Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

*The ACTIVE Writing Group on behalf of the ACTIVE Investigators**

Summary

Background **Oral anticoagulation therapy reduces risk of vascular events in patients with atrial fibrillation. However, long-term monitoring is necessary and many patients cannot achieve optimum anticoagulation. We assessed whether clopidogrel plus aspirin was non-inferior to oral anticoagulation therapy for prevention of vascular events.**

Methods **Patients were enrolled if they had atrial fibrillation plus one or more risk factor for stroke, and were randomly allocated to receive oral anticoagulation therapy (target international normalised ratio of 2·0–3·0; n=3371) or clopidogrel (75 mg per day) plus aspirin (75–100 mg per day recommended; n=3335). Outcome events were adjudicated by a blinded committee. Primary outcome was first occurrence of stroke, non-CNS systemic embolus, myocardial infarction, or vascular death. Analyses were by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00243178.**

Results **The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3·93%) and 234 in those on clopidogrel plus aspirin (annual risk 5·60%; relative risk 1·44 (1·18–1.76; p=0.0003). Patients on oral anticoagulation therapy who were already receiving this treatment at study entry had a trend towards a greater reduction in vascular events (relative risk 1·50, 95% CI 1·19–1·80) and a significantly (p=0·03 for interaction) lower risk of major bleeding with oral anticoagulation therapy (1.30; 0.94–1.79) than patients not on this treatment at study entry (1·27, 0·85–1·89 and 0·59, 0·32–1·08, respectively).**

Conclusion **Oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke, especially in those already taking oral anticoagulation therapy.**

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Introduction

Atrial fibrillation is a common cardiac arrhythmia, especially in the elderly, and affects over 1% of the population. It increases the risk of stroke and other vascular events.[1,2] Oral anticoagulation therapy such as warfarin reduces stroke by two-thirds compared with no treatment.[3,4] Compared with aspirin, oral anticoagulation therapy reduces the risk of stroke by 45% and reduces cardiovascular events by 29%.[5] However, it increases the risk of major bleeding by about 70%[5] compared with aspirin. Oral anticoagulation therapy is currently the treatment of choice for patients at high risk of stroke.[6]

The response to oral anticoagulation therapy is affected by gut flora, variations in hepatic function, interactions with several drugs, and diet,[7] requiring regular monitoring of the level of anticoagulation. Therefore, only about half of potentially eligible patients receive oral anticoagulation therapy.[8] An effective, simple and safe alternative to this treatment could be of great clinical value.

Both aspirin and clopidogrel are antiplatelet agents that act through different mechanisms and are effective in preventing vascular events in patients at high risk.[9] Aspirin reduces risk of stroke in patients with atrial fibrillation by 22%.[3,4] The additive benefits of combining a thienopyridine with aspirin have been clearly shown in patients undergoing percutaneous coronary intervention, in those with acute coronary syndrome or acute myocardial infarction.[10-13] Since aspirin has a documented protective effect in atrial fibrillation, it is reasonable to expect that the addition of clopidogrel to aspirin will provide incremental benefits so that this combination would be non-inferior to oral anticoagulation therapy alone in preventing vascular events. We aimed to assess whether clopidogrel plus aspirin was statistically non-inferior to oral anticoagulation therapy for prevention of vascular events in patients with atrial fibrillation at high risk of stroke and eligible for oral anticoagulation therapy.

Methods

Participants

Three separate inter-related trials comprise the ACTIVE programme. Patients eligible for and willing to take oral anticoagulation therapy were enrolled into ACTIVE W, in which clopidogrel plus aspirin was compared to oral

