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 W [2] - 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 I - 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** [PLAVIX] **75mg daily + ASA 75-100mg daily** to reduce vascular events [(Stroke; non-CNS systemic embolism; MI; Death)] 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; 55-74 yrs+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: ♂[~60%]; any ethnicity [~63% from Europe & Israel]; Age [mean]: 71; $CHADS_{mean}$= 2 {70% were CHADS 1 or 2; (0=2.8%, 1=36.1%, 2=33.5%, 3=16.5%, 4=8%, 5=2.7%, 6=0.4%)}; BP=136/81, HR=75 bpm; Hx of: permanent AF [64%], ↑BP [85%], stroke/TIA [13%], on ASA [83%]; having specific bleed risk [23%].

Results - over the median 3.6 years of follow-up

{ITT analysis; per protocol analysis also done as recommended for non-inferiority trial, but CI quite wide !}

	Clinical Endpoints	ASA+Clopidogrel n=3772	ASA n=3782	ARR	NNT/NNH (95% CI)	Comments
1°	Composite Major Vascular Events: Stroke; non-CNS systemic embolism; MI; Death	22.1% {n=832} (6.8%/yr)	24.4% {n=924} (7.6%/yr)	2.37% (RR↓=10%)	**42** (95% CI: 23-213)	1°: RR = 0.89 (95% CI: 0.81-0.98; p=0.01) {HTN, LDL etc. not evaluated}
2°	Stroke, Any	7.8% RR = 0.72 **(2.4%/yr)**	10.8% **(3.3%/yr)**	2.94% (RR↓=27%)	34 (95% CI: 23-60)	Subgroup analysis: • 1° benefit greatest in age 65-74; neutral effect in age ≥75. • patient preference not to go on warfarin was more strongly associated with benefit than bleed risk or physician judgment.
	Stroke, non-disabling	2.8%	4%	1.2%	82 (95% CI: 49-254)	
	Stroke, disabling or fatal	5.3%	7.1%	1.8%	55 (95% CI: 35-138)	
	Non-CNS systemic embolism	1.4%	1.4%	NS	-	
	Death from vascular causes	15.9%	15.8%	NS	-	
	All-cause death	21.9% (6.4%/yr)	22.2%	NS	-	Overall: • potential to benefit from combination equal to ↑ risk of major bleed (e.g. NNT=42 & NNH=42 / ~ 3.6yr)
	Major Bleed (severe or fatal)	6.7% (2.0%/yr)	4.3% (1.3%/yr)	2.4% (RR↑=55%)	**42** (95% CI: 29-74)	
	Minor Bleed	10.8%	4.6%	6.2%	16 (95% CI: 14-20)	

AF=atrial fibrillation CI=confidence interval DVT=clot LVEF=left ventricular ejection fraction MI=myocardial infarction NNH=number needed to harm NNT=number needed to treat NS=not significant PE=pulmonary embolism RR=relative risk
*Time to 1st event; **Other endpoints: no difference in malignancies, pneumonia; possible ↑ in non-serious but not serious macular edema. Per Protocol Analysis: HR: 1.02 (0.85-1.21) but excluded if 30days after transfer from dual treatment

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]
  {Clopidogrel is a prodrug requiring metabolism before being activated by CYP2C19. 30% of blacks & whites, and >50% of Asians have a polymorphism that causes decreased activation of clopidogrel; exposure to active form of clopidogrel may be ↓ by ~1/3 in these patients.[4] Some data suggests the interaction may not be real.[5]}
- Application of findings limited to patients at $CHADS_2$ score of 1 or 2 who were not at high risk of bleeding

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. NNT= 42 / ~3.6yrs; NNH= 42 / ~3.6yrs.***
{Consider individualized risk & values; e.g. some may value the stroke endpoint more than the major bleed endpoint or cost.}

⇨ **Drug cost per patient per year: ASA+clopidogrel = $1,260; ASA = $95** **{Per one less 1° outcome per year: $ 175,000 [6]}**

⇨ **Assess risk of bleed vs any potential benefit for individual patient.** {If high bleed risk, may avoid warfarin & ASA+clopidogrel tx.}

