ACTIVE A: ASA +/- Clopidogrel in Atrial Fibrillation (AF) ¹

in patients who have one or more additional stroke risk factors & for whom warfarin is not an option for whatever reason.

**Background – ACTIVE trials**

**ACTIVE W²** - open noninferiority trial of clopidogrel plus ASA vs Warfarin oral anticoagulation in pts with AF and at least 1 risk factor for stroke. **ACTIVE A** - randomized, double-blind, allocation concealed, placebo-controlled trial of clopidogrel in similar pts with AF and at least 1 risk factor for stroke who receive ASA because they have a contraindication to, or are unwilling to take an oral anticoagulant (e.g., poor adherence for INR).

**(ACTIVE W** - partial factorial, double-blind, placebo-controlled trial of irbesartan in pts participating in ACTIVE A or ACTIVE W who do not require an ARB agent and whose systolic BP ≤110 mm Hg.)

**Trial Background Data - Active A**

- randomized, double-blind, multicenter, international, placebo-controlled trial – ASA 75-100mg daily vs clopidogrel 75mg daily – **ACTIVE A** 75-100mg daily to reduce vascular events (Stroke; non-CNS systemic embolism; MI; Death) ² in AF; n=7554 pts with AF
- **INCLUSION**: AF at enrollment or 2 intermittent episodes ≤6mo & at least 1 risk factor for stroke (≥75yrs; HTN; previous stroke, TIA, PE or DVT; LVEF>45%; PVD; 55-74yrs+DM or CAD) who are unable, unsuitable not defined or unwilling to take an oral anticoagulant.
- **EXCLUSION**: required Vitamin K antagonist OR clopidogrel OR had a risk factor for hemorrhage (recent peptic ulcer disease ≤6mo; hx of intracerebral hemorrhage; significant thrombocytopenia; ongoing alcohol abuse)
- **POPULATION @baseline**: any ethnicity <63% from Europe & Israel, Age mean: 71; CHADS₂mean= 2 (70% were CHADS 1 or 2; [0.9/<1.6%]; 2=33.5%, 3=16.5%, 4=6%, 5=2.7%, 6=0.4%); BP=136/81, HR=75 bpm; Hx of: permanent AF 64%, TIA 19%, Stroke/TIA 13%, on ASA 83%, having specific bleed risk 23%

**Results - over the median 3.6 years of follow-up**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>ASA+Clopidogrel=n=3772</th>
<th>ASA=n=3782</th>
<th>ARR</th>
<th>NNT/NNH (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Major Vascular Events</td>
<td>22.1% (n=832)</td>
<td>24.4% (n=924)</td>
<td>2.37% (RR=1.0%);</td>
<td>42 (95% CI: 23-213)</td>
<td>¹: RR = 0.89 (95% CI: 0.81-0.98; p=0.01) (HTN, LDL etc. not evaluated)</td>
</tr>
<tr>
<td>Stroke, Any</td>
<td>7.8% (2.4%/yr)</td>
<td>10.8% (3.3%/yr)</td>
<td>2.94% (RR=27%);</td>
<td>34 (95% CI: 23-60)</td>
<td>Overall: potential to benefit from combination equal to risk of major bleed</td>
</tr>
<tr>
<td>Stroke, non-disabling</td>
<td>2.8%</td>
<td>4%</td>
<td>1.2% (RR=27%);</td>
<td>82 (95% CI: 49-254)</td>
<td></td>
</tr>
<tr>
<td>Stroke, disabling or fatal</td>
<td>5.3%</td>
<td>7.1%</td>
<td>1.8% (NNT=100);</td>
<td>55 (95% CI: 35-138)</td>
<td></td>
</tr>
<tr>
<td>Non-CNS systemic embolism</td>
<td>1.4%</td>
<td>1.4%</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>15.9%</td>
<td>15.8%</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>21.9% (6.4%/yr)</td>
<td>22.2%</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Major Bleed (severe or fatal)</td>
<td>6.7% (2.0%/yr)</td>
<td>4.3% (1.3%/yr)</td>
<td>2.4% (RR=65%);</td>
<td>42 (95% CI: 20-74)</td>
<td></td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>10.8%</td>
<td>4.6%</td>
<td>6.2%</td>
<td>16 (95% CI: 14-20)</td>
<td></td>
</tr>
</tbody>
</table>

α=Relative risk; β=Confidence interval; DNT=Double non-inferiority trial; LVEF=left ventricular ejection fraction; MMH=myocardial infarction; MRH=number needed to harm; NNT=number needed to treat; NS=not significant; PE=pulmonary embolism; RR=risk ratio.