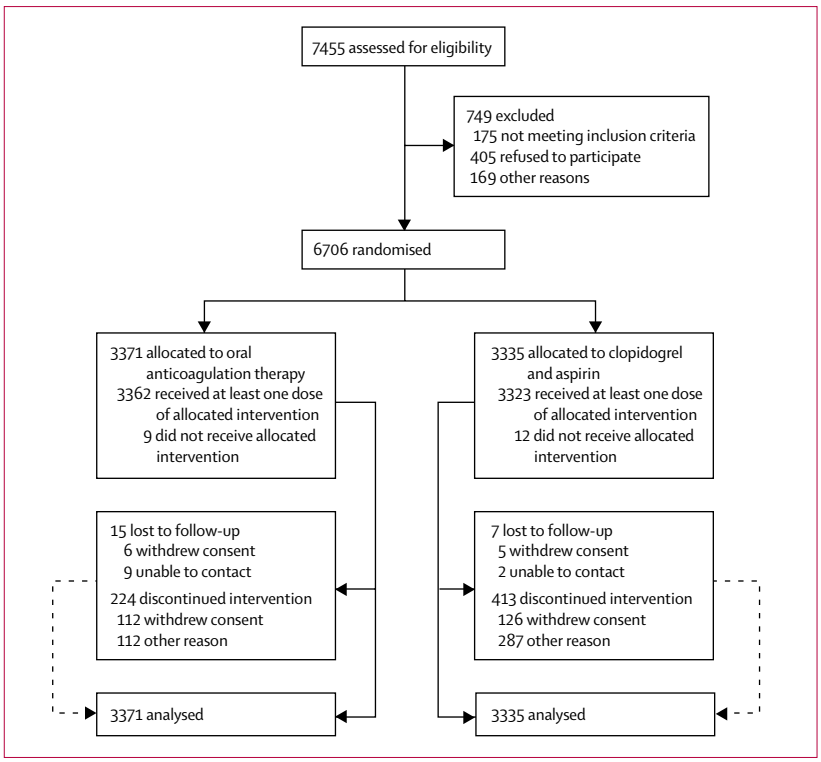


Figure 1: **Trial profile**

anticoagulation therapy Patients ineligible for or unwilling to take oral anticoagulation therapy were enrolled into ACTIVE A, in which clopidogrel was compared with placebo in patients receiving aspirin. ACTIVE I was a randomised placebo-controlled trial of irbesartan for eligible patients from either ACTIVE A or ACTIVE W. Only the results of ACTIVE W are reported here; ACTIVE A and ACTIVE I are ongoing.

Patients were eligible for ACTIVE W if they had electrocardiographic evidence of atrial fibrillation and at least one of the following: age 75 years or older; on treatment for systemic hypertension; previous stroke, transient ischaemic attack, or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction less than 45%; peripheral arterial disease; if patients were aged 55–74 years and did not have one of the other inclusion criteria they were required to have either diabetes mellitus requiring drug therapy or previous coronary artery disease. Patients were excluded if they had any of the following: contraindication for clopidogrel or for oral anticoagulant (such as prosthetic mechanical heart valve); documented peptic ulcer disease within the previous 6 months; previous intracerebral haemorrhage; significant thrombocytopenia (platelet count $<50\times10^9$/L); or mitral stenosis.

Procedures

Patients were randomised by an automated central interactive voice response system, in a 1:1 ratio, to receive clopidogrel plus aspirin or oral anticoagulation therapy. Treatment was open, with blinded adjudication of outcomes. Patients randomised to oral anticoagulation therapy received the vitamin K antagonist in use in their country and were monitored to keep the international normalised ratio (INR) between 2·0 and 3·0. The dose of oral anticoagulant was managed by study investigators or by local anticoagulation clinics. INR was measured at least monthly. The quality of INR control was evaluated by averaging all INR values for each month of treatment for each patient to generate the average monthly INR for that patient. INR was not measured in patients randomised to clopidogrel plus aspirin. They received clopidogrel 75 mg, once daily in addition to aspirin (75–100 mg per day recommended).

The primary outcome was the first occurrence of stroke, non-CNS systemic embolism, myocardial infarction, or vascular death. Strokes were subclassified into those that were ischaemic, primary haemorrhagic, or of uncertain type, and the severity of stroke was measured with the modified Rankin score at the time of discharge from hospital or at 7 days after the event. Subdural haematomas were included as intracranial haemorrhages, but not classified as haemorrhagic strokes. Haemorrhagic transformation of ischaemic stroke was not considered to be a primary intracerebral haemorrhage. Myocardial infarction was diagnosed according to guidelines of the American Heart Association and the American College of Cardiology.[14]

Vascular death was any death that was clearly not due to non-vascular cause such as trauma. Major bleeding was defined as any bleeding requiring transfusion of at least two units of red blood cells or equivalent of whole blood, or which was severe. Severe bleeding was bleeding associated with any of the following: death, drop in haemoglobin of at least 50 g/L, substantial hypotension with the need for inotropic agents, intraocular bleeding leading to substantial loss of vision, bleeding requiring surgical intervention (other than vascular site repair), symptomatic intracranial haemorrhage, or requirement for a transfusion of a least four units of blood. Minor bleeding was any other bleeding requiring modification of the study drug regimen. All major outcomes were adjudicated by a blinded committee and all strokes were adjudicated by neurologists.