⇨ **If patient is on clopidogrel + a PPI, reassess need for clopidogrel &/or need for a PPI.** {Consider alternatives to the PPI such as an H2RA or misoprostol; if PPI needed, consider one with less potential for a drug interaction (pantoprazole? or rabeprazole?). Or consider ASA monotherapy.}

- The **ACTIVE-W** trial found that in atrial fibrillation patients with at least 1 risk factor for stroke (most moderate risk), warfarin decreased the chance of having a vascular event compared to ASA+clopidogrel. {For every 47 patients treated for 1.3years, one extra vascular event (1° outcome) was prevented (NNT= 47)}
  There was no difference in the major bleeding rate (Warfarin 3.03%; ASA+clopidogrel 2.76% over the duration of trial). Overall bleeding was higher in the ASA+clopidogrel arm than with warfarin. Note: ↑ major bleed risk often without benefit also found in previous ASA+clopidogrel combination trials: MATCH and CHARISMA.
  [MATCH: TIA hx [21%] or ischemic stroke [79%] →PLAVIX +/-ASA [75mg od] {ischemic events [15.7 combo vs 16.7%, non-significant]; major bleeding [2.6 combo vs 1.3%; n=7599 ~18month]}
  CHARISMA: PLAVIX + ASA no better than ASA [75-162mg/d] [CV death, MI, or stroke 6.8 vs 7.3%] in atherosclerosis/high CV risk pts (but ↑bleeding [Moderate 2.1 vs 1.3%, NNH=125; Severe 1.7 vs 1.3%]) n=15,603 ~28mon Subgroups: Asymptomatic pts: ↑ harm (bleed, ↑CV events, ↑CV death); Documented atherosclerosis pts: some benefit NNT=100 but ↑bleed.]
- It is important to remember that both the ACTIVE trials did not involve very many patients with high CHADS scores and excluded patients with major bleeding risk.
- 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.

See also:
- RxFiles Chart - Antithrombotics: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf
- RxFiles Q&A – Clopidogrel & PPI Interaction: http://www.rxfiles.ca/rxfiles/uploads/documents/Clopidogrel-PPI-interaction-QandA.pdf
- RxFiles ACTIVE W Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-W-Trial-Summary.pdf

Extras

The $CHADS_2$ 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).

	Condition	Points
C	Congestive heart failure	1
H	Hypertension (or treated hypertension)	1
A	Age >75 years	1
D	Diabetes	1
S_2	Prior Stroke or TIA	2

Score	Stroke Risk	Therapy Chest'08 (9), ACC'06 (10)
0-1	Low (≤ 3%/year)	Aspirin (esp. if age ≥60yrs) [11]
1-2	Moderate (~ 3-4%/year)	VKA (e.g. warfarin) or alternatives; see below. {Warfarin most effective in decreasing stroke risk.}
3-5	High (~ 6-12%/year)	
6	Very High (~ 18%/year)	

VKA=vitamin K antagonist

AF Patient Description	Treatment Option(s)
Moderate → high risk for stroke + no contraindication (CI) to VKA	**VKA e.g warfarin (target INR 2 - 3) unless contraindicated*** (demonstrates max stroke prevention with an acceptable major bleed risk; esp. if $CHADS_2 \geq 2$, >85yr of age if no bleed hx, or an ischemic stroke hx [13])
Moderate → high risk for stroke + cannot/will not tolerate VKA OR high-quality anticoag not achieved with VKA OR low risk for stroke	**ASA monotherapy** 75-100mg daily **or** **Clopidogrel** 75mg daily **+ ASA** 75-100mg daily 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 PRADAX 110-150mg cap BID 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=173/yr but with similar bleeding rates. {Note: the rate of MI was slightly higher NNH=527/yr 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) Rivaroxaban XARELTO: currently being evaluated in ROCKET AF, a phase 3 trial in AF patients.

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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?

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

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 <50x10^9/L, mitral stenosis.

