4% (n=319)	-	-																	
MI (fatal or not)	1.6% (n=59)	1.6% (n=62)	-	-																	
Vascular death	1.8% (n=69)	1.9% (n=74)	-	-																	
Rehospitalisation for acute ischemic event (UA, worsening PAD requiring therapeutic intervention, urgent revascularisation, TIA)	4.5% (n=169)	4.8% (n=181)	-	-																	
Any stroke (ischemic, primary intracranial hemorrhage, non-classifiable (fatal or not))*	8.9% (n=339)	9.1% (n=347)	NS																		
Death (all cause)*	5.3% (n=201)	5.3% (n=201)	NS																		

Event rates were calculated from the raw data, & therefore may be different from the published values.

*First event counted (independently from the first outcome from the composite of the primary endpoint)

RESULTS continued follow-up: 18 months

TABLE 2: SAFETY *

CLINICAL ENDPOINTS	CLOPIDOGREL 75MG + ASA 75MG DAILY n=3759	CLOPIDOGREL 75MG + PLACEBO DAILY n=3787	Δ% between DAPT vs. clopidogrel (95% CI)	ARR /ARI	NNT/NNH x18 MONTHS¶	COMMENTS
Life-threatening bleeding (fatal bleeding, ↓Hgb ≥50g/L, hypotension requiring inotropes)	3% {n=96}	1% {n=49}	1.26 (0.64 to 1.88)	1.26	80	Kaplan-Meier curve for primary intracranial hemorrhage: no ↑ noted in the first 3 months, but cumulative event rate significant at 18 month** 
Fatal bleeding	0.4% {n=16}	0.3% {n=11}	0.13 (-0.14 to 0.40)	-	-	
Non-fatal bleeding	2.2% {n=81}	1% {n=38}	1.15 (0.59 to 1.71)	-	-	
Symptomatic intracranial hemorrhage	1.1% {n=40}	0.7% {n=25}	0.4 (-0.01 to 0.82)	-	-	
Primary intracranial hemorrhage	0.9% {n=32}	0.4% {n=17}	0.40 (0.04 to 0.76)	0.4	250‡	
Major bleeding (significantly disabling with persistent sequelae)	2% {n=73}	1% {n=22}	1.36 (0.86 to 1.86)	1.36	74	
Minor bleeding	3% {n=120}	1% {n=39}	2.16 (1.51 to 2.81)	2.16	47	
GI bleed	1.4% {n=51}	0.6% {n=21}	Not reported	-	-	

*safety evaluation was based on patients who were randomized AND received ≥1 dose study medication

**Acute stroke trials usually measure outcomes at 90 days, and Chest 2012 guidelines recommend following patient-important outcomes at 90 days^{10,11}

¶ NNH calculated from raw data

‡ The p-value for the difference in primary intracranial hemorrhage was not reported, but the confidence interval is 0.04 to 0.76.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Follow up visits 1, 3, 6, 12, 18 months, and monthly telephone calls to patient
- At follow-up, data were available for 96% of patients

LIMITATIONS:

- Sanofi-Synthelabo contracted Parexel International to undertake site monitoring and data management, had input into the study, had 1 of 10 votes on the steering committee, and paid study-related expenses to other committee members.
- Sample size of 7600 was not achieved (randomized n=7599)
- Other risk factors for stroke (ethnicity and family history of stroke) not reported at baseline. However as other baseline characteristics imbalances were not detected, it is unlikely these were imbalanced.
- Discontinuation rate: clopidogrel + ASA (7%), clopidogrel (7%)
- The period of time after a stroke or TIA is important, as the estimated risk of recurrent stroke is 11.5% at 7 days, 15% at one month, and 18.5% at 3 months after a minor stroke, and 8%, 11.5% and 17.3% respectively after a TIA.¹² In **MATCH** the mean time to randomization was 26.5 days, and this delay resulted in the enrollment of patients at lower risk of recurrent stroke who are less likely to benefit.
- The presence of ≥1 risk factor may decrease generalizability of **MATCH** because of the low prevalence of patients with ≥1 risk factor, and it might skew recruitment and over-represent patients with risk factors (e.g. diabetes was over-represented)¹³

UNCERTAINTIES:

- The subgroup analysis did not include all risk factors for stroke (missing smoking, hyperlipidemia, ethnicity), so it is unknown what the hazard ratio for recurrent the primary endpoint is in these subgroups.
- Would earlier treatment with antiplatelets, for a shorter duration be beneficial in strokes due to small vessel occlusion?
- Was the trial population too heterogeneous (i.e. stroke and TIA are heterogeneous syndromes), and subtypes need to be studied separately?¹³ For example, 53% of patients had small-vessel occlusion, and 34% had large artery atherosclerosis, so more than half the **MATCH** patients were at lower risk of recurrent stroke.¹⁴
- Were any patients resistant to ASA?
 - 80% of patients were on ASA at randomization. It is unknown what % were on ASA at time of qualifying event, as this may help determine whether patients were resistant to ASA (i.e. did they have a stroke while on ASA, was there a current cardiac event while on ASA).¹⁵
 - The authors dismiss the notion of resistance using the increased bleeds as on clopidogrel + ASA as evidence¹⁵
- Would a loading dose of antiplatelet therapy have made a difference?
- Would results be significant if ASA, instead of clopidogrel, was the comparator arm?¹⁵
- It is unknown how stroke and other endpoints were confirmed (e.g. what type of neuroimaging was used, was there an adjudication committee for endpoints?)

RxFILES RELATED LINKS

- RxFiles DAPT & Triple Therapy newsletter & chart: <http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT%20and%20Triple%20Therapy%20Newsletter%20and%20Chart.pdf>
- Canadian Family Physician Journal – RxFiles article on DAPT post stroke: <http://www.cfp.ca/content/62/8/640.full.pdf+html?sid=aa5c799f-c58e-4ca9-ad79-f96a3abe4367>
- **SPS3** Antiplatelet Trial Summary: <http://www.rxfiles.ca/rxfiles/uploads/documents/SPS3%20antiplatelet-Trial%20Summary.pdf>
- **SPS3** Systolic Blood Pressure Trial Summary: <http://www.rxfiles.ca/rxfiles/uploads/documents/SPS3%20SBP-Trial%20Summary.pdf>
- **CHANCE** Trial Summary: <http://www.rxfiles.ca/rxfiles/uploads/documents/CHANCE-Trial%20Summary.pdf>

♂=male Δ=difference **ARI**=absolute risk increase **ARR**=absolute risk reduction **CAD**=coronary artery disease **CI**=confidence interval **DAPT**=dual antiplatelet therapy **GI**=gastrointestinal **Hgb**=hemoglobin **MI**=myocardial infarction **NNT**=number need to treat **NNH**=number needed to harm **PAD**=peripheral arterial disease **RRR**=relative risk reduction **SD**=standard deviation **TIA**=transient ischaemic attack **UA**=unstable angina **yr**=year

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