Statistical analysis

The goal of ACTIVE W was to establish that clopidogrel plus aspirin is statistically non-inferior to oral anticoagulation therapy. A meta-analysis based on individual patients' data from six randomised controlled trials of oral anticoagulation against placebo or usual care showed a hazard ratio of 0·42 (95% CI 0·27–0·54) for the outcome of stroke, myocardial infarction, vascular death, or non-CNS systemic embolus (calculations based on data provided by Carl van Walraven, University of

Ottawa). This value yields an excess hazard of 1·73 for control versus oral anticoagulation therapy with a lower confidence limit of 1·37; 50% of which provides a non-inferiority margin of 1·186. Based on an expected annual event rate of 7%, 2 years of enrolment, 2 further years of follow-up, a 5% dropout rate over 3 years, and a one-sided α of 0·025, a trial of 6500 patients was planned in order to have 85% power to show non-inferiority. Kaplan-Meier curves were constructed for time to event and were compared by log rank tests. Continuous variables were compared using Student's *t* test. The ethics committee at all study centres approved the study and all patients signed informed consent. A data and safety monitoring board reviewed the data periodically for safety and efficacy. They could recommend stopping the study if a benefit in favour of oral anticoagulation therapy was shown, such that the hazard ratio for clopidogrel plus aspirin versus oral anticoagulation therapy exceeded 1·0 by more than 3 SD at either of two formal interim analyses, timed to occur when 50% or 75% of events had occurred. Before data analysis, the steering committee recognised previous use of oral anticoagulation therapy as a factor that might affect response to treatment, and alerted the data and safety monitoring board to this issue before study termination. All data were managed at the Population Health Research Institute (Hamilton, ON, Canada) under the supervision of the Writing Group who had unrestricted access to all data. Analyses were by intention-to-treat.

This study is registered with ClinicalTrials.gov, number NCT00243178.

Role of the funding source

The sponsor of the study participated in study design with the Principal Investigators and Steering Committee, but had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

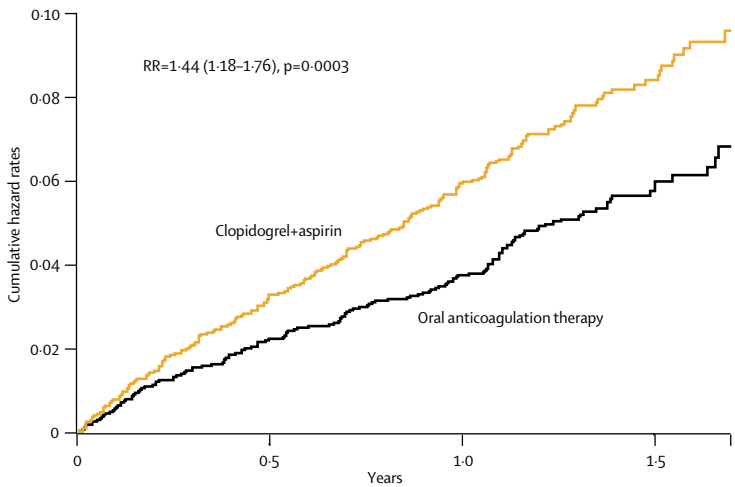
Patients were enrolled between June, 2003, and December, 2004. Patient enrolment was briefly re-opened in July, 2005, because overall event rates were lower than expected. On August 25, 2005, the data and safety monitoring board recommended that the study be stopped due to clear evidence of superiority of oral anticoagulation over clopidogrel plus aspirin. Investigators were notified to discontinue study medication and to treat study patients according to current guidelines. The data and safety monitoring board recommended that ACTIVE A and ACTIVE I should continue. The trial profile is shown in figure 1. Median follow-up duration was 1·28 years.

Patients' characteristics are shown in table 1. Atrial fibrillation was permanent in most patients, and was longstanding (>2 years) in 59%. Sinus rhythm was present on the baseline electrocardiogram in 13%. Previous stroke or transient ischaemic attack had occurred in 15%. 17% of patients had previous myocardial infarction and 28% had evidence of coronary artery disease. Most patients (77%) were receiving oral anticoagulation before randomisation. The cumulative risk of permanent discontinuation of study medication