³Time to 1st event; ²Other endpoints: no difference in malignancies, pneumonia; possible in patients who have one or more additional stroke risk factors & for whom warfarin is not an option for whatever reason.

**Strengths, Limitations & Uncertainties**

**Strengths**: important clinical endpoints; reasonable duration; blinded trial

**Limitations/Uncertainties**: too few patients & events with CHADS score >2 to assess benefit/risk in those at higher risk.

- Lack data on concurrent medications; specifically lack data on use of GI ulcer prophylaxis with PPIs which has recently been associated with a possible decrease in the effectiveness of clopidogrel as well as lower risk of a GI bleed.³
- Clinical Endpoints: important clinical endpoints; reasonable duration; blinded trial
- Drug cost per patient per year: ASA+Clopidogrel = $1,260; ASA = $95
- ASA+Clopidogrel reduces strokes more than ASA but not warfarin, & has bleeding rates comparable to warfarin.

**ACTIVE A Trial: Bottom Line:**

➤ In patients with atrial fibrillation at low/moderate risk of stroke (most CHADS 1-2), who are not suitable for warfarin therapy, the combination of ASA+clopidogrel is associated with a decrease in vascular event risk that is **equal to** the increase in risk of major bleeding. ⁶

**Consider individualized risk & values**: e.g., some may value the stroke endpoint more than the major bleed endpoint or cost.

**Assess drug cost per patient per year**: ASA+Clopidogrel = $1,260; ASA = $95

**Assess risk of bleed vs any potential benefit for individual patient**: [if high bleed risk, may avoid warfarin & ASA+clopidogrel bx.]

If patient is on clopidogrel +/- a PPI, reassess need for clopidogrel &/or need for a PPI.

- The ACTIVE-W² trial found that in atrial fibrillation patients with at least 1 risk factor for stroke (mostly moderate risk), warfarin decreased the chance of having a vascular event compared to ASA+clopidogrel. (For every 47 patients treated for 1.3 years, one extra vascular event (1st outcome) was prevented (NNT= 47)).

Overall bleeding was higher in the ASA+clopidogrel arm than with warfarin. ⁶

Note: Major bleed risk often without benefit also found in previous ASA+clopidogrel combination trials: MATCH and CHARISMA.

MATCH: TIA hx21% or ischemic stroke33%+PLAVIX +/-ASA 75mg od (ischemic events 15.7% combo vs 16.7%, non-significant; major bleeding 2.6 combo vs 1.3%; n=7999 +18month);

CHARISMA: PLAVIX + ASA vs ASA 75-162mg od; CV death, MI, or stroke 6.8% vs 7.3% in atherosclerosis/high CV risk pts but ¹bleeding Moderate 2.1 vs 1.3%, NNT=125; Moderate 2.1 vs 1.3%, NNT=125; Potential to benefit from combination equal to risk of major bleed (e.g. NNT=42 & NNH=42 = 3.6y)

- ASA: use in low stroke risk pts or high bleed risk pts; Warfarin: use in high stroke risk pts if not high bleed risk; ASA+clopidogrel reduces strokes more than ASA but not warfarin, & has bleeding rates comparable to warfarin.
The CHADS2 Score 7,8: Stroke Risk in Atrial Fibrillation

Algorithm for predicting the risk of stroke in pts with AF. The score assigns points for various risk factors, as follows: 1 point for CHF, HTN, age ≥75 yrs, DM. 2 points for history of stroke or TIA. The score = sum of points (range 0-6).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension (or treated hypertension)</td>
<td>1</td>
</tr>
<tr>
<td>A Age &gt;75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>S2 Prior Stroke or TIA</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke Risk</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Low (≤ 3%/year)</td>
<td>Aspirin (esp. if age ≥60yrs) 11</td>
</tr>
<tr>
<td>1-2</td>
<td>Moderate (~ 3-4%/year)</td>
<td>VKA (e.g. warfarin) or alternatives; see below. (Warfarin most effective in decreasing stroke risk.)</td>
</tr>
<tr>
<td>3-5</td>
<td>High (~ 6-12%/year)</td>
<td>VKA= vitamin K antagonist</td>
</tr>
<tr>
<td>6</td>
<td>Very High (~18%/year)</td>
<td></td>
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</tbody>
</table>

