**MATCH: Clopidogrel + ASA versus Clopidogrel in high-risk Patients with recent stroke or recent transient ischaemic attack (TIA)**

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.

**BACKGROUND**

- ASA is beneficial for secondary prevention of ischemic stroke. 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.
- 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 SP3 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. 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.

**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**

**TABLE 1: EFFICACY**

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL ENDPOINTS</strong></td>
</tr>
<tr>
<td>First instance of ischemic stroke, MI, or vascular death or rehospitalization for acute ischemic event</td>
</tr>
</tbody>
</table>

**SECONDARY ENDPOINTS**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel 75mg + ASA 75mg daily</th>
<th>Clopidogrel 75mg + placebo daily</th>
<th>RRR 95% CI</th>
<th>ARR /ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke (fatal or not)</td>
<td>7.9% (n=299)</td>
<td>8.4% (n=319)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MI (fatal or not)</td>
<td>1.6% (n=59)</td>
<td>1.6% (n=62)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vascular death</td>
<td>1.8% (n=69)</td>
<td>1.9% (n=74)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rehospitalisation for acute ischemic event (UA, worsening PAD requiring therapeutic intervention, urgent revascularisation, TIA)</td>
<td>4.5% (n=169)</td>
<td>4.8% (n=181)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any stroke (ischemic, primary intracranial hemorrhage, non-classifiable (fatal or not))</td>
<td>8.9% (n=339)</td>
<td>9.1% (n=347)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Death (all cause)*</td>
<td>5.3% (n=201)</td>
<td>5.3% (n=201)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

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

TABLE 2: SAFETY *

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

* 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? 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 antplatelet 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?)
References