	Clopidogrel+aspirin	Oral anticoagulation therapy
Number of patients	3335	3371
Age (years)	70·2 (9·4)	70·2 (9·5)
Blood pressure (mm Hg)		
Systolic	133 (19·1)	133 (18·8)
Diastolic	79·3 (11·7)	79·4 (12·1)
Heart rate	74·3 (14·2)	74·3 (14·1)
Body-mass index	28·9 (4·9)	28·7 (5·0)
CHADS-2 score	2·0 (1·1)	2·0 (1·1)
Male	2219 (67%)	2211 (66%)
Atrial fibrillation type		
Permanent	2300 (69%)	2305 (68%)
Persistent	426 (13%)	468 (14%)
Paroxysmal	605 (18%)	594 (18%)
Duration of atrial fibrillation		
<6 months	700 (21%)	665 (20%)
6 months–2 years	645 (19%)	717 (21%)
>2 years	1986 (60%)	1987 (59%)
History of hypertension	2755 (83%)	2767 (82%)
History of stroke or TIA	510 (15%)	510 (15%)
History of ischaemic heart disease		
Myocardial infarction	573 (17%)	591 (18%)
CABG surgery	288 (9%)	294 (9%)
Angiographic CAD	346 (10%)	374 (11%)
Diabetes mellitus	712 (21%)	717 (21%)
Peripheral artery disease	117 (4%)	118 (4%)
Heart failure	991 (30%)	1040 (31%)
Cardiac Pacemaker	451 (14%)	449 (13%)
Baseline ECG		
Atrial fibrillation	2699 (81%)	2737 (81%)
Atrial flutter	32 (1%)	37 (1%)
Sinus rhythm	447 (13%)	445 (13%)
Left ventricular hypertrophy	446 (13%)	453 (13%)
Baseline medications		
Oral anticoagulant	2526 (76%)	2627 (78%)
Aspirin	1005 (30%)	884 (26%)
Clopidogrel	87 (3%)	78 (2%)
Angiotensin receptor antagonist	508 (15%)	488 (15%)
ACE inhibitor	1772 (53%)	1857 (55%)
Beta blocker	1944 (58%)	1897 (56%)
Digoxin	1218 (37%)	1234 (37%)
Antiarrhythmic	645 (19%)	644 (19%)
Statin	1281 (38%)	1254 (37%)

Data are number (%) or mean (SD). CABG=coronary artery bypass graft. CAD=coronary artery disease. ECG=electrocardiograph. TIA=transient ischaemic attack. ACE=angiotensin-converting enzyme.

Table 1: **Patients' clinical characteristics**

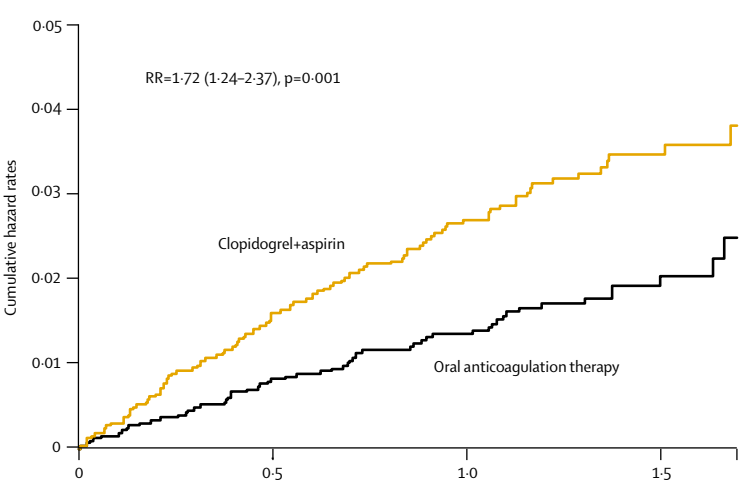


Number at risk

Clopidogrel +aspirin	3335	3152	2389	927
Oral anticoagulation therapy	3371	3221	2458	924

Figure 2: **Cumulative risk of primary outcome**

at 18 months was 7·8% for the oral anticoagulation group and 13·8% for the clopidogrel group. Of those followed-up for 18 months, 323 (11·8%) in the oral anticoagulation group were receiving aspirin. During the study, patients on oral anticoagulation therapy had INR values in the therapeutic range (2·0–3·0) 63·8% of the time; below 2·0, 20.8% of the time; and above 3·0, 15·4% of the time.



Number at risk

Clopidogrel +aspirin	3335	3168	2419	941
Oral anticoagulation therapy	3371	3232	2466	930

Figure 3: **Cumulative risk of stroke**

There were 164 primary outcome events (stroke, non-CNS systemic embolus, myocardial infarction, or vascular death) on oral anticoagulation therapy (annual risk 3·90%) compared with 234 events on clopidogrel plus aspirin (annual risk 5·60%; relative risk [RR] 1.44, 95% CI 1·18–1·76; p=0·0003). Figures 2 and 3 show the cumulative risks for the primary outcome and for stroke with the two treatments. As shown in table 2, there were more events for each component of the primary outcome with clopidogrel plus aspirin compared with oral anticoagulation therapy. However, the main advantage with oral anticoagulation therapy was seen in stroke (RR 1·72, 95% CI 1·24–2·37; p=0·001) and in non-CNS systemic embolism (4·66, 1·58–13·8; p=0·005). Myocardial infarction occurred at rates of less than 1% per year in both groups and was not significantly different between the treatments. Rates of vascular death were slightly higher with clopidogrel plus aspirin than with oral anticoagulation therapy, but total mortality rates were similar in the two groups (RR 1·01, 95% CI 0·81–1·26; p=0·91). The net benefit (primary outcome event plus major haemorrhage) favoured oral anticoagulation therapy (1·41, 1·19–1·67; p<0·0001).