AF Patient Description

Moderate → high risk for stroke
+ no contraindication (CI) to VKA

Choice depends on overall bleed risk & cost considerations:
- ASA+clopidogrel will lower stroke/vascular risk marginally over ASA; however, ASA will have lowest bleed risk and is lower cost. Bleed risk with ASA+clopidogrel is similar to that with warfarin; ∴ those who are not suitable for warfarin due to bleed risk, may also not be suitable for ASA+clopidogrel.
- Thus ASA+clopidogrel option really only suitable for patients who are not candidates for warfarin due to factors other than high risk of bleeding e.g. purple toe syndrome, lack of access to lab for required INR tests, likely not to be adherent to therapy/INR testing requirements, etc.

High risk of bleed & low-moderate stroke risk

ASA (75-100mg daily)

* VKA contraindications (e.g., history of falls especially frequent, Clinically significant GI bleeding, inability to obtain regular INR testing)

On the horizon:
1) Dabigatran PREVAREL 150-50mg tab BD will offer an alternative to warfarin (RE-LY trial 2yr trial)12. At the lower dose, it was as effective as warfarin with less bleeding; at the higher dose it was more effective than warfarin NNT=175yr but with similar bleeding rates. (Note: the rate of MI was slightly higher NNT=627yr and there were more dropouts tartaric acid in cap in the dabigatran group 21% vs 17%; Abnormal liver function was not a problem in dabigatran patients compared to warfarin 0.2% vs 0.3%)2
2) Rivaroxaban XARELTO currently being evaluated in ROCKET AF, a phase 3 trial in AF patients.

References

6. Cost calculation based on: cost difference for ASA vs ASA+clopidogrel ($1,165) x NNT/yy (Approximately 150 for 1 y).
ACTIVE W: Clopidogrel + ASA vs. oral anticoagulation* (VKA) for Atrial Fibrillation (AF) ¹

Is clopidogrel plus ASA non-inferior to oral anticoagulation for preventing vascular events in AF?

Background
- A vitamin K antagonist (VKA) such as warfarin is the treatment of choice for AF patients at high stroke risk ²,³, yet only ½ of potentially eligible patients receive therapy ⁴. VKA is patient-unfriendly, difficult to monitor, and is associated with a risk of severe bleeding (generally 1-4% a year). ASA is inferior to VKA in AF patients at high risk of stroke, and it would be desirable to have a treatment that was more effective than ASA but with lower bleeding risk than warfarin ⁵.

Trial Background Data
- Randomized, multicentre, open label (blinded adjudication of outcomes), non-inferiority trial funded by Sanofi-Aventis & Bristol-Myers Squibb.
  - 7455 screened, 6706 randomized; 77% already taking VKA (enrolled in ACTIVE A ⁶ if unwilling or ineligible for VKA)
  - INCLUSION: EKG evidence of AF and one of: age ≥75, HTN, previous stroke, TIA or non-CNS embolism, LVEF <45%, PAD, age 55-74 with DM or previous CAD.
  - EXCLUSION: Contraindication to study medications, documented PUD within ≤6 months, intracerebral hemorrhage, platelets <50x10⁹/L, mitral stenosis.
- Active Control group vs. Treatment group:
  - VKA (e.g. warfarin) n=3371. Titrate to INR 2.0-3.0 (measured ≤1 month) versus Clopidogrel (75mg/day) + ASA (75-100 mg/day) n=3335.
  - Baseline: n=6706; AF; age mean 70 (66% ♂), CHADS2 mean 2; History of HTN 83%, Stroke/TIA 15%, MI 17%, DM 21%, HF 31%, CAD 28%. Med Hx: ASA 28%, Clopidogrel 2%, ARB 15%, ACEI 54%, β-blocker 57%, Digoxin 37%, Antiarrhythmic 19%, Statin 38%

Results - over the median 1.28 years of follow-up
⇒ Trial stopped early because of superiority of VKA over clopidogrel+ASA. (More benefit & less harm!)