- **Active Control group vs. Treatment group:**
- **VKA (e.g. warfarin)**$_{n=3371}$: Titrate to INR 2.0-3.0$_{(measured \le 1\ month)}$ versus **Clopidogrel$_{(75mg/day)}$ + ASA $_{(75\text{-}100\ mg/day)}$** $_{n=3335}$.
- Baseline: n=6706, AF; age$_{mean}$ 70 (66% ♂), CHADS$_{2\ mean}$ 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!)

Clinical Endpoints	Clopidogrel + ASA n=3335	VKA n=3371	ARR	NNT/NNH (95% CI) over ~ 1.3 years	Comments
Composite (stroke, non-CNS embolus, MI, vascular death) (1°)*	7 % n=234 (5.6%/yr)	4.9 % n=165 (3.9%/yr)	↑ 2.1 % (RR↑ 43%)	NNH=47 (95% CI: 31-101)	◆INR therapeutic 64% of the time. ◆Discontinuation rate of VKA was significantly ↓ & INR control was significantly better for patients entering on VKA. Subgroup analysis: ◆No prior VKA: Difference between 1° outcome and major bleeding not statistically significant ◆Prior VKA: risk of 1° outcome higher with clopidogrel + ASA p=0.0005 and no significant difference in bleeding ◆Event #'s not provided for 2° outcomes.
Stroke	3 % n=100 (2.4%/yr)	1.8 % n=59 (1.4%/yr)	↑ 1.3 % (RR↑ 71%)	NNH=80 (95% CI: 51-191)	
MI	1.1 %	0.7 %	NS	-	
Vascular death	3.6 %	3.1 %	NS	-	
Total Mortality	4.8 %	4.7 %	NS	-	
Non-CNS embolus	0.5 % n=18 (0.4%/yr)	0.1 % n=4 (0.1%/yr)	↑ 0.4 % (RR↑ 354%)	NNH=238 (95% CI: 144-191)	
Major Hemorrhage**	3% (2.4%/yr)	2.8% (2.2%/yr)	NS	-	
Minor Hemorrhage***	17 % n=568 (13%/yr)	14.3 % n=481 (11%/yr)	↑ 2.7% (RR↑ 19%)	NNH=37 (95% CI: 23-104)	

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 MI=myocardial infarction NNH=number needed to harm 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
* Time to 1st event, ** Death, ↓ Hgb by ≥ 50g/L, HTN needing inotrope, intraocular bleed→loss of vision, surgery needed, symptomatic intracranial hemorrhage or transfusion of ≥4 units blood, *** Other bleeding requiring regimen modification

Strengths, Limitations & Uncertainties

Strengths: Well designed RCT✓; Blinded 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 in favour of VKA therapy. This may have translated into improved outcomes for VKA therapy (e.g. major bleeding). ◆Rates of stroke and other vascular events were lower than in previous trials, resulting in small absolute differences in events between groups [7]. ◆Per-protocol analysis was not included (is generally recommended in non-inferiority trials [8]).

Uncertainties: ◆Patients identified as having AF with high risk of stroke. Difficult to determine if all patients were high stroke risk. Mean CHADS$_2$ score of 2 (±1.1) suggest patients more closely resemble a moderate risk population. Comparing guideline [2,3] risk schemes to ACTIVE W patients suggests a moderate-high risk population. ◆Variation in the number of dropouts between groups (VKA n=239, Clopidogrel + ASA n=420). ◆Clopidogrel+ASA a consideration if not able to maintain therapeutic INR.

Bottom Line:

⇨ ***Warfarin is SUPERIOR to clopidogrel + ASA for prevention of vascular events in patients with AF and at least 1 stroke risk factor*** $_{CHADS_2=2\ (\pm 1.1)}$***, 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 low-moderate risk patients Clopidogrel + ASA reduces the risk of major vascular events compared with ASA alone (NNT=42/3.6 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 [9]) and rivaroxaban (ROCKET AF study [10])
  - ◆Cost/Patient/Year → Clopidogrel+ASA = ~$1260; Warfarin = ~$156-$216 for ≤5mg/day {Note cost of INR not included.}

References

See also:
- RxFiles Chart - Oral Antiplatelet & Antithrombotic agents: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf
- RxFiles ACTIVE A Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf

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