The severity of stroke, measured before hospital discharge or at 7 days with the modified Rankin scale is shown in table 3. Strokes with modified Rankin scores of 0–2 were non-disabling. At each level of severity of stroke, there were more strokes with clopidogrel plus aspirin; however, the relative risk of clopidogrel plus aspirin versus oral anticoagulation therapy decreased with increasing stroke severity (p=0·027). Therefore, compared with clopidogrel plus aspirin, oral anticoagulation therapy reduced all strokes, but was significantly more likely to prevent a minor stroke than a more serious stroke.

Rates of major haemorrhage were similar in the two groups (table 2). However, significantly more minor bleeds occurred with clopidogrel plus aspirin than with oral anticoagulation therapy. Total bleeds were also significantly more likely with clopidogrel plus aspirin than with oral anticoagulation therapy. Fatal bleeds were rare. Intracranial bleeds (including subdural haematoma) were more common with oral anticoagulation therapy than with clopidogrel plus aspirin (21 *vs* 11; p=0.08).

77% of patients were receiving oral anticoagulation therapy at the time of study entry (table 4). We had hypothesised in advance of knowledge of study results that patients receiving this treatment at the time of enrolment were more likely to have a favourable response to oral anticoagulation therapy during the study because of better tolerability and improved INR control, compared with those who had not previously been on oral anticoagulation therapy. Patients on oral

	Clopidogrel+aspirin		Oral anticoagulation		Clopidogrel+aspirin *vs* oral anticoagulation	
	Number	Risk (% per year)	Number	Risk (% per year)	RR (95% CI)	p
Composite of stroke, non CNS embolus, myocardial infarction, vascular death	234	5·60	165	3·93	1·44 (1·18–1·76)	0·0003
Non-CNS embolus	18	0·43	4	0·10	4·66 (1·58–13·8)	0·005
Myocardial infarction	36	0·86	23	0·55	1·58 (0·94–2·67)	0·09
Stroke	100	2·39	59	1·40	1·72 (1·24–2·37)	0·001
Ischaemic	90	2·15	42	1·00	2·17 (1·51–3·13)	<0·0001
Haemorrhagic	5	0·12	15	0·36	0·34 (0·12–0·93)	0·036
Stroke severity						
Non-disabling	42	1·00	17	0·40	2·49 (1·42–4·37)	0·002
Disabling	58	1·39	40	0·95	1·47 (0·98–2·20)	0·06
Fatal	14	0·33	15	0·36	0·93 (0·45–1·94)	0·85
Total mortality	159	3·80	158	3·76	1·01 (0·81–1·26)	0·91
Vascular death	120	2·87	106	2·52	1·14 (0·88–1·48)	0·34
Non-vascular death	39	0·93	52	1·24	0·76 (0·50–1·15)	0·20
Haemorrhage						
Major (includes severe and fatal)	101	2·42	93	2·21	1·10 (0·83–1·45)	0·53
Severe	71	1·70	66	1·57	1·09 (0·78–1·52)	0·62
Fatal	7	0·17	11	0·26	0·64 (0·25–1·66)	0·36
Minor	568	13·58	481	11·45	1·23 (1·09–1·39)	0·0009
Total	644	15·40	555	13·21	1·21 (1·08–1·35)	0·001
Net benefit						
Primary outcome and major bleed	316	7·56	229	5·45	1·41 (1·19–1·67)	<0·0001
Primary outcome, major bleed, and death	348	8·32	271	6·45	1·31 (1·12–1·54)	0·0008

Table 2: **Primary and secondary outcomes**

anticoagulation at study entry were more likely to have permanent atrial fibrillation and slightly less likely to have hypertension than those who were not (table 4). The two groups had almost identical CHADS2 risk scores.[15]

The groups who were and were not on oral anticoagulation therapy at study entry responded differently to oral anticoagulation therapy during the study. Although rates of discontinuation of clopidogrel plus aspirin were similar, the rates of discontinuation of oral anticoagulation therapy were significantly lower for patients who entered the study already on oral anticoagulant compared with those who did not (p=0.008). For example, at 1 year the discontinuation rate of oral anticoagulation therapy was 8·7% for patients who entered on oral anticoagulation therapy and 15·3% for those who did not. Furthermore, INR control was significantly better (p<0·0001) for patients entering the study on oral anticoagulation therapy. For example, at 3 months INR values were therapeutic in 62·4% of patients already on the treatment at entry, compared with 57·2% of patients who were not; at 18 months the corresponding data were 67·8% and 65·1%, respectively.