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Clopidogrel + ASA</th>
<th>VKA</th>
<th>ARR</th>
<th>NNT/NNH (95% CI) over ~1.3 years</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite (stroke, non-CNS embolus, MI, vascular death)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7% (n=234)</td>
<td>4.9% (n=165)</td>
<td>↑ 2.1%</td>
<td>NNT=47 (95% CI: 31-101)</td>
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<tr>
<td>Stroke</td>
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</tr>
<tr>
<td>3% (n=100)</td>
<td>1.8% (n=69)</td>
<td>↑ 1.3%</td>
<td>NNH=80 (95% CI: 51-191)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1.1%</td>
<td>0.7%</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>Vascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.6%</td>
<td>3.9%</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.8%</td>
<td>4.7%</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CNS embolus</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0.5% (0.4%/yr)</td>
<td>0.1% (0.0%/yr)</td>
<td>↑ 0.4%</td>
<td>NNH=238 (95% CI: 144-191)</td>
<td></td>
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</tr>
<tr>
<td>Major Hemorrhage**</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>3% (2.4%/yr)</td>
<td>2.6% (2.2%/yr)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Minor Hemorrhage***</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>17% (13%/yr)</td>
<td>14.3% (11%/yr)</td>
<td>↑ 2.7%</td>
<td>NNH=37 (95% CI: 23-104)</td>
<td></td>
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</tr>
</tbody>
</table>

*Risk of 1st outcome higher with clopidogrel + ASA p=0.0005 and no significant difference in bleeding Event # is not provided for 2nd outcomes.

AF: atrial fibrillation; ARR: absolute risk reduction; CAD: coronary artery disease; CI: confidence interval; CNS: central nervous system; DM: diabetes mellitus; HTN: hypertension; LVEF: left ventricular ejection fraction; MB: myocardial infarction; NNT: number needed to treat; NS: not significant; PAD: peripheral arterial disease; PUD: peptic ulcer disease; RR: relative risk; TIA: transient ischemic attack; VKA: vitamin K antagonist.

¹ Time to 1st event, **Death, ♂ Hgb by ≥50g/L, HTN needing inotrope, intraocular bleed or transfusion of ≥2 units blood, *** Other bleeding requiring regimen modification

* Patients randomized to oral anticoagulation received the vitamin K antagonist (e.g. warfarin) in use in their country

Strengths, Limitations & Uncertainties

Strengths: Well designed RCT; Blind adjudication of outcomes; Important clinical endpoints considered.

Limitations: • Open label design leaves room for bias. • Unequal previous exposure to VKA may have created a selection bias.

- Rates of stroke and other vascular events were lower than in previous trials, resulting in small absolute differences in events between groups ⁷.
- No prior VKA: Difference between 1st outcome and major bleeding not statistically significant.
- Prior VKA: risk of 1st outcome higher with clopidogrel + ASA p=0.0005 and no significant difference in bleeding.

In favor of VKA therapy. This may have translated into improved outcomes for VKA therapy (e.g. major bleeding). Comparing guideline schemes to ACTIVE W patients suggests a moderate-high risk population.

Bottom Line:
⇒ Warfarin is SUPERIOR to clopidogrel + ASA for prevention of vascular events in patients with AF and at least 1 stroke risk factor CHADS² ≥2 (1.1), especially in those already taking VKA therapy.

- After ACTIVE W there is no indication to change the current standard of care for stroke prevention in patients with AF.
- Major bleeding: similar rate for Clopidogrel + ASA vs warfarin 3 vs 2.8%, but more minor bleeding Clopidogrel + ASA in Active W.
- For patients naïve to both treatments, the benefits of VKA therapy relative to clopidogrel + ASA are less certain.
- Other considerations & unanswered questions:
  - Results of ACTIVE A suggest that in lower-risk patients Clopidogrel + ASA reduces the risk of major vascular events compared with ASA alone (NNT=42;0.6 yr), but increases the risk of major bleeding (NNH=42;3.6 yr).
  - Majority of patients in ACTIVE W and ACTIVE A were not at high risk for stroke.
  - Role of warfarin may be challenged by the availability of dabigatran (RE-LY study) and rivaroxaban (ROCKET AF study).
  - Cost/Patient/Year → Clopidogrel + ASA = ~$1260; Warfarin = ~$156-$216 for ≤5mg/day (Note cost of INR not included.)
References

See also:


7 Sloan MA. Clopidogrel plus aspirin was inferior to oral anticoagulation for preventing vascular events in atrial fibrillation. ACP J Club. 2006 Nov-Dec;145(3):58.