For patients not already on oral anticoagulation therapy, the risk of a primary outcome event was only moderately higher on clopidogrel plus aspirin than on oral anticoagulation therapy; but for those already on oral anticoagulation therapy at entry the risk was much higher on clopidogrel plus aspirin (table 5). Patients not

	Clopidogrel+aspirin		Oral anticoagulation therapy		Clopidogrel+aspirin *vs* oral anticoagulation therapy	
	Number	Risk (% per year)	Number	Risk (% per year)	RR (95% CI)	p for trend
Total strokes	100	2·39	59	1·40	1·72 (1·25–2·37)	0·03
0–2 (no or minor disability)	42	1·00	17	0·40	2·49 (1·42–4·37)	
3 (moderate disability)	15	0·36	7	0·17	2·18 (0·89–5·35)	
4–5 (severe disability)	29	0·69	19	0·45	1·54 (0·87–2·76)	
6 (fatal stroke)	14	0·33	15	0·36	0·93 (0·45–1·94)	

Modified Rankin score was missing for one patient allocated to clopidogrel plus aspirin and for one patients allocated to oral anticoagulation therapy.

Table 3: **Stroke severity**

	On oral anticoagulation therapy at entry	Not on oral anticoagulation therapy at entry	p
Number of patients	5153	1553	..
Age (years)	70·3 (9·4)	70·0 (9·6)	0·25
Blood pressure (mm Hg)			
Systolic	133 (19)	134 (18)	0·043
Diastolic	79 (12)	80 (12)	0·002
Heart rate	74 (14)	74 (15)	0·86
CHADS2 score	2·0 (1·1)	1·97 (1·1)	0·32
Male	3447 (67%)	983 (63%)	0·009
Permanent atrial fibrillation	3706 (72%)	899 (58%)	<0·0001
Atrial fibrillation duration <6 months	816 (16%)	549 (35%)	<0·0001
History of hypertension	4200 (82%)	1322 (85%)	0·001
History of stroke or TIA	777 (15%)	243 (16%)	0·58
Myocardial infarction	910 (18%)	254 (16%)	0·23
Diabetes mellitus	1122 (22%)	307 (20%)	0·09
Peripheral artery disease	194 (4%)	41 (3%)	0·035
Heart failure	1591 (31%)	440 (28%)	0·056
Baseline ECG			
Atrial fibrillation	4213 (82%)	1223 (79%)	0·008
Atrial flutter	51 (1%)	18 (1%)	0·56
Sinus rhythm	622 (12·1)	270 (17%)	<0·0001
Baseline medications			
Oral anticoagulant	5153 (100%)	0	<0·0001
Aspirin	749 (15%)	1140 (73 %)	<0·0001
Clopidogrel	19 (<1%)	146 (9%)	<0·0001

Data are number (%) or mean (SD). ECG=electrocardiograph. TIA=transient ischaemic attack. AF=atrial fibrillation.

Table 4: Baseline characteristics of patients by use of oral anticoagulation at study entry

on oral anticoagulation therapy at entry had less major bleeding with clopidogrel plus aspirin than with oral anticoagulation therapy. On the other hand, those already on oral anticoagulation therapy at entry had more major bleeding with clopidogrel plus aspirin than with oral anticoagulation therapy. For the outcome of net benefit (a composite of the primary outcome and major bleeding) the relative risk was 1·10 for those who were not on oral anticoagulation therapy at entry compared to 1·52 for those who were (p interaction=0·11).

Discussion

We have shown that oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke who do not have contraindications to oral anticoagulation therapy. This finding was driven largely by higher rates of stroke and non-CNS systemic embolus with clopidogrel plus aspirin. Stroke and non-CNS systemic embolus are thought to result predominantly from cardiac thrombus formation in patients with atrial fibrillation, suggesting that oral anticoagulation therapy is particularly effective against left atrial thrombosis and that, in spite of previous observations on the protective effect of aspirin, platelet activation is not the predominant pathway in the pathogenesis of stroke in atrial fibrillation. Based on experience in patients with acute coronary syndrome, in which the addition of clopidogrel to aspirin resulted in substantial reductions in myocardial infarction and other vascular events compared with just aspirin,[10] some reduction in myocardial infarction with clopidogrel plus aspirin compared with oral anticoagulation therapy might have been expected. However, oral anticoagulation therapy is also effective in patients with ischaemic heart disease.[16]

A reduction in vascular events with oral anticoagulation therapy would be expected to lead to a reduction in total mortality. However mortality rates were the same with the two treatments. There were slightly fewer vascular deaths with oral anticoagulation therapy than with clopidogrel plus aspirin; however, this trend was offset by a similar increase in non-vascular deaths. The absence of effect on mortality is partly explained by a tendency for oral anticoagulation therapy, compared with clopidogrel plus aspirin, to substantially reduce the less severe vascular events but to have little effect on the more severe and fatal events. Oral anticoagulation therapy (relative to clopidogrel plus aspirin) was significantly more effective against non-disabling stroke than against disabling stroke. There were more haemorrhagic strokes, which are usually fatal or disabling, with oral anticoagulation therapy than with

	Risk (% per year)		Clopidogrel+aspirin *vs* oral anticoagulation		
	Clopidogrel +aspirin	Oral anticoagulation therapy	RR (95% CI)	p	p (interaction)
Primary outcome					
Oral anticoagulation therapy at entry	5·50	3·72	1·50 (1·19–1·89)	0·0005	0·43
No oral anticoagulation therapy at entry	5·89	4·71	1·27 (0·85–1·89)	0·24	
Major haemorrhage					
Oral anticoagulation therapy at entry	2·63	2·02	1·30 (0·94–1·79)	0·11	0·028
No oral anticoagulation therapy at entry	1·73	2·92	0·59 (0·32–1·08)	0·09	
Net benefit					
Oral anticoagulation therapy at entry	7·60	5·11	1·52 (1·25–1·85)	<0·0001	0·11
No oral anticoagulation therapy at entry	7·41	6·73	1·10 (0·78–1·55)	0·57	

Table 5: **Clinical outcomes and use of oral anticoagulation therapy at study entry**

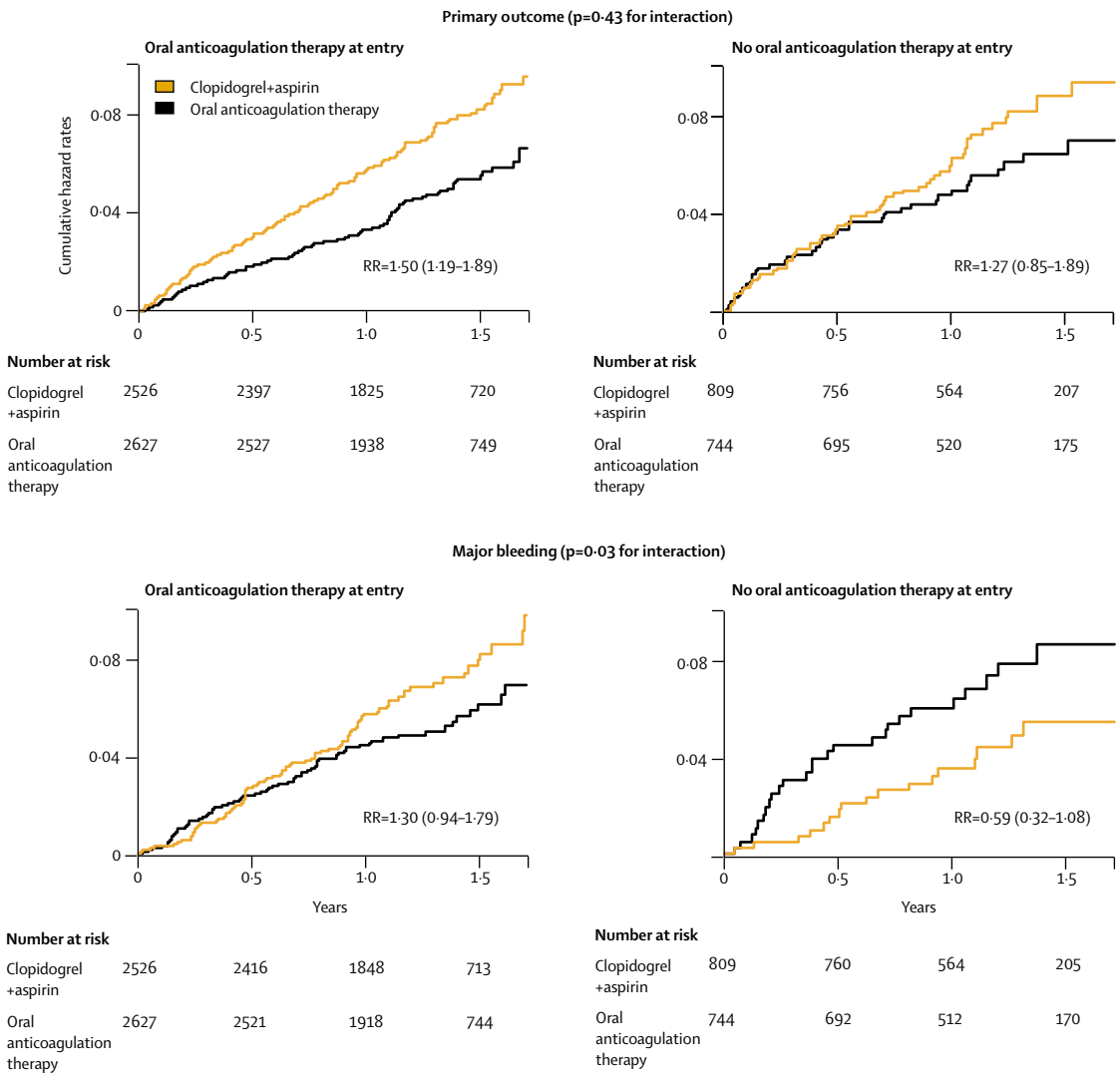


Figure 4: **Use of oral anticoagulant therapy at study entry and outcomes**
Values shown on plots are RR (95% CI).

clopidogrel plus aspirin. The number of fatal strokes were similar in the two groups. Although there were significantly fewer minor bleeds with oral anticoagulation therapy, there were similar numbers of major bleeds, and slightly more fatal bleeds.

The rates of stroke and other vascular events in both treatment groups in ACTIVE W were lower than the rates on oral anticoagulation therapy in trials done in the 1990s,[3–5] but similar to those reported in the recent SPORTIF 3 and 5 trials in patients receiving oral anticoagulation therapy.[17,18] The lower rates of stroke in both treatment arms in ACTIVE W may be due to selection of lower risk patients, more aggressive treatment of hypertension, increased use of lipid lowering agents, or better management of oral anticoagulation. There is good evidence of more aggressive treatment of blood pressure in recent trials. Mean baseline systolic blood pressure in ACTIVE was 6–8 mm Hg lower than in SPAF3,[19] despite similar enrolment criteria. Another factor explaining a low event rate might be tighter control of the INR in recent studies compared with many trials of the early 1990s. However, the event rate on clopidogrel plus aspirin is also much lower than observed previously with aspirin alone. The stroke rate in ACTIVE of 2·4% per year with clopidogrel plus aspirin was less than half that seen in SPAF 3 with aspirin. With such low event rates, even though there is a large relative difference in risk in stroke with clopidogrel plus aspirin compared with oral anticoagulation therapy (relative risk 1·72), the absolute

difference in stroke is 1% per year and the absolute difference in disabling stroke is less than 0·5% per year.

The best way to compare oral anticoagulation therapy with clopidogrel plus aspirin would be in patients not previously exposed to either treatment, because previous exposure could identify patients with good and poor responses to the drugs. Patients with previous poor response to a drug are less likely to continue it or to consider using it again and are therefore less likely to be enrolled in trials. Unequal previous exposure to the two treatments potentially creates a bias in favour of the treatment with greater previous exposure. Due to high rates of use of oral anticoagulation therapy in clinical practice, most patients entering ACTIVE W had received this treatment previously. However, very few patients had tried clopidogrel plus aspirin. A selection bias in favour of oral anticoagulation therapy treatment might have occurred in patients entering ACTIVE W. Patients already receiving oral anticoagulation therapy at enrolment had better drug compliance with oral anticoagulation therapy but not with clopidogrel plus aspirin; and if they stayed on oral anticoagulation therapy they also had better INR control. This pattern seems to have translated into relatively improved outcomes with oral anticoagulation therapy, especially for major bleeding, for which there was a significant interaction related to whether or not patients were receiving oral anticoagulation therapy at study entry. In patients who were already on oral anticoagulation therapy at the time of study entry, those randomised to oral anticoagulation therapy had less bleeding than if randomised to clopidogrel plus aspirin. By contrast, patients not already on oral anticoagulation therapy, who were randomised to this treatment, had more bleeding than those randomised to clopidogrel plus aspirin.

Our findings clearly showed that oral anticoagulation therapy was a better treatment than clopidogrel plus aspirin for the population we investigated. With oral anticoagulation therapy there was an absolute reduction of one stroke per 100 patient-years of treatment and of two major vascular events or major bleeds (net benefit) per 100 patient years. The number of patients who need to be treated for 1 year with oral anticoagulation therapy to prevent a stroke is about 100. These results apply primarily to patients previously exposed to oral anticoagulation therapy. For patients new to both treatments, the benefits of oral anticoagulation therapy relative to clopidogrel plus aspirin are not well defined by this study. We have not addressed whether clopidogrel provides additional benefit when added to aspirin; this question will be addressed in the ACTIVE A study.

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Conflict of interest statement

S Connolly has received research grants for ACTIVE and other studies, and is a speaker for Bristol-Myers Squibb and Sanofi-Aventis. S Yusuf has received grants and honoraria from Bristol-Myers Squibb and Sanofi-Aventis. S Hohnloser is an adviser to Bristol-Myers Squibb and Sanofi-Aventis. M Pfeffer received grant support from Sanofi-Aventis from the ACTIVE trial. R G Hart and J Pogue declare that they have no conflict of interest.